3,4-Methylenedioxymethamphetamine (MDMA):
A Review of the English-Language Scientific and Medical Literature

Matthew Baggott, B.A. (matt@baggott.net)
Lisa Jerome, Ph.D. (ljerome@bigplanet.com)
Reid Stuart, M.A.

August 1, 2001
INTRODUCTION ............................................................................................................................................................................. 1

CONCLUSIONS AND SUMMARY ............................................................................................................................................................................. 3

CONCLUSIONS ......................................................................................................................................................................................................... 3
SUMMARY OF CHAPTER 2: CLINICAL MDMA STUDIES ................................................................................................................................. 4
SUMMARY OF CHAPTER 3: DEMOGRAPHICS AND SELF-REPORTED EFFECTS OF ILLICIT ECSTASY USE ......................................................................................................................................................................................................... 5
SUMMARY OF CHAPTER 4: NEUROTOXICITY RESEARCH IN ANIMALS ................................................................................................................................. 6
SUMMARY OF CHAPTER 5: NEUROTOXICITY RESEARCH IN HUMANS ................................................................................................................................. 7
SUMMARY OF CHAPTER 6: ADVERSE EVENTS IN ILLICIT USERS ................................................................................................................................. 9
RECOMMENDATIONS FOR FUTURE PSYCHOTHERAPY RESEARCH ................................................................................................................................. 11
CONCLUDING REMARK ..................................................................................................................................................................................................... 11

PREVIOUS HUMAN EXPERIENCE: CONTROLLED CLINICAL TRIALS AND PHARMACOLOGY ........................................................................................................................................................................................................ 13

INTRODUCTION AND OVERVIEW ............................................................................................................................................................................. 13
A NOTE ON USE OF MDMA IN THERAPY ............................................................................................................................................................................. 14
Table 2.1: Peak Acute Physiological Effects of MDMA ............................................................................................................................................................................. 15
Figures 2.1 & 2.2: Peak Acute Increase in Diastolic BP and Heart Rate ............................................................................................................................................................................. 16
ACUTE PHYSIOLOGICAL EFFECTS ............................................................................................................................................................................. 17
ACUTE AND SUBACUTE SIDE EFFECTS OF MDMA ............................................................................................................................................................................. 18
Table 2.2: Acute Side Effects of MDMA ............................................................................................................................................................................. 19
Table 2.3: Subacute (Up To Post 24 H) Side Effects Of MDMA ............................................................................................................................................................................. 20
Table 2.4: Late Subacute (72 H+) Side Effects Of MDMA ............................................................................................................................................................................. 21
ACUTE HORMONAL/NEUROENDOCRINE EFFECTS ............................................................................................................................................................................. 21
ACUTE SELF-REPORTED/SUBJECTIVE MDMA EFFECTS ............................................................................................................................................................................. 22
ACUTE SELF-REPORTED/SUBJECTIVE MDMA EFFECTS ............................................................................................................................................................................. 22
Table 2.5: Unaltered Neurocognitive Performance after Two MDMA Exposures ............................................................................................................................................................................. 24
NEUROCOGNITIVE AND PSYCHOMOTOR PERFORMANCE EFFECTS OF MDMA ............................................................................................................................................................................. 24
ACUTE AND SUBACUTE IMMUNOMODULATING EFFECTS OF MDMA ............................................................................................................................................................................. 25
ACUTE AND CHRONIC FUNCTIONAL CEREBRAL IMAGING STUDIES ............................................................................................................................................................................. 26
GENERIC DIFFERENCES IN THE PSYCHOLOGICAL AND PHYSIOLOGICAL EFFECTS OF MDMA ............................................................................................................................................................................. 26
DRUG INTERACTION STUDIES AND THE NEUROTRANSMITTER SYSTEMS MEDIATING THE EFFECTS OF MDMA ............................................................................................................................................................................. 27
PHARMACOKINETICS OF MDMA ............................................................................................................................................................................. 28
Table 2.6: MDMA Pharmacokinetic Parameters ............................................................................................................................................................................. 29
Figure 2.3: Metabolic Pathways of MDMA in Humans ............................................................................................................................................................................. 31

DEMOGRAPHICS AND SELF-REPORTED EFFECTS OF ILLICIT ECSTASY USE ............................................................................................................................................................................. 33

INTRODUCTION AND OVERVIEW ............................................................................................................................................................................. 33
Table 3.1: Estimated Prevalence of Ecstasy Use in the United States ............................................................................................................................................................................. 34
DEMOGRAPHICS OF ECSTASY USE: HISTORY AND CURRENT TRENDS ............................................................................................................................................................................. 34
Table 3.2: Demographics of Ecstasy Users (Age 19-32) in the United States ............................................................................................................................................................................. 36
Table 3.3: Estimated Frequency of Ecstasy Use by U.S. High School Students ............................................................................................................................................................................. 37
AN OVERVIEW OF RETROSPECTIVE OR UNCONTROLLED STUDIES ADDRESSING DRUG EFFECTS......................................................................................................................... 38
ACUTE PSYCHOLOGICAL EFFECTS REPORTED IN RETROSPECTIVE STUDIES............ 40
   Table 3.4: Effects of Ecstasy Reported by 100 Undergraduates .......................... 40
ACUTE PHYSIOLOGICAL EFFECTS OF ECSTASY REPORTED IN RETROSPECTIVE STUDIES ........................................................................................................... 42
SUB-ACUTE AND LONG-TERM EFFECTS OF ECSTASY REPORTED IN RETROSPECTIVE STUDIES ........................................................................................................... 43
SUB-ACUTE SEQUELAE REPORTED AFTER ECSTASY USE ...................................... 43
LONG-TERM SEQUELAE REPORTED AFTER ECSTASY USE .................................... 44
COMPARISONS BETWEEN ECSTASY, HALLUCINOGENS AND PSYCHOSTIMULANTS .... 46
   Table 3.5: Frequently Reported Effects of Ecstasy, Amphetamines, and Hallucinogens ........................................................................................................... 47
DECLINE IN DRUG EFFECTS AFTER REPEATED USE OR “LOSS OF MAGIC” .......... 48
COADMINISTRATION OF ECSTASY WITH SSRIS IN ILLICIT ECSTASY USERS ........ 49
OTHER AVENUES OF INVESTIGATING THE EFFECTS OF ECSTASY / MDMA ......... 49
MDMA NEUROTOXICITY: STUDIES IN NONHUMAN ANIMALS ............................... 51

INTRODUCTION AND OVERVIEW ........................................................................... 51
DEFINITIONS .............................................................................................................. 52
MDMA CAN INDUCE LONG-TERM SEROTONERGIC CHANGES ................................. 52
SEROTONERGIC CHANGES ARE ACCOMPANIED BY STRUCTURAL CHANGES TO AXONS . 53
NON-SEROTONERGIC INDICATORS OF CELL DAMAGE ARE INCONSISTENTLY AFFECTED BY MDMA .......................................................... 54
THE ROLE OF OXIDATIVE STRESS IN MDMA NEUROTOXICITY ............................... 55
PROPOSED SOURCES OF OXIDATIVE STRESS .......................................................... 56
ENERGY EXHAUSTION OR IMPAIRMENT AS A SOURCE OF OXIDATIVE STRESS .... 57
MDMA METABOLITES AS A SOURCE OF OXIDATIVE STRESS .................................. 57
   Table 4.1. Studies of the Neurotoxicity of Putative MDMA Metabolites ............... 58
DOPAMINE METABOLITES AS A SOURCE OF OXIDATIVE STRESS ....................... 64
THERE IS CURRENTLY LITTLE EVIDENCE THAT 5HT METABOLITES ACT AS TOXINS ... 66
GLUTAMATE DOES NOT APPEAR TO PLAY A MAJOR ROLE IN MDMA NEUROTOXICITY 66
A POSSIBLE ROLE FOR Ca\(^{2+}\) IN MDMA NEUROTOXICITY .................................. 67
EXTENT OF NEUROTOXICITY DEPENDS ON DOSE, ROUTE OF ADMINISTRATION, ANIMAL AGE, AND SPECIES ................................................................. 67
SPECIES AND STRAIN DIFFERENCES IN VULNERABILITY ....................................... 68
WHY ARE SUCH HIGH DOSES USED IN NEUROTOXICITY RESEARCH? ................. 70
EXTENT OF NEUROTOXICITY IN RATS IS INFLUENCED BY ENVIRONMENT, ESPECIALLY AMBIENT TEMPERATURE ................................................................. 72
   Table 4.2. Studies of Drugs Modifying MDMA Neurotoxicity and Hyperthermia ... 73
DRUGS MODIFYING MDMA NEUROTOXICITY ....................................................... 88
TIME COURSE OF CHANGES AND EXTENT OF RECOVERY ..................................... 88
MDMA-INDUCED APOPTOSIS (PROGRAMMED CELL DEATH) ............................... 90
NON-SEROTONERGIC MDMA NEUROTOXICITY IN THE SOMATOSENSORY CORTEX ..... 90
BEHAVIORAL AND FUNCTIONAL CORRELATES OF MDMA EXPOSURE IN ANIMALS ....... 91
   Table 4.3.  Studies of Long-term Behavioral or Functional Changes after MDMA Exposure in Animals ..................................................................................... 92
BEHAVIORAL EFFECTS OF OTHER SEROTONERGIC NEUROTOXINS ........................ 98
NEUROTOXICITY RESEARCH IN HUMANS

INTRODUCTION AND OVERVIEW

LIMITATIONS OF THE RESEARCH LITERATURE

Table 5.1: Summary of Common Study Limitations

Table 5.2: Comparison of PET and Autoradiography Measures of SERT Density

INTERPRETING STUDIES FOR RISK ASSESSMENT

EVIDENCE OF SEROTONERGIC DIFFERENCES BETWEEN ECSTASY USERS AND NONUSERS

Table 5.3: Cerebral Spinal Fluid Levels of 5HIAA in Ecstasy Users and Nonusers

Figure 5.1: Relationship between ecstasy exposure and CSF 5HIAA in 4 studies

OTHER (POSSIBLY NONSEROTONERGIC) NEUROFUNCTIONAL DIFFERENCES BETWEEN ECSTASY USERS AND NONUSERS

Table 5.4: Reported Neurofunctional Differences Between Ecstasy Users and Nonusers

MOOD, PERSONALITY, BEHAVIORAL, AND NEUROCOGNITIVE USER-NONUSER DIFFERENCES

Table 5.5: Mood Alterations in Ecstasy Users

Table 5.6: Summary of Significant Neurocognitive Findings

Table 5.7: Immediate Verbal Memory in Ecstasy Users Compared to Nonusers

Table 5.8: Delayed Verbal Memory in Ecstasy Users Compared to Nonusers

Table 5.9: Executive Functioning in Ecstasy Users Compared to Nonusers

Figure 5.2: Relationship between Number of Exposures and Executive Function

Figure 5.3: Relationship between Abstinence from Ecstasy and Executive Function

Table 5.11: Memory Performance in Chronic Cocaine Users

POSSIBLE SIGNIFICANCE OF NEUROCOGNITIVE DIFFERENCES AND MDMA NEUROTOXICITY

RISKS OF NEUROTOXICITY IN CLINICAL MDMA STUDIES

MONITORING FOR CHRONIC NEUROTOXICITY IN CLINICAL MDMA STUDIES

MEDICAL EMERGENCIES AND ADVERSE EVENTS IN ECSTASY USERS

INTRODUCTION AND OVERVIEW

EMERGENCY DEPARTMENT (ED) VISITS AFTER ECSTASY USE

Figure 6.1: Emergency Department (ED) cases involving MDMA

ESTIMATING THE FREQUENCY OF EMERGENCY DEPARTMENT VISITS AFTER ECSTASY USE

Table 6.1: Relationship Between Ecstasy Exposures and ED Visits in 329 Users

WHAT TYPES OF ADVERSE EVENTS ARE MOST COMMON?

Table 6.2: Features of 48 Sequential Ecstasy-related ED Visits

USE OF OTHER HEALTH CARE SERVICES BY ECSTASY USERS

DEATHS AFTER ECSTASY USE
Table 6.3: Estimated Annual Ecstasy-related Death Rate in England and Scotland

Table 6.4: Clinical Manifestations of Hyponatremic Encephalopathy

Table 6.5. Traffic Accidents Involving Drivers Under the Influence of MDMA

Table 6.6: Blood Concentrations of MDMA in Published Fatalities

Table 6.7 Blood Concentrations of MDMA in Survivors of Adverse Events

Contents of Ecstasy Pills

Table 6.8. Potency of MDMA-Containing Ecstasy Pills

Table 6.9. Non-MDMA Contents of Ecstasy Pills

Table 6.10. DSM-IV Criteria for Substance Dependence

REFERENCES

APPENDIX A: STRUCTURED ABSTRACTS OF REPORTS ON CLINICAL MDMA RESEARCH

Anderson et al. (1978). Absolute configuration and psychotomimetic activity.
Boone et al. (In Preparation). Neuropsychological Effects of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy).
Cam et al. (2000). Human pharmacology of 3,4-methylenedioxymethamphetamine (“Ecstasy”): psychomotor performance and subjective effects.
Chang et al. (2000). Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow; a co-registered SPECT and MRI study.
De la Torre et al. (2000). Non-linear pharmacokinetics of MDMA (“Ecstasy”) in humans.
De la Torre et al. (2000). Pharmacology of MDMA in humans.
Fallon et al. (1999). Stereospecific analysis and enantiomeric disposition of 3,4-methylenedioxymethamphetamine (Ecstasy) in humans.
GAMMA ET AL. (2000). 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA) MODULATES CENTRAL AND LIMBIC BRAIN ACTIVITY AS MEASURED BY [H215O]-PET IN HEALTHY HUMANS. ................................................................. 234
GREER & TOLBERT (1986). SUBJECTIVE REPORTS OF THE EFFECTS OF MDMA IN A CLINICAL SETTING ....................................................................................................................... 236
GROB ET AL. (1996). PSYCHOBIOLOGIC EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE IN HUMANS: METHODOLOGICAL CONSIDERATIONS AND PRELIMINARY OBSERVATIONS. ........................................................................ 238
GROB ET AL. (IN PREPARATION). PSYCHOLOGICAL, PHYSIOLOGICAL AND NEUROENDOCRINE EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, "ECSTASY") IN HEALTHY HUMANS........................................................................... 240
HELMLIN & BRENNISEN (1992). DETERMINATION OF PSYCHOTROPIC PHENYLALKYLAMINE DERIVATIVES IN BIOLOGICAL MATRICES IN HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY WITH PHOTO DIODE-ARRAY DETECTION. .......................................................................................... 242
HELMLIN ET AL. (1996). ANALYSIS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA) AND ITS METABOLITES IN PLASMA AND URINE BY HPLC-DAD AND GC-MS. ........................................ 242
HENRY ET AL. (1998). LOW-DOSE MDMA ("ECSTASY") INDUCES VASOPRESSIN SECRETION.......................................................................................................................... 244
HENSLEY & CODY (1999). SIMULTANEOUS DETERMINATION OF AMPHETAMINE, METHAMPHETAMINE, METHYLENEDIOXYAMPHETAMINE (MDA), METHYLENEDIOXYMETHAMPHETAMINE (MDMA) AND METHYLENEDIOXYETHYLAMPHETAMINE (MDEA) ENANTIOMERS BY GC-MS. ............. 245
LANZ ET AL. (1997). ENANTIOSELECTIVE DETERMINATION OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE AND TWO OF ITS METABOLITES IN HUMAN URINE BY CYCLODEXTRIN-MODIFIED CAPILLARY ZONE ELECTROPHORESIS......................................................................................... 246
LESTER ET AL. (2000). THE CARDIOVASCULAR EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, "ECSTASY") ............................................................. 247
LIECHTI ET AL. (2000). ACUTE PSYCHOLOGICAL EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, "ECSTASY") ARE ATTENUATED BY THE SEROTONIN UPTAKE INHIBITOR CITALOPRAM...................................................... 248
LIECHTI ET AL. (2000). PSYCHOLOGICAL AND PHYSIOLOGICAL EFFECTS OF MDMA ("ECSTASY") AFTER PRETREATMENT WITH THE 5HT2 ANTAGONIST KETANSERIN IN HEALTHY HUMANS.................................................. 250
LIECHTI & VOLLENWEIDER (2000). ACUTE PSYCHOLOGICAL AND PHYSIOLOGICAL EFFECTS OF MDMA ("ECSTASY") AFTER TREATMENT WITH HALOPERIDOL IN NORMAL HEALTHY HUMANS...................................................................................... 252
LIECHTI & VOLLENWEIDER (2000). THE SEROTONIN UPTAKE INHIBITOR CITALOPRAM REDUCES ACUTE CARDIOVASCULAR AND VEGETATIVE EFFECTS OF MDMA ("ECSTASY") IN HEALTHY VOLUNTEERS. ........................................................................................................ 255
LIECHTI ET AL. (2001). GENDER DIFFERENCES IN THE SUBJECTIVE EFFECTS OF MDMA. .... 257
LIECHTI ET AL. (2001) EFFECTS OF MDMA (ECSTASY) ON PRE-PULSE INHIBITION............. 259
MAS ET AL. (1999). CARDIOVASCULAR AND NEUROENDOCRINE EFFECTS AND PHARMACOKINETICS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE IN HUMANS. .................. 263
PACIFICI ET AL. (1999). IMMUNOMODULATING PROPERTIES OF MDMA ALONE AND IN COMBINATION WITH ALCOHOL; A PILOT STUDY ........................................................... 265
PACIFICI ET AL. (2000). IMMUNOMODULATING ACTIVITY OF MDMA ................................ 267
PACIFICI ET AL. (2001). ACUTE EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE ALONE AND IN COMBINATION WITH ETHANOL ON THE IMMUNE SYSTEM IN HUMANS............. 268
SHULGIN & NICHOLS (1978). CHARACTERIZATION OF THREE NEW PSYCHOTOMIMETICS. ... 270
APPENDIX B: STRUCTURED ABSTRACTS OF REPORTS ON HUMAN ECSTASY NEUROTOXICITY RESEARCH

ALLEN ET AL. (1993). PERSISTENT EFFECTS OF (+/-)3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, “ECSTASY”) IN HUMAN SLEEP. ........................................................... 281


BOONE ET AL. (IN PREPARATION). NEUROPSYCHOLOGICAL EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA OR ECSTASY). .................................................. 285


CHANG ET AL. (2000). EFFECT OF ECSTASY [3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA)] ON CEREBRAL BLOOD FLOW; A CO-REGISTERED SPECT AND MRI STUDY. ................. 288

CHANG ET AL. (1999). CEREBRAL H-MRS ALTERATIONS IN RECREATIONAL 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, “ECSTASY”) USERS. ................................................. 290

CROFT ET AL. (2001). THE RELATIVE CONTRIBUTION OF ECSTASY AND CANNABIS TO COGNITIVE IMPAIRMENT. ...................................................................................... 292

DAFTERS ET AL. (1999). LEVEL OF USE OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA OR ECSTASY) IN HUMANS CORRELATES WITH EEG POWER AND COHERENCE. ............ 295

GAMMA ET AL. (2001). NO DIFFERENCE IN BRAIN ACTIVATION DURING COGNITIVE PERFORMANCE BETWEEN ECSTASY (MDMA) USERS AND CONTROLS: A [H2-150]-PET STUDY. .................................................. 297

GAMMA ET AL. (2000). MOOD STATE AND BRAIN ELECTRIC ACTIVITY IN ECSTASY USERS. .................................................. 299

GERRA ET AL. (2000). LONG-LASTING EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (ECSTASY) ON SEROTONIN SYSTEM FUNCTION IN HUMANS. .................................................. 301

GERRA ET AL. (1998). SEROTONIN FUNCTION AFTER (+/-) 3,4-METHYLENEDIOXYMETHAMPHETAMINE (“ECSTASY”) IN HUMANS. .................................................. 304

GOUZOULIS-MAYFRANK ET AL. (2000). IMPAIRED COGNITIVE PERFORMANCE IN DRUG FREE USERS OF RECREATIONAL ECSTASY (MDMA). .......................................................... 306

KLUGMAN ET AL. (1999). TOXIC EFFECTS OF MDMA ON BRAIN NEURONS (LETTER). .................................................. 308

KRYSTAL ET AL. (1992). CHRONIC 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA) USE: EFFECTS ON MOOD AND NEUROPSYCHOLOGICAL FUNCTION? .................................................. 310

MCCANN ET AL. (1994). SEROTONERGIC NEUROTOXICITY AFTER 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, “ECSTASY”): A CONTROLLED STUDY IN HUMANS. .................................................. 312

MCCANN ET AL. (1998). POSITRON EMISSION TOMOGRAPHIC EVIDENCE OF TOXIC EFFECT OF MDMA (“ECSTASY”) ON BRAIN SEROTONIN NEURONS IN HUMAN BEINGS. .................................................. 314
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCCANN ET AL. (1999)</td>
<td>ALTERED NEUROENDOCRINE AND BEHAVIORAL RESPONSES TO M-CHLOROPHENYLPIPERAZINE IN 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA) USERS.</td>
<td>316</td>
</tr>
<tr>
<td>MCCANN ET AL. (1999)</td>
<td>COGNITIVE PERFORMANCE IN 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA) USERS: A CONTROLLED STUDY.</td>
<td>319</td>
</tr>
<tr>
<td>MORGAN (1998)</td>
<td>RECREATIONAL USER OF “ECSTASY” (MDMA) IS ASSOCIATED WITH ELEVATED IMPULSIVITY (STUDY 1)</td>
<td>322</td>
</tr>
<tr>
<td>MORGAN (1998)</td>
<td>RECREATIONAL USER OF “ECSTASY” (MDMA) IS ASSOCIATED WITH ELEVATED IMPULSIVITY (STUDY 2)</td>
<td>325</td>
</tr>
<tr>
<td>MORGAN (1998)</td>
<td>RECREATIONAL USER OF “ECSTASY” (MDMA) IS ASSOCIATED WITH ELEVATED IMPULSIVITY (ANALYSIS OF POOLED DATA FROM STUDIES 1 AND 2)</td>
<td>327</td>
</tr>
<tr>
<td>MORGAN (1999)</td>
<td>MEMORY DEFICITS ASSOCIATED WITH RECREATIONAL USE OF “ECSTASY” (MDMA).</td>
<td>329</td>
</tr>
<tr>
<td>OBROCKI ET AL. (1999)</td>
<td>ECSTASY: LONG TERM EFFECTS ON THE HUMAN CENTRAL NERVOUS SYSTEM REVEALED BY POSITRON EMISSION TOMOGRAPHY.</td>
<td>331</td>
</tr>
<tr>
<td>PARROTT &amp; LASKY (1998)</td>
<td>ECSTASY (MDMA) EFFECTS ON MOOD AND COGNITION; BEFORE, DURING AND AFTER A SATURDAY NIGHT DANCE</td>
<td>333</td>
</tr>
<tr>
<td>PARROTT ET AL. (1998)</td>
<td>COGNITIVE PERFORMANCE IN RECREATIONAL USERS OF MDMA OR “ECSTASY”: EVIDENCE FOR MEMORY DEFICITS</td>
<td>335</td>
</tr>
<tr>
<td>PARROTT ET AL. (2000)</td>
<td>PSYCHOBIOLOGICAL PROBLEMS IN HEAVY ‘ECSTASY’ (MDMA) POLYDRUG USERS.</td>
<td>337</td>
</tr>
<tr>
<td>PRICE ET AL. (1989)</td>
<td>NEUROENDOCRINE AND MOOD RESPONSES TO INTRAVENOUS L-TRYPTOPHAN IN 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA) USERS: PRELIMINARY OBSERVATIONS.</td>
<td>340</td>
</tr>
<tr>
<td>RENEMAN ET AL. (2000)</td>
<td>MEMORY DISTURBANCES IN “ECSTASY” USERS ARE CORRELATED WITH AN ALTERED BRAIN SEROTONIN TRANSMISSION.</td>
<td>342</td>
</tr>
<tr>
<td>RENEMAN ET AL. (2000)</td>
<td>MDMA (“ECSTASY”) AND ITS ASSOCIATION WITH CEREBROVASCULAR ACCIDENTS; PRELIMINARY FINDINGS.</td>
<td>344</td>
</tr>
<tr>
<td>RICAURTE ET AL. (1990)</td>
<td>AMINERGIC METABOLITES IN CEREBROSPINAL FLUID OF HUMANS PREVIOUSLY EXPOSED TO MDMA: PRELIMINARY OBSERVATIONS.</td>
<td>346</td>
</tr>
<tr>
<td>RODGERS (2000)</td>
<td>COGNITIVE PERFORMANCE AMONGST RECREATIONAL USERS OF “ECSTASY.”</td>
<td>348</td>
</tr>
<tr>
<td>SCHIFANO ET AL. (1998)</td>
<td>MDMA (“ECSTASY”) CONSUMPTION IN THE CONTEXT OF POLYDRUG ABUSE; A REPORT ON 150 PATIENTS.</td>
<td>350</td>
</tr>
<tr>
<td>SEMPLE ET AL. (1999)</td>
<td>REDUCED IN VIVO BINDING TO THE SEROTONIN TRANSPORTER IN THE CEREBRAL CORTEX OF MDMA (“ECSTASY”) USERS.</td>
<td>352</td>
</tr>
<tr>
<td>TUCTIONHAGEN ET AL. (2000)</td>
<td>HIGH INTENSITY DEPENDENCE OF AUDITORY EVOKED DIPOLE SOURCE ACTIVITY INDICATES DECREASED SEROTONERGIC ACTIVITY IN ABSTINENT ECSTASY (MDMA) USERS.</td>
<td>355</td>
</tr>
<tr>
<td>VERKES ET AL. (2000)</td>
<td>COGNITIVE PERFORMANCE AND SEROTONERGIC FUNCTION IN USERS OF ECSTASY.</td>
<td>358</td>
</tr>
<tr>
<td>ZAKZANIS &amp; YOUNG (2001)</td>
<td>MEMORY IMPAIRMENT IN ABSTINENT MDMA (“ECSTASY”) USERS: A LONGITUDINAL INVESTIGATION.</td>
<td>364</td>
</tr>
</tbody>
</table>
Introduction

This document is a review of English-language scientific and medical reports on MDMA/ecstasy. This literature review was commissioned by the Multidisciplinary Association for Psychedelic Studies (MAPS). The goal of this review is to act as a resource for researchers, regulatory agencies, and other interested parties. It is hoped that this review will aid in designing and conducting clinical MDMA research in a manner that reduces risks to volunteers and carefully balances potential benefits against these risks.

This document is divided into five chapters, each summarizing an area of MDMA research: clinical studies; information on illicit users, neurotoxicity research in animals; neurotoxicity research in humans; and adverse events in illicit users. Appendix A contains structured abstracts for all available clinical MDMA studies. Appendix B contains structured abstracts for all available neurotoxicity studies in ecstasy users. Findings from each chapter are summarized below. The document is incomplete in that a planned chapter on the acute neurochemical effects and behavioral pharmacology of MDMA is not included. This chapter is of little relevance to risk assessment and it was considered better to release this document now then to wait for the chapter’s completion.

At this time, 1044 MDMA-related papers have been identified using Medline, PsychInfo, and examination of the bibliographies of MDMA-related papers. The most recent search of Medline was conducted on 5/14/2001. It is anticipated that updates of this literature review will be made at regular intervals. We attempted to define “scientific and medical literature” sufficiently broadly so as to avoid excluding any MDMA papers that would be useful for designing and conducting clinical MDMA studies. Although this literature review focuses on papers published in peer-reviewed journals, publications that were not peer-reviewed are discussed if they contain data that are not otherwise available. In addition, several researchers have kindly supplied manuscripts or findings that have not yet been published. These data are also discussed.

Much of the data on MDMA toxicity in humans involves illicit “ecstasy”, not all of which is pure MDMA. In this review, we include any cases that may have involved MDMA, and only exclude so-called ecstasy cases in which subsequent analysis excluded the presence of MDMA. Even in cases where MDMA was confirmed, impurities or other drugs may have been present. Throughout this report, the term “ecstasy” is used instead of “MDMA” whenever the identity of the consumed drug is in question.

As a companion project to this literature review, we are obtaining and digitizing all published scientific and medical papers on MDMA. As of this time, 1083 papers have been obtained and digitally formatted. This number is larger than 1044 (the number of published scientific papers on MDMA that we have identified) because additional relevant documents have been scanned. These include a patent, testimony from the MDMA Scheduling Hearings, and articles on MDA. Digitized documents are being collected on a CD that will be submitted to the FDA. In addition, MAPS hopes to make
all digitized documents available on the MAPS website (http://www.maps.org/wwwpb/index). We have not yet been able to obtain approximately 90 published MDMA-related papers, mostly from European journals. Based on the abstracts of these papers, it is not anticipated that the conclusions of the present report will be substantially changed by the contents of these currently unavailable papers.

Readers who are familiar with the history of MDMA-assisted psychotherapy or who have personal knowledge of MDMA’s effects may be surprised or even dismayed by the focus of this review. This focus reflects that of the scientific and medical literature, which has been primarily concerned with the potential toxicity of MDMA. Until proper clinical trials are carried out, this situation is not likely to change. Most of the discussion about MDMA’s reportedly therapeutic effects has taken place in the lay literature. Although we note these discussions in passing, it was not appropriate to give them detailed treatment in this review. The reader may wish to bear in mind the conservative biases of the medico-scientific literature when reading this document.

The primary author of this review, Matthew Baggott, received a B.A. in Philosophy from the University of Chicago and has engaged in psychopharmacology research for over a decade. He assisted in behavioral neurotoxicity research at the University of Chicago and, more recently, investigated the clinical psychopharmacology of illicit drugs (including MDMA) at the University of California, San Francisco. Lisa Jerome earned a doctorate in psychology from the University of Maryland-College Park in 1999. She co-authored most chapters and was additionally responsible for statistical analysis. Reid Stuart contributed to Chapter 5 and was invaluable in editing the entire manuscript. He received a M.A. in psychology with a specialization in addiction studies from the Graduate School of Professional Psychology at John F. Kennedy University in Orinda, CA.

Research and editorial assistance by Michael Bauer, Kate Chapman, Earth & Fire Erowid, Ben Hidalgo, Zachary Plaut, Graham Scanlon, and Emily Schiller is gratefully acknowledged.
Conclusions and Summary
Matthew Baggott, B.A., Lisa Jerome, Ph.D., and Reid Stuart, M.A.

Conclusions

In reviewing the literature, the authors particularly focused on issues relating to clinical MDMA research. Before summarizing the individual chapters of this document, we will comment on the risks posed to participants in clinical MDMA research. A broad body of research confirms that MDMA can be safely administered in a clinical setting. As of this time, 33 papers have been published describing the effects of MDMA in at least ten independent samples of volunteers. In addition, numerous animal studies, including a FDA-required 28-day toxicity study in dogs and rats, have characterized the potential of MDMA to produce toxicity. Millions of individuals have self-administered ecstasy in uncontrolled settings and rare instances of serious toxicity have been documented in the medical literature. The conclusion that clinical MDMA research can be conducted with low risks is therefore supported by considerable evidence. However, clinical research should proceed cautiously because serious acute adverse reactions, though rare, are possible and the risks of neurotoxicity are incompletely understood.

The risks of neurotoxicity require special consideration. This is because it is not known what dose would produce neurotoxicity in a clinical setting and the consequences of neurotoxicity are poorly understood. If neurotoxicity occurred in a clinical study, it currently appears unlikely that it would produce clinically significant impairment. This is because even multiple exposures to illicit ecstasy in uncontrolled settings are associated with differences that are clinically subtle. Nevertheless, the relative lack of known consequences of MDMA neurotoxicity is not conclusive evidence that neurotoxicity has no consequences of import. Therefore, the potential benefits of carrying out MDMA research must be weighed against the partially unknown risks of neurotoxicity with each proposed protocol. MDMA exposure should be limited to the lowest dose and number of exposures required for the research goals. Whenever practicable, volunteers should be monitored for possible neurotoxicity.

The primary purpose of this review is to aid researchers. However, some of the findings are relevant to illicit users. The probability of a serious acute adverse event after ecstasy use is low, but the consequences of such an event can include serious illness or death. Outcome often depends on receiving prompt medical care, which may not be available in illicit settings. Although it may be possible to minimize ecstasy-related risks, these risks cannot be entirely eliminated and should be carefully considered by prospective users. There is evidence of neurotoxicity in some repeated users and pharmacokinetic estimates suggest there may be a narrow margin of safety between pharmacologically active and neurotoxic doses. Since the amount contained within each dose of illicit ecstasy varies, the cumulative likelihood that an individual will be exposed to a neurotoxic dose increases with each exposure. The possibility of neurotoxicity should therefore be taken seriously by repeated illicit users. In addition, warm ambient temperatures and co-administration of some other drugs, such as psychedelics/hallucinogens, may increase
extent of neurotoxicity. Although the consequences of this neurotoxicity appear to be clinically subtle and do not noticeably affect functioning in everyday life, research in this area is inadequate and any long-term consequences have not been studied.

Summary of Chapter 2: Clinical MDMA Studies

The second chapter of this document summarizes available information on clinical studies in which MDMA was administered. Three research groups in the United States and three more in Europe have conducted controlled clinical studies with MDMA. Thirty-three publications have documented the effects of MDMA in at least ten independent groups of volunteers. Pharmacokinetics and physiological, neuroendocrine, psychological, neurocognitive, cerebrofunctional, and immunological effects of MDMA have been reported. Studies have also used pharmacological probes to investigate the neurochemical mechanisms that produce the psychological and physiological effects of MDMA. In addition, several reports have been published describing clinical work carried out before MDMA became a controlled substance. Detailed descriptions of individual studies are available in Appendix A. There has been no reported evidence of serious or lasting toxicity to volunteers in these studies or to patients in MDMA-assisted psychotherapy.

MDMA has been administered in controlled clinical studies using doses of up to 2.5 mg/kg, with most studies employing doses equivalent to 1.5 to 1.7 mg/kg MDMA. Earlier, uncontrolled studies and reports employed higher doses (e.g., up to 4.18 mg/kg in Downing 1986), but collected few and somewhat inconsistent data on drug effects.

The intoxication produced by MDMA in recent clinical studies is consistent with earlier reports of an easily controlled state characterized by euphoria, increased well being, increased sociability, and decreased anxiety. These effects are also consistent with the hypothesis that MDMA represents a novel class of pharmacological agent although further research is needed. Participants reportedly experience modest alterations in perception of surroundings and pleasurable loosening of ego boundaries. Subjective effects are accompanied by robust sympathomimetic cardiovascular effects. Acute increases in circulating cortisol, prolactin, ACTH, and antidiuretic hormone occur.

MDMA has been generally well tolerated, with hypertensive episodes being the most important acute adverse effect noted. Other commonly reported side effects include decreased appetite, jaw clenching, and impaired balance/gait. The acute effects of MDMA peak between one and three hours after drug administration and have largely resolved by six hours after drug administration. Documented effects persisting beyond this point include altered immune functioning, probably lasting about two days, and altered cerebral blood flow, lasting at least several weeks. Some volunteers also report feelings of lethargy and other symptoms for several days after MDMA exposure.

Serotonin release seems to be integral to many of the psychological and physiological effects of MDMA, but 5HT2 receptors and dopamine release have also been shown to be involved in producing specific MDMA effects.
MDMA has nonlinear pharmacokinetics with decreased non-renal clearance occurring at higher doses, probably due to inhibition of one metabolic pathway, cytochrome P-450 (CYP) isozyme 2D6. Pharmacological studies suggest that CYP 2D6 may be inactivated by MDMA and may therefore have a limited role in MDMA metabolism. Other enzymes playing a role in MDMA metabolism include CYP 2B6, 1A2, and 3A4.

**Summary of Chapter 3: Demographics and Self-Reported Effects of Illicit Ecstasy Use**

The third chapter discusses surveys that examine the demographics of ecstasy use and the effects of ecstasy as retrospectively described by illicit ecstasy users. Findings from these retrospective studies are compared with findings from clinical studies. Throughout this report, the term “ecstasy” is used instead of “MDMA” whenever the identity of the consumed drug is in question.

Surveys of ecstasy users are useful for documenting patterns of drug use and common effects of ecstasy in uncontrolled settings. Yet they are limited by both the questions researchers ask and the participants, who may not have experienced the full range of rewarding and adverse drug effects. Therefore, the therapeutic potential of MDMA is better documented in reports of its use in psychotherapy, as described in Chapter 2. Similarly, adverse effects of ecstasy are more adequately documented in the case reports and studies described in Chapters 5 and 6.

Ecstasy use is highest among individuals between the ages of 16 and 25, with the drug most strongly associated with dance and “rave” sub-cultures. However, ecstasy use is not limited to one age group or sub-culture. In the United States, prevalence of ecstasy use in the last year was estimated to be 3.1% for eighth graders, and 8.2% for 12 graders in 2000, and estimated to be 5.5% for college students, and 3.6% for young adults (ages 19-28) in 1999.

In surveys of ecstasy users, commonly reported effects of ecstasy are generally consistent with effects seen in clinical MDMA studies, as described in Chapter 2. However in some surveys, users of illicit ecstasy reported ecstasy-induced hallucinations and increases in sexual arousal, two effects either not reported or contradicted by descriptions appearing in other reports. Differences between clinical studies and retrospective surveys are probably due to a variety of factors, including differences in measurement techniques, differences in respondents’ understanding of terms used in measures, and the varying identity, potency, and purity of illicit ecstasy. Comparisons of the effects of ecstasy, amphetamines, and psychedelics/hallucinogens by experienced users support the hypothesis that MDMA has novel psychopharmacological effects.

Few of the reports reviewed in this chapter assessed possible long-term effects of ecstasy use and only a minority of volunteers in these reports described long-term benefits or difficulties. Most users of illicit ecstasy report decreased drug effects (short-term tolerance) when one dose of ecstasy is rapidly followed by another. However, lasting
decrease of drug effects (long-term tolerance) has not been confirmed by all studies asking respondents about this phenomenon.

**Summary of Chapter 4: Neurotoxicity Research in Animals**

Numerous studies have examined nonhuman animals and tissue cultures for evidence of MDMA-induced neurotoxicity. These studies are important because they allow controlled investigation of toxic changes that may occur in humans. These studies can be divided into three areas of neurochemical investigation: (1) monoaminergic neurotoxicity; (2) non-monoaminergic neurotoxicity; and (3) *in vitro* decreases in neural cell viability. The possible damage identified in each of these areas cannot always be equated. Nonetheless, any study of functioning in intact MDMA-exposed animals implicitly investigates all types of neurotoxicity.

High or repeated-dose MDMA regimens can produce long-term changes in indices of monoaminergic and axonal functioning in animals. Increasing evidence indicates that these changes are at least partially the result of damage. The magnitude of these changes varies with dose, species, and route of administration. Rodent studies have shown that changes in the core temperature of animals can increase or decrease MDMA neurotoxicity, although this finding has not been confirmed in primates. While some recovery does occur, a study in squirrel monkeys suggests that there may be permanent changes in axonal distribution. Oxidative stress appears to play an important role in MDMA neurotoxicity, but the exact mechanisms are poorly understood. The sustained acute pharmacological effects of MDMA may exhaust neuronal energy sources and antioxidant defenses, leading to damage. Metabolites of MDMA are another possible source of oxidative stress. The risks of monoaminergic neurotoxicity in humans are controversial and are discussed in the next chapter.

Research has also uncovered MDMA-induced non-monoaminergic neurotoxicity in rats. Measures of neural cell injury indicate that MDMA, like methamphetamine, can damage non-monoaminergic cell bodies in the somatosensory cortex. Another area of research uses cultured cell lines and has suggested that sustained exposure to MDMA can decrease neural cell viability and trigger programmed cell death. These neural cell changes have only been detected after high MDMA exposures that are unlikely to occur in clinical settings.

Few behavioral correlates of neurotoxic MDMA exposure have been found in drug-free nonhuman animals, despite dramatic serotonergic changes, alterations in neurofunctioning, and changes in response to drugs. Changes in MDMA-exposed animals include thermoregulatory impairment, decreased locomotor activity, and neurocognitive impairment. Lasting thermoregulatory impairment has been demonstrated in MDMA-exposed animals by two research groups. Rats exposed to a neurotoxic MDMA regimen showed reductions in diurnal and nocturnal locomotor activity at 7 to 14 days after drug treatment. Two studies have suggested that neurotoxic MDMA exposure may cause neurocognitive impairment in rats. The first study used adult animals and the second study used newborn rats. In contrast, at least 9 other studies failed to find evidence of neurocognitive impairment in MDMA-exposed animals. These
studies indicate that neurotoxic MDMA exposures can cause behavioral changes. These changes have been difficult to detect and it is not known whether they are temporary or permanent.

**Summary of Chapter 5: Neurotoxicity Research in Humans**

The fifth chapter reviews the studies that explore the possibility of neurotoxicity in ecstasy users. Studies of illicit ecstasy users are useful in assessing risk because they identify possible areas of toxicity and identify the possible severity of toxic changes. Studies of ecstasy users are limited because it is not always possible to distinguish the effects of MDMA exposure from other factors with confidence and many questions have not been adequately studied. This chapter attempts to interpret findings in a manner that produces a conservative risk assessment.

Most research on ecstasy users can be categorized into two areas of study: neurofunctional measures and neurocognitive measures. In this document, “neurofunctional” is loosely used to indicate measures of how the brain is working and measures of the concentration or density of neurochemicals. “Neurocognitive measures” refers to performance on standardized tests of mental abilities. Research on ecstasy users supports associations between MDMA exposure and alterations in both neurofunctional and neurocognitive measures. Measures that do not cleanly fit either of these categories include those examining mood and personality in ecstasy users. These measures are also reviewed, even though they are difficult to interpret and have questionable relevance for neurotoxicity risk assessment.

Reported neurofunctional differences between ecstasy users and nonusers include concentration of a serotonin metabolite in cerebrospinal fluid (CSF 5HIAA levels), serotonin transporter (SERT) density, 5HT2A receptor density, neuroendocrine response to serotonergic drugs, EEG measures, altered sleep architecture, cerebral myo-inositol concentration, cerebral glucose utilization, and cerebral blood flow/volume. There is insufficient evidence to assess the permanence or reversibility of most reported neurofunctional differences.

Statistically significant correlations have been reported between ecstasy exposure and specific neurofunctional measures, such as CSF 5HIAA levels, SERT density, global brain volume, myo-inositol increases, 5HT2A receptor density, and EEG alterations. The most conservative interpretation of these correlations is to regard them as evidence that ecstasy exposure caused the neurofunctional differences. A less conservative interpretation would be that differences in these neurofunctional measures predate ecstasy exposure and indicate a tendency to use ecstasy. The authors find this interpretation to be implausible.

In some cases, there are questions as to whether these changes can be considered evidence of serotonergic neurotoxicity rather than responses to the nontoxic pharmacological effects of MDMA. To distinguish between neurotoxicity and responses to pharmacological effects of MDMA, it is helpful to consider (1) animal data on the
effects of MDMA and other serotonergic neurotoxins and (2) human data on the effects of drugs that are not serotonergic neurotoxins, particularly stimulants. When these additional data are considered, some neurofunctional differences can conservatively be regarded as evidence of serotonergic neurotoxicity in users, because they are documented in animals after neurotoxic regimens of MDMA and other serotonergic neurotoxins. These differences include decreases in serotonin transporter and CSF 5HIAA.

Nonetheless, most neurofunctional differences are not clear evidence of selective serotonergic neurotoxicity. Some, such as increased alpha and beta EEG and altered sleep architecture, occur in users of stimulant drugs that do not cause serotonergic neurotoxicity. Others, such as cerebral blood flow/volume and cerebral glucose utilization, are altered in the opposite direction in ecstasy users compared to neurotoxin-exposed animals. Still others, such as increased 5HT2A receptor density, have not been seen in animals exposed to serotonergic neurotoxins. These reported differences are of unknown significance.

Neurocognitive performance studies suggest that, under some conditions or patterns of use, ecstasy exposure can decrease performance in some measures of neurocognitive functioning into the lower range of what is considered clinically normal. There is no conclusive evidence that a specific domain of cognitive functioning is impaired in ecstasy users, although some have suggested that a category of mental abilities called “executive function” that includes the ability to plan ahead may be specifically altered. Measures of verbal memory have most consistently detected differences between ecstasy users and nonusers, but many other measures have also sometimes detected differences.

We do not know the relationship between these neurocognitive changes and serotonergic neurotoxicity. Decreased neurocognitive performance can occur in users of other drugs of abuse, such as cocaine or marijuana. Only 2 of at least 11 studies have found evidence of long-term impairment in the neurocognitive performance of animals exposed to neurotoxic MDMA regimens. This suggests that serotonergic neurotoxicity might occur in the absence of neurocognitive performance changes and that neurocognitive performance changes in ecstasy users may or may not be caused by serotonergic neurotoxicity.

There are not yet sufficient data to conclude whether these neurocognitive differences would lessen after the discontinuation of frequent ecstasy exposure. One study and one analysis described in this document found evidence of recovery, while another study and a second analysis in this document found no evidence of recovery. The issue of recovery is worrisome because even small changes in illicit users could be important if they were permanent.

It is possible that impairment will manifest as users age. Some hypothesize that serotonergic neurotoxicity could lead to depression and anxiety disorders as individuals’ serotonergic systems undergo age-related decreases in functioning. Although age-related decreases in serotonergic functioning appear relatively modest compared to those seen in the dopaminergic system, age-related changes in the brain are not sufficiently understood.
to make predictions about the possible long-term consequences of serotonergic neurotoxicity with any confidence.

Furthermore, there is currently no direct evidence on this issue. There are no published studies with rodents or other animals with short lifespans suggesting MDMA exposure causes significant toxicity that only becomes apparent in the aged animal. There are also no published studies or other evidence of problems developing in humans. MDMA has been widely used for over 20 years and similar drugs with similar capacity for long-term serotonergic changes (e.g., 3,4-methylenedioxyamphetamine, MDA) have been used since the 1960s without evidence of dramatic age-related toxicity. Methamphetamine, which produces both long-term serotonergic and dopaminergic changes, has been used clinically for over 60 years without reported incidents of neurocognitive deficits appearing with age. This lack of evidence of problems developing with age is reassuring, but not conclusive. Until appropriate studies are conducted, lack of evidence of problems cannot be taken as evidence of lack of problems.

Overall, it is very likely that repeated ecstasy exposure causes neurofunctional changes in some illicit users. It is also very likely that some of these changes are due to serotonergic neurotoxicity. Nevertheless, the reported differences between matched groups of ecstasy users and nonusers are clinically subtle and can, so far, only be detected with sensitive neurofunctional and neurocognitive measures. Studies of illicit ecstasy users give no indication that one or two exposures to MDMA in a clinical setting would produce significant or lasting toxicity. Preliminary data from clinical MDMA studies support this conclusion. However, the risks and benefits of proposed MDMA studies must be assessed on an individual basis.

Summary of Chapter 6: Adverse Events in Illicit Users

The final chapter is a summary of the literature on medical emergencies and adverse events related to MDMA/ecstasy. Published analyses suggest that most ecstasy pills contain MDMA. However, many other drugs have been detected in these pills, and some pills sold as ecstasy do not contain any MDMA. This chapter does not discuss cases involving drugs sold as ecstasy that were determined to contain no MDMA. Because serious adverse events are rare after illicit ecstasy exposure, they are even less likely in clinical settings. Nonetheless, this chapter may be useful for assessing and minimizing the risks of acute toxicity in clinical studies.

In 1999, there were 2,848 emergency department (ED) cases involving ecstasy in the United States. 78% of these cases also involved other drugs, most commonly alcohol. Most ecstasy-related ED cases occurred in young adults (age 18 to 25), as would be expected given the demographics of ecstasy use in the United States. Given the distribution of ecstasy use among young adults, it can be estimated that 2.9 to 3.6 in 10,000 ecstasy exposures in young adults resulted in an ED visit. A survey of 329 Australian ecstasy users suggests that this estimate is realistic. In this Australian survey, the equivalent of at least 11 ED visits in 10,000 ecstasy exposures occurred. Deaths relating to ecstasy use are poorly documented in the US. Gore (1999) estimated that 0.21
ecstasy-related deaths per 10,000 illicit users occurred annually in England from 1995-96 and 0.87 ecstasy-related deaths per 10,000 illicit users occurred annually in Scotland from 1995-97. Of course, the probability of an ED visit or death after ecstasy use is not evenly distributed among users. Possible risk factors for ecstasy-related medical emergencies or fatalities are discussed at a later point.

Serious adverse effects occurring after ecstasy use are documented in case reports in the medical literature. Before discussing these reports, it is worth considering that they may not indicate the true frequency of various adverse events. First, published case reports are probably often more severe than cases that go unpublished. Second, they probably under-represent adverse effects of ecstasy that do not require emergency treatment. Three reports – two from poison control centers and one from an emergency department (ED) – suggest that most ecstasy-related ED visits result from symptoms that are modest in severity. Signs and symptoms of ecstasy intoxication documented in these reports are similar to those of amphetamines.

We have obtained over 205 published case reports of adverse events in ecstasy users. Some of these reports describe severe forms of common side effects of ecstasy (difficulty urinating, dental problems), motor vehicle accidents, and other injuries due to intoxication. When these reports are excluded, 199 case reports remain. The most common categories of diagnosis are hyperthermia-related syndromes (24.6% of cases), psychiatric complications (22.1% of cases), hepatotoxicity (16.1% of cases), and hyponatremia (9.5% of cases). Other reported problems include cardiovascular and cerebrovascular, neurological, hematological, respiratory (pneumomediastinum and subcutaneous emphysema), ophthalmic, dermatological, teratological, and dental problems.

Ecstasy-related hyperthermia is described in adverse case reports. While most cases of ecstasy-related hyperthermia were known to have occurred in dance settings, some cases involved individuals who were apparently not involved in “risky” behavior (aside from ecstasy ingestion).

There are reports of hepatotoxicity (liver damage) in ecstasy users. Three in vitro studies have confirmed that pure MDMA can damage liver cells and one of these studies found that hyperthermia increases vulnerability to this damage. Although the MDMA concentrations used in these studies are high, they could be attained in individuals taking high doses or having impaired MDMA metabolism (due to pharmacological interactions with other drugs or previous liver damage).

Cases of ecstasy-related hyponatremia (low salt levels) have been reported. The pharmacological effects of MDMA appear to place the user at increased risk of hyponatremia. Consumption of large volumes of water that would normally be safe may lead to symptoms of “water intoxication” after ecstasy ingestion.

The possible dose-dependence of ecstasy toxicity is discussed. It is argued that dose is probably a risk factor for toxicity, but that other risk factors (some of them unknown) are
important and may mask the significance of dose. Probable risk factors include exercise, dehydration, over-hydration, and hot or humid settings. More frequent use or greater total lifetime dose may be risk factors for psychological problems. While rare, serious ecstasy toxicity cannot be predicted beforehand, and in many specific cases cannot be explained afterwards. Serious adverse reactions or even death can occur after modest amounts of ecstasy in the absence of known risk factors.

Finally, it is noted that a minority of users can be classified as dependent on ecstasy, using standard criteria.

**Recommendations for Future Psychotherapy Research**

With proper precautions, MDMA research should pose low risks to volunteers. Nonetheless, clinical MDMA research is likely to be accompanied by controversy for the next several years due to both scientific and extra-scientific reasons. Given this controversy, the authors of this document suggest to MAPS that a particularly cautious psychotherapy research program could begin with collecting evidence that doses in the vicinity of 125 mg have benefits to treatment-resistant patients before increasing MDMA exposure. Recommended doses around 125 mg were conservatively chosen because they have been widely used in research without evidence of toxicity and with preliminary evidence of non-neurotoxicity. Additionally, the pharmacokinetics of 125 mg have been well-characterized by the Spanish research team. Because higher doses have been administered with apparent safety, 125 mg provides a conservative margin of acute safety while producing sufficient pharmacological effects for research purposes.

**Concluding Remark**

The illicit use of ecstasy by millions of people is, by itself, a compelling reason to study MDMA. Reports that it is helpful in psychotherapy increase the importance of this research. In order to answer concerns and hopes involving MDMA, research must include studies in which MDMA is administered to carefully selected volunteers in controlled clinical settings.
Previous Human Experience: Controlled Clinical Trials and Pharmacology
Matthew Baggott, B.A., and Lisa Jerome, Ph.D.

Introduction and Overview

This chapter summarizes available information on clinical studies in which MDMA was administered. Three research groups in the United States and three more in Europe have conducted controlled clinical studies with MDMA. Thirty-three publications have documented the effects of MDMA in at least ten independent groups of volunteers. Pharmacokinetics and physiological, neuroendocrine, psychological, neurocognitive, cerebrofunctional, and immunological effects of MDMA have been reported. Studies have also used pharmacological probes to investigate the neurochemical mechanisms that produce the psychological and physiological effects of MDMA. In addition, several reports have been published describing clinical work carried out before MDMA became a controlled substance. Detailed descriptions of individual studies are available in Appendix A. There has been no reported evidence of serious or lasting toxicity to volunteers in these studies or to patients in MDMA-assisted psychotherapy.

MDMA has been administered in controlled clinical studies using doses of up to 2.5 mg/kg, with most studies employing doses equivalent to 1.5 to 1.7 mg/kg MDMA. Earlier, uncontrolled studies and reports employed higher doses (e.g., up to 4.18 mg/kg in Downing 1986), but collected few and somewhat inconsistent data on drug effects.

The intoxication produced by MDMA in recent clinical studies is consistent with earlier reports of an easily controlled state characterized by euphoria, increased well being, increased sociability, and decreased anxiety. These effects are also consistent with the hypothesis that MDMA represents a novel class of pharmacological agent, although further research is needed. Participants reportedly experience modest alterations in perception of surroundings and pleasurable loosening of ego boundaries. Subjective effects are accompanied by robust sympathomimetic cardiovascular effects. Acute increases in circulating cortisol, prolactin, ACTH, and antidiuretic hormone occur.

MDMA has been generally well tolerated, with hypertensive episodes being the most important acute adverse effect noted. Other commonly reported side effects include decreased appetite, jaw clenching, and impaired balance/gait. The acute effects of MDMA peak between one and three hours after drug administration and have largely resolved by six hours after drug administration. Documented effects persisting beyond this point include altered immune functioning, probably lasting about two days, and altered cerebral blood flow, lasting at least several weeks. Some volunteers also report feelings of lethargy and other symptoms for several days after MDMA exposure.

Serotonin release seems to be integral to many of the psychological and physiological effects of MDMA, but 5HT2 receptors and dopamine release have also been shown to be involved in producing specific MDMA effects.
MDMA has nonlinear pharmacokinetics with decreased non-renal clearance occurring at higher doses, probably due to inhibition of one metabolic pathway, cytochrome P-450 (CYP) isozyme 2D6. Pharmacological studies suggest that CYP 2D6 may be inactivated by MDMA and may therefore have a limited role in MDMA metabolism. Other enzymes playing a role in MDMA metabolism include CYP 2B6, 1A2, and 3A4.

A Note on Use of MDMA in Therapy

It is worth noting that there is considerable previous human experience with the use of MDMA in the context of psychotherapy. Before MDMA was classified as a controlled substance, a number of therapists employed it as an adjunct to psychotherapy. Although no blinded or placebo-controlled trials were conducted, these therapists concluded that MDMA was clinically useful and could be safely administered to a variety of patient populations. Few published reports of this work qualify for inclusion in this review (most of these reports were not published in peer-reviewed journals). Nonetheless, available reports document the clinical experience of these therapists. Reid Stuart's (2000) annotated bibliography on MDMA psychotherapy is a helpful summary of this literature.

The DEA hearings on the scheduling of MDMA provide a useful overview of therapeutic work with MDMA. Rick Ingrasci, MD, MPH, (1985) reported conducting approximately 150 MDMA sessions with about 100 patients, 11 of them cancer patients. Approximately one-third of these 150 sessions were with couples. Joseph Downing, M.D., (1985) reported use of MDMA with 8 patients, 5 of whom were felt to have shown accelerated therapeutic progress. Philip Wolfson, M.D., (1985; 1986) administered MDMA to 3 psychotic patients in the context of family therapy, reporting short-term but no clear long-term benefits of MDMA. George Greer, M.D., (Greer and Strassman 1985; Greer and Tolbert 1986; 1990; 1998) administered MDMA to about 80 individuals. Although not described at the DEA hearings, therapeutic work with MDMA was also carried out in other countries. Manuel Madriz Marin, M.D., chief psychiatrist of a Nicaraguan military hospital, used MDMA in the treatment of 20 patients with “anxiety or depressive disorders” (Saunders and Doblin 1996). After MDMA was made a controlled substance, Samuel Widmer, MD, Peter Gasser, MD, and other members of the Swiss Medical Society for Psycholytic Therapy received permission to administer MDMA to patients from 1988 to 1993 (Gasser 1994; Widmer 1997). During this time, 171 patients received MDMA. In a follow-up survey, 85.1% of 121 responding patients reported good or slight improvement during therapy, which included $6.8 \pm 4.3 (1 - 16)$ MDMA sessions administered in the context of on-going therapy (Gasser 1994).

Based on this clinical experience, MDMA was considered to possess a “unique action that enhanced communication” (Greer 1985), especially between people in a significant emotional relationship. Reductions in defenses and fear of emotional injury and a heightened capacity for introspection were reported. MDMA was reported to enhance retrieval of previously suppressed memories, leading to reduction of symptoms (Grinspoon and Bakalar 1986). These effects of MDMA were achieved with relatively modest reported side effects and no indications of chronic toxicity. While these
Table 2.1: Peak Acute Physiological Effects of MDMA

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Heart Rate (BPM)</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
<th>Body Temp (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 mg/kg</td>
<td>2 (1M, 1F)</td>
<td>-7 ± 4</td>
<td>17 ± 21</td>
<td>18 ± 9</td>
<td>-1.36 ± 0.44</td>
<td>Grob et al. 1996</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>4 (2M, 2F)</td>
<td>6 ± 4</td>
<td>13 ± 8</td>
<td>11 ± 10</td>
<td>0.4 ± 0.4</td>
<td>Grob et al. 1996</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>8 (5 M, 3F)</td>
<td>1 ± 4</td>
<td>4 ± 7</td>
<td>4 ± 4</td>
<td>0.1 ± 0.4</td>
<td>Lester et al. 2000</td>
</tr>
<tr>
<td>50 mg</td>
<td>2</td>
<td>?</td>
<td>7 ± 8</td>
<td>1 ± 5</td>
<td>0.95 ± 0.1</td>
<td>de la Torre et al. 2000b</td>
</tr>
<tr>
<td>0.75 mg/kg</td>
<td>4 (3M, 1F)</td>
<td>12 ± 15</td>
<td>19 ± 6</td>
<td>11 ± 3</td>
<td>0.5 ± 0.3</td>
<td>Grob et al. 1996</td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>12 (7M, 5F)</td>
<td>16 ± 17</td>
<td>25 ± 20</td>
<td>18 ± 14</td>
<td>1.0 ± 0.8</td>
<td>Tancer, pers. com.</td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>4 (3M, 1F)</td>
<td>25 ± 11</td>
<td>25 ± 14</td>
<td>19 ± 7</td>
<td>0.3 ± 0.3</td>
<td>Grob et al. 1996</td>
</tr>
<tr>
<td>75 mg/70 kg</td>
<td>5F</td>
<td>17 ± 18</td>
<td>21 ± 9</td>
<td>10 ± 6</td>
<td>na</td>
<td>Tancer, pers. com.</td>
</tr>
<tr>
<td>75 mg</td>
<td>10</td>
<td>24</td>
<td>25 ± 3</td>
<td>12 ± 3</td>
<td>0.36 ± 0.1</td>
<td>de la Torre et al. 2000b</td>
</tr>
<tr>
<td>1.25 mg/kg</td>
<td>4 (2M, 2F)</td>
<td>24 ± 23</td>
<td>31 ± 13</td>
<td>26 ± 15</td>
<td>0.4 ± 0.4</td>
<td>Grob et al. 1996</td>
</tr>
<tr>
<td>100 mg</td>
<td>13</td>
<td>na</td>
<td>31 ± 5</td>
<td>14 ± 3</td>
<td>0.4 ± 0.1</td>
<td>de la Torre et al. 2000b</td>
</tr>
<tr>
<td>1.5 mg/kg</td>
<td>4 (3M, 1F)</td>
<td>20 ± 8</td>
<td>31 ± 5</td>
<td>21 ± 12</td>
<td>0.9 ± 0.2</td>
<td>Grob et al. in preparation</td>
</tr>
<tr>
<td>1.5 mg/kg</td>
<td>8 (5M, 3F)</td>
<td>26 ± 20</td>
<td>20 ± 10</td>
<td>13 ± 5</td>
<td>0.3 ± 0.4</td>
<td>Lester et al. 2000</td>
</tr>
<tr>
<td>110 mg/70 kg</td>
<td>5 (1M, 4F)</td>
<td>23 ± 14</td>
<td>25 ± 5</td>
<td>22 ± 6</td>
<td>na</td>
<td>Tancer, pers. com.</td>
</tr>
<tr>
<td>125 mg</td>
<td>8</td>
<td>na</td>
<td>34 ± 7</td>
<td>15 ± 2</td>
<td>0.41 ± 0.1</td>
<td>de la Torre et al. 2000b</td>
</tr>
<tr>
<td>1.35 – 1.8 mg/kg</td>
<td>20F</td>
<td>13 ± 13</td>
<td>22 ± 12</td>
<td>10 ± 7</td>
<td>0.3 ± 0.3</td>
<td>Liechti et al. 2001</td>
</tr>
<tr>
<td>1.35 – 1.8 mg/kg</td>
<td>54M</td>
<td>9 ± 13</td>
<td>34 ± 16</td>
<td>18 ± 11</td>
<td>0.3 ± 0.4</td>
<td>Liechti et al. 2001</td>
</tr>
<tr>
<td>1.75 mg/kg</td>
<td>4 (3M, 1F)</td>
<td>21 ± 17</td>
<td>29 ± 16</td>
<td>20 ± 12</td>
<td>0.7 ± 0.9</td>
<td>Grob et al. in preparation</td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>4 (3M, 1F)</td>
<td>18 ± 8</td>
<td>39 ± 22</td>
<td>24 ± 9</td>
<td>0.8 ± 0.7</td>
<td>Grob et al. in preparation</td>
</tr>
<tr>
<td>145 mg/70 kg</td>
<td>5 (4 M, 1 F)</td>
<td>18 ± 13</td>
<td>31 ± 6</td>
<td>25 ± 10</td>
<td>na</td>
<td>Tancer, pers. com.</td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>12 (7M, 5F)</td>
<td>25 ± 15</td>
<td>36 ± 19</td>
<td>23 ± 10</td>
<td>1.2 ± 0.8</td>
<td>Tancer, pers. com.</td>
</tr>
<tr>
<td>150 mg</td>
<td>2</td>
<td>na</td>
<td>43 ± 2</td>
<td>20 ± 2</td>
<td>0.65 ± 0.6</td>
<td>de la Torre, et al. 2000b</td>
</tr>
<tr>
<td>2.25 mg/kg</td>
<td>4 (3M, 1F)</td>
<td>13 ± 9</td>
<td>52 ± 41</td>
<td>15 ± 13</td>
<td>0.5 ± 0.1</td>
<td>Grob et al. in preparation</td>
</tr>
<tr>
<td>2.5 mg/kg</td>
<td>2 (1M, 1F)</td>
<td>22 ± 20</td>
<td>36 ± 7</td>
<td>25 ± 5</td>
<td>0.2 ± 0.2</td>
<td>Grob et al. in preparation</td>
</tr>
</tbody>
</table>

Values are Mean ± SD and represent mean peak change from baseline, except for those from de la Torre et al. 2000b, which are maximal value reported (but possibly not peak). Reported statistical significance is not indicated here. Report by Liechti et al. 2001, averages physiological measures from 0-75 min and 75-150 min. na = not available (either not measured or not reported).
Figures 2.1 & 2.2: Peak Acute Increase in Diastolic BP and Heart Rate

Error bars represent SEM

- Mean Peak Change in Diastolic BP (mmHg)
- Mean Peak Change in Heart Rate (BPM)

MDMA Dose (mg/kg)
experiences were not achieved using properly controlled trials and standardized outcome measures, they nonetheless provide an indication of the acute safety and potential therapeutic utility of MDMA when used in a clinical context.

**Acute Physiological Effects**

MDMA has significant acute cardiovascular effects, as would be expected from its norepinephrine-releasing (Johnson et al. 1991; Rothman et al. 2001) and α-2 adrenergic agonist (Lavelle et al. 1999) properties. MDMA dose-dependently produces robust increases in heart rate and blood pressure (de la Torre et al. 2000a; de la Torre et al. 2000b; Grob et al. In preparation; Lester et al. 2000; Mas et al. 1999; O'Cain et al. 2000; Vollenweider et al. 1998a). Peak cardiovascular effects occur between 1 and 2 hours after MDMA administration and largely subside within 6 hours of drug administration. Lester and colleagues (2000) compared echocardiograms taken one hr after administering 0.5 and 1.5 mg / kg MDMA to eight volunteers with echocardiograms made after administering a series of increasing doses of the beta agonist dobutamine. Echocardiograms conducted after 1.5 mg / kg MDMA indicate that MDMA did not possess positive ionotropic effects, a sign that the heart may be consuming more oxygen than would be predicted from measuring heart rate or blood pressure alone. **Table 2.1** summarizes the peak changes in physiological measures reported after different doses of MDMA. As can be seen, the physiological effects of MDMA are, on the average, robust but clinically insignificant in healthy volunteers.

The relationship between MDMA dose and cardiovascular effects was suggested to be supralinear by de la Torre et al. (2000a) who reported unexpectedly high drug exposures (measured as AUC\text{plasma} for MDMA) and diastolic blood pressure increases in two volunteers given 150 mg MDMA. While pharmacokinetic data (discussed below) suggest MDMA has nonlinear kinetics, there is no clear evidence of supralinear relationships between dose and blood pressure or heart rate when available data are graphed (**Figures 2.1 and 2.2**). In fact, there may be less increase in heart rate after higher doses. Although this comparison is across individuals and requires further confirmation, the tendency toward less heart rate increase with higher dose is consistent with a study using both conscious and anesthetized rats (O'Cain et al. 2000). In this rat study, 3 mg/kg IV MDMA decreased heart rate, while lower doses tended to increase it or leave it unchanged.

There is some interindividual variation in cardiovascular effects and a significant minority of volunteers have experienced clinically significant hypertension. Grob et al. (In preparation) reported a transient blood pressure elevation (200/100 mm Hg) in a 26-year-old male who had been administered 1.75 mg/kg MDMA. This response was possibly related to the volunteer’s previously undisclosed use of Ventolin [salbutamol/albuterol], an alpha-2-adrenergic agonist and CYP3A substrate (Manchee et al. 1996). A 60-year-old male administered 2.5 mg/kg MDMA by the same research group displayed blood pressures of 220/120 mm Hg for approximately 2 hours. In another study, conducted by Vollenweider et al. (1998a) a 49-year-old male with no previous MDMA experience displayed peak blood pressure values of 240/145 mm Hg.
(but no other signs of hypertensive crisis) for about 20 minutes. Cardiovascular indices in all three individuals returned to baseline levels without intervention. Mas et al. (1999) note that four of eight volunteers met diagnostic criteria for hypertension after each of the MDMA doses (75 mg and 125 mg) in their study. Given the small number of volunteers studied, the frequency of these hypertensive episodes highlights the need for careful prescreening and monitoring of volunteers.

In uncontrolled settings, serious acute toxicity after MDMA use is often related to prolonged hyperthermia. In contrast, the administration of MDMA in clinical settings has been associated with small, clinically insignificant increases in core temperature that only achieve statistical significance in some studies (Liechti et al. 2000b). The temperature changes seen in clinical studies are similar in magnitude to those achieved after modest oral doses of other sympathomimetic amphetamines (Mas et al. 1999). Some of this slight increase in core temperature may be secondary to short-lived drug-induced vasoconstriction (Fitzgerald and Reid 1994), which can reduce heat loss and skin temperature. Research conducted by De la Torre and his colleagues may offer some support for this conjecture (de la Torre et al. 2000b). They found a slight decrease in body temperature one hour after MDMA administration followed by an elevation in body temperature two to four hours after MDMA administration in volunteers given MDMA at doses ranging from 75 mg to 150 mg. Peripheral vasoconstriction was offered as a possible explanation for the slight dip in body temperature seen prior to the elevation in body temperature after MDMA administration. Alternatively, central mechanisms may mediate MDMA-induced body temperature changes. Microinjection of 5HT into the anterior hypothalamus can cause an initial decrease followed by an increase in cell temperature in rats and primates (Myers 1975, 1968).

Other measurable acute physiological effects of MDMA include mydriasis (increases in pupillary diameter) and esophoria (altered eye alignment due to increased extraocular muscle tension) (Cami et al. 2000; de la Torre et al. 2000b; Downing 1986). Nystagmus also occurs in some volunteers, as is can be seen in Table 2.2.

**Acute and Subacute Side Effects of MDMA**

Reported side effects of MDMA are modest and generally not associated with great discomfort by volunteers. Reported acute side effects are summarized in Table 2.2, subacute effects are listed in Table 2.3 and 2.4. Decreased appetite, jaw clenching, and dry mouth are commonly reported during peak MDMA effects, while fatigue may be felt up to several days after MDMA. Less commonly, mild anxiety and depressed mood are reported one and three days after MDMA administration (Liechti et al. 2000b; Liechti and Vollenweider 2000a; b; Vollenweider et al. 1998a). The time course of these symptoms is similar to that reported for amphetamines (Watson et al. 1972). Not all reports have described side effects of MDMA in enough detail to allow inclusion in these tables. Most notably, side effects have not been reported by Grob and colleagues or by the Spanish researchers.
Table 2.2: Acute Side Effects of MDMA

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N: 13-57</td>
<td>13-112</td>
<td>10</td>
<td>16</td>
<td>29</td>
<td>14</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>MDMA Dose(s): 0</td>
<td>0.5-4.18 mg/kg</td>
<td>1.7-4.18 mg/kg</td>
<td>1.7 mg/kg</td>
<td>75-150, 200 mg</td>
<td>1.5 mg/kg</td>
<td>1.5 mg/kg</td>
<td>1.5 mg/kg</td>
</tr>
<tr>
<td>Measurement Time:</td>
<td>2-5 h</td>
<td>0-100 min</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>0-360 min</td>
</tr>
<tr>
<td>Lack Of Appetite: 2%</td>
<td>70%</td>
<td>100%</td>
<td>63%</td>
<td>97%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Jaw Clenching: 0%</td>
<td>63%</td>
<td>60%</td>
<td>64%</td>
<td>76%</td>
<td>57%</td>
<td>71%</td>
<td>44%</td>
</tr>
<tr>
<td>Dry Mouth: na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Thirst: 4%</td>
<td>48%</td>
<td>50%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Restless Legs: 0%</td>
<td>45%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Impaired Balance/Gait: 0%</td>
<td>44%</td>
<td>70%</td>
<td>na</td>
<td>10%</td>
<td>71%</td>
<td>43%</td>
<td>50%</td>
</tr>
<tr>
<td>Difficulty Concentrating: 16%</td>
<td>42%</td>
<td>30%</td>
<td>50%</td>
<td>3%</td>
<td>71%</td>
<td>50%</td>
<td>63%</td>
</tr>
<tr>
<td>Dizziness: 2%</td>
<td>40%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>57%</td>
<td>21%</td>
<td>50%</td>
</tr>
<tr>
<td>Restlessness: 0%</td>
<td>39%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>50%</td>
<td>29%</td>
<td>44%</td>
</tr>
<tr>
<td>Sensitivity To Cold: 7%</td>
<td>38%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Private Worries: 23%</td>
<td>38%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Heavy Legs: na</td>
<td>38%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Palpitations: 0%</td>
<td>33%</td>
<td>na</td>
<td>na</td>
<td>38%</td>
<td>na</td>
<td>43%</td>
<td>21%</td>
</tr>
<tr>
<td>Feeling Cold: 4%</td>
<td>33%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>43%</td>
<td>23%</td>
</tr>
<tr>
<td>Perspiration: 0%</td>
<td>30%</td>
<td>na</td>
<td>50%</td>
<td>na</td>
<td>36%</td>
<td>na</td>
<td>0%</td>
</tr>
<tr>
<td>Drowsiness: 50%</td>
<td>23%</td>
<td>na</td>
<td>na</td>
<td>14%</td>
<td>43%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Nyctagmus: na</td>
<td>23%</td>
<td>80%</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Hot Flashes: 0%</td>
<td>23%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>23%</td>
</tr>
<tr>
<td>Nausea: 4%</td>
<td>21%</td>
<td>10%</td>
<td>na</td>
<td>24%</td>
<td>36%</td>
<td>na</td>
<td>8%</td>
</tr>
<tr>
<td>Trismus: na</td>
<td>21%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>57%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Inner Tension: 0%</td>
<td>17%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>43%</td>
<td>14%</td>
<td>19%</td>
</tr>
<tr>
<td>Insomnia: 0%</td>
<td>17%</td>
<td>0%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>31%</td>
</tr>
<tr>
<td>Anxiety: 0%</td>
<td>16%</td>
<td>na</td>
<td>na</td>
<td>17%</td>
<td>14%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Weakness: 0%</td>
<td>16%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>36%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Urge To Urinate: 8%</td>
<td>15%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>15%</td>
</tr>
<tr>
<td>Tremor: 0%</td>
<td>14%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>21%</td>
<td>14%</td>
<td>31%</td>
</tr>
<tr>
<td>Muscle Aches / Tension:</td>
<td>na</td>
<td>14%</td>
<td>na</td>
<td>na</td>
<td>21%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Forgetfulness: 0%</td>
<td>14%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>38%</td>
</tr>
<tr>
<td>Fatigue: 26%</td>
<td>13%</td>
<td>na</td>
<td>na</td>
<td>7%</td>
<td>na</td>
<td>29%</td>
<td>na</td>
</tr>
<tr>
<td>Parasthesias: 0%</td>
<td>12%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>31%</td>
</tr>
<tr>
<td>Lack Of Energy: 14%</td>
<td>12%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>29%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Brooding: 0%</td>
<td>12%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>29%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Fainting: na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Blurred Vision: na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Lip Swelling: na</td>
<td>2%</td>
<td>na</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>0%</td>
</tr>
<tr>
<td>Headaches: na</td>
<td>2%</td>
<td>0%</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>0%</td>
<td>na</td>
</tr>
</tbody>
</table>

Page 19 of 367
Table 2.3: Subacute (Up To Post 24 H) Side Effects Of MDMA

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10-86</td>
<td>10</td>
<td>10</td>
<td>29</td>
<td>14</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Dose(s)</td>
<td>-</td>
<td>1.76-4.18 mg/kg</td>
<td>75-150, 200 mg</td>
<td>1.5 mg/kg</td>
<td>1.5 mg/kg</td>
<td>1.7 mg/kg</td>
<td>1.5 mg/kg</td>
</tr>
<tr>
<td>Measurement Time</td>
<td>-</td>
<td>At 24 h</td>
<td>8-24 h</td>
<td>At 24 h</td>
<td>At 24 h</td>
<td>At 24 h</td>
<td>At 24 h</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47%</td>
<td>na</td>
<td>55%</td>
<td>na</td>
<td>50%</td>
<td>38%</td>
<td>38%</td>
</tr>
<tr>
<td>Heavy Legs</td>
<td>38%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>38%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>36%</td>
<td>na</td>
<td>na</td>
<td>36%</td>
<td>36%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Lack of appetite</td>
<td>29%</td>
<td>na</td>
<td>7%</td>
<td>29%</td>
<td>50%</td>
<td>38%</td>
<td>46%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>29%</td>
<td>0%</td>
<td>38%</td>
<td>14%</td>
<td>36%</td>
<td>na</td>
<td>38%</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>29%</td>
<td>na</td>
<td>na</td>
<td>29%</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Weakness</td>
<td>25%</td>
<td>na</td>
<td>na</td>
<td>21%</td>
<td>29%</td>
<td>19%</td>
<td>31%</td>
</tr>
<tr>
<td>Thirst</td>
<td>25%</td>
<td>na</td>
<td>na</td>
<td>21%</td>
<td>36%</td>
<td>0%</td>
<td>46%</td>
</tr>
<tr>
<td>Private worries</td>
<td>23%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>23%</td>
</tr>
<tr>
<td>Sensitivity to cold</td>
<td>23%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>23%</td>
</tr>
<tr>
<td>Trismus</td>
<td>21%</td>
<td>na</td>
<td>na</td>
<td>21%</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Jaw tension / tight jaw</td>
<td>21%</td>
<td>na</td>
<td>21%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>20%</td>
<td>20%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Lack of energy</td>
<td>18%</td>
<td>na</td>
<td>na</td>
<td>7%</td>
<td>0%</td>
<td>19%</td>
<td>46%</td>
</tr>
<tr>
<td>Difficulty Concentrating</td>
<td>17%</td>
<td>na</td>
<td>3%</td>
<td>14%</td>
<td>29%</td>
<td>25%</td>
<td>31%</td>
</tr>
<tr>
<td>Headaches</td>
<td>16%</td>
<td>0%</td>
<td>0%</td>
<td>29%</td>
<td>44%</td>
<td>15%</td>
<td>na</td>
</tr>
<tr>
<td>Need more sleep</td>
<td>15%</td>
<td>na</td>
<td>na</td>
<td>14%</td>
<td>na</td>
<td>na</td>
<td>15%</td>
</tr>
<tr>
<td>Perspiration</td>
<td>15%</td>
<td>na</td>
<td>na</td>
<td>7%</td>
<td>na</td>
<td>na</td>
<td>23%</td>
</tr>
<tr>
<td>Jaw clenching</td>
<td>14%</td>
<td>10%</td>
<td>10%</td>
<td>21%</td>
<td>0%</td>
<td>na</td>
<td>31%</td>
</tr>
<tr>
<td>Restlessness</td>
<td>12%</td>
<td>na</td>
<td>na</td>
<td>14%</td>
<td>0%</td>
<td>0%</td>
<td>38%</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>12%</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>31%</td>
</tr>
<tr>
<td>Urge to urinate</td>
<td>12%</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>31%</td>
</tr>
<tr>
<td>Exhaustibility</td>
<td>12%</td>
<td>na</td>
<td>na</td>
<td>0%</td>
<td>na</td>
<td>31%</td>
<td>0%</td>
</tr>
<tr>
<td>Brooding</td>
<td>10%</td>
<td>na</td>
<td>3%</td>
<td>21%</td>
<td>na</td>
<td>0%</td>
<td>23%</td>
</tr>
<tr>
<td>Muscle aches / tension</td>
<td>10%</td>
<td>na</td>
<td>14%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>0%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5%</td>
<td>na</td>
<td>7%</td>
<td>0%</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Nausea</td>
<td>5%</td>
<td>na</td>
<td>7%</td>
<td>0%</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>4%</td>
<td>na</td>
<td>na</td>
<td>0%</td>
<td>na</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>3%</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Body odor</td>
<td>3%</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Constipation</td>
<td>3%</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>3%</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>3%</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Visual Illusion</td>
<td>3%</td>
<td>na</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Inner tension</td>
<td>2%</td>
<td>na</td>
<td>na</td>
<td>7%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Impaired balance / gait</td>
<td>1%</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>na</td>
</tr>
</tbody>
</table>

na: not available
Table 2.4: Late Subacute (72 H+) Side Effects Of MDMA

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N:</td>
<td>14-73</td>
<td>29</td>
<td>14</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>MDMA Dose:</td>
<td>75 mg – 1.5 mg/kg</td>
<td>75-150, 200 mg</td>
<td>1.5 mg/kg</td>
<td>1.5 mg/kg</td>
<td>1.5 mg/kg</td>
</tr>
<tr>
<td>Measurement Time:</td>
<td>-</td>
<td>3 days - 1 wk later</td>
<td>At 72 h</td>
<td>At 72 h</td>
<td>At 72 h</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29%</td>
<td>na</td>
<td>na</td>
<td>29%</td>
<td>na</td>
</tr>
<tr>
<td>Irritability</td>
<td>25%</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>25%</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>14%</td>
<td>na</td>
<td>14%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Brooding</td>
<td>14%</td>
<td>10%</td>
<td>7%</td>
<td>na</td>
<td>25%</td>
</tr>
<tr>
<td>Lack of energy</td>
<td>9%</td>
<td>na</td>
<td>7%</td>
<td>21%</td>
<td>0%</td>
</tr>
<tr>
<td>Lack of appetite</td>
<td>7%</td>
<td>3%</td>
<td>0%</td>
<td>29%</td>
<td>0%</td>
</tr>
<tr>
<td>Trismus</td>
<td>7%</td>
<td>na</td>
<td>7%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Need more sleep</td>
<td>7%</td>
<td>na</td>
<td>7%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7%</td>
<td>na</td>
<td>7%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Gloomy thoughts</td>
<td>7%</td>
<td>na</td>
<td>0%</td>
<td>0%</td>
<td>19%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4%</td>
<td>na</td>
<td>7%</td>
<td>0%</td>
<td>na</td>
</tr>
<tr>
<td>Jaw clenching</td>
<td>4%</td>
<td>na</td>
<td>7%</td>
<td>0%</td>
<td>na</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>3%</td>
<td>3%</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Thirst</td>
<td>2%</td>
<td>na</td>
<td>7%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Restlessness</td>
<td>2%</td>
<td>na</td>
<td>7%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

na: not available

Acute Hormonal/Neuroendocrine Effects

MDMA dose-dependently increases cortisol, prolactin and adrenocortictropic hormone concentrations (Grob et al. 1996; Mas et al. 1999), while growth hormone is unchanged by up to 125 mg MDMA (Mas et al. 1999). Increases in cortisol and prolactin peak at about 2 hours after MDMA administration. These findings are consistent with rat studies showing MDMA-induced increases in corticosterone and prolactin (Nash et al. 1988).

Henry et al. (1998) reported that 40 mg MDMA increased circulating levels of antidiuretic hormone (arginine vasopressin). MDMA may therefore produce modest alterations in fluid balance. Increased retention of fluid is unlikely to be of any consequences in a clinical setting. However, this finding is consistent with reports of
hyponatremia in illicit users (Box et al. 1997; Hall 1997b; Holmes et al. 1999; Kessel 1994; Magee et al. 1998; Maxwell et al. 1993; O’Connor et al. 1999; Parr et al. 1997; Watson et al. 1997; Wilkins 1996). This finding is probably unrelated to the difficulty urinating experienced by some during acute MDMA intoxication. This occasional side effect of MDMA is more likely to be due to stimulation of α-adrenergic receptors on muscles in the bladder (Bryden et al. 1995).

Acute Self-Reported/Subjective MDMA Effects

MDMA has been hypothesized to represent a new class of psychoactive agents, called entactogens (Nichols 1986), producing feelings of closeness to others and empathy, well being and insightfulness, with little perceived loss of control or hallucinatory effect (Grinspoon and Bakalar 1986; Hegadoren et al. 1999; Nichols 1986; Shulgin and Nichols 1978). As discussed below, clinical studies generally support this hypothesis, although it is also clear that the effects of MDMA overlap with those of psychostimulants and, to a lesser extent, hallucinogens.

Many of the effects of MDMA resemble those of psychostimulants and include self-reported increases in positive mood, activation and self-confidence (Cami et al. 2000; Downing 1986; Gamma et al. 2000b; Greer and Tolbert 1986; Grob et al. 1996; Liechti et al. 2000a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; Vollenweider et al. 1998a). Psychostimulants are characterized in most healthy volunteers by acute, dose-dependent effects such as euphoria and increased positive affect, feelings of vigor and alertness, increased self-confidence, occasional anxiety, and cardiovascular pressor effects (Chait et al. 1986; Johanson and Uhlenhuth 1980; Mendelson et al. 1995; Uhlenhuth et al. 1981). The cardiovascular pressor effects and many of the side effects (dry mouth, jaw or muscle tension, paresthesias) reported by volunteers after MDMA administration are reminiscent of psychostimulants. One effect that clearly distinguishes MDMA from typical psychostimulants is the sedative-like effect reported by Cami et al. (2000). These researchers found that 125 mg MDMA increased self-reported visual analogue ratings of “drunken” and scores on the ARCI questionnaire sedation (“PCAG”) subscale.

A few of the self-reported effects of MDMA are consistent with mild hallucinogen-like activity. Hallucinogens characteristically produce sensory and perceptual distortions, alterations in perception of meaning, impaired attention, unpredictable and often rapid mood changes, and feelings of loss of control often leading to anxiety (Haertzen 1966; Hermle et al. 1992; Katz et al. 1968; Langs and Barr 1968; Vollenweider et al. 1998b). MDMA has been found to produce modest sensory and perceptual changes, primarily intensification of colors and tactile awareness and changes in the quality of sounds. Visual illusions such as 3-dimensional vision of flat objects, micropsia, macropsia, and illusory movement have also been noted (Cami et al. 2000; Vollenweider et al. 1998a). True hallucinations have not, however, been reported. Hallucinogen-like alterations in the perception of meanings occur after MDMA administration (Liechti et al. 2000a; Liechti et al. 2000b; Liechti and Vollenweider 2000a). The altered sense of meaning is accompanied by moderate thought disturbances such as accelerated thinking, thought
blocking, and impaired decision making (Vollenweider et al. 1998a). Moderate
derealization also occurs, with volunteers reporting that their surroundings feel different
or unreal (Cami et al. 2000; Vollenweider et al. 1998a). MDMA also produces
alterations in time perception (Vollenweider et al. 1998a), an effect also associated with
hallucinogens. Both MDMA and hallucinogens induce self-reported difficulty in
concentrating (Cami et al. 2000; Liechti and Vollenweider 2000a), although MDMA-
induced changes in neurocognitive performance are less consistently detected (see
“Neurocognitive and Psychomotor Performance Effects of MDMA”).

Despite these similarities between MDMA and hallucinogens, MDMA differs from
typical hallucinogens in several important ways. The subjective effects of MDMA
appear to be more consistently pleasurable than those of hallucinogens, which produce
labile and unpredictable mood changes. The depersonalization induced by MDMA is
modest and has been described as a pleasurable loosening of ego boundaries
(Vollenweider et al. 1998a) rather than the profound depersonalization and anxious
passivity associated with hallucinogens. In summary, to the extent that MDMA
resembles a hallucinogen, it resembles one given at a dose too low to consistently
produce the dramatic effects of hallucinogens.

In addition to effects resembling those of psychostimulants and hallucinogens, MDMA
has been reported to have effects not typical of either drug class. These reported effects
include increased feelings of closeness to others, sociability, and empathy. While these
effects were apparently not formally measured (aside from individual items in self-report
questionnaires), both the Swiss and Spanish MDMA research groups have noted that
volunteers spontaneously reported some entactogenic effects (Cami et al. 2000;
Vollenweider et al. 1998a; Vollenweider et al. 1999b). In addition, nearly all subjects
participating in an uncontrolled investigation of MDMA psychotherapy reported feeling
closer to others (Greer and Tolbert 1986). Vollenweider et al. (1998, p. 247) state
“subjects reported experiencing an increased responsiveness to emotions, a heightened
openness, and a sense of closeness to other people.”

There are a number of issues raised in attempting to measure potentially unique
entactogenic effects. One issue concerns appropriate and validated instruments. A
number of self-report instruments have been developed to measure empathy (Chlopan et
al. 1985; Davis 1983; Layton and Wykle 1990) and sociability and empathy scales exist
on some personality instruments (e.g., Eysenck et al. 1985). However, empathy and
related constructs are often conceived as ‘traits’ rather than ‘states.’ Accordingly, these
instruments are not appropriate for use in repeated-measures drug studies. A second
issue involves interpreting findings. No consistent relationship has been found between
self-ratings of empathy and actual empathic accuracy or initiation of helping behaviors
(Davis and Kraus 1997; Eisenberg and Miller 1987). Therefore, feelings of empathy are
not necessarily evidence that MDMA is therapeutically useful. Behavioral protocols do
exist for measuring empathic accuracy (Iekes et al. 1990) and observer-ratings of
empathic rapport have been used in psychotherapy research. These measures may prove
useful in establishing the existence and possible usefulness of uniquely “entactogenic”
effects.
Overall, data are consistent with the hypothesis that MDMA is a member of a novel pharmacological class with effects only partially overlapping those of psychostimulants and hallucinogens. Most groups conducting MDMA or MDE research have employed the term “entactogen” in their publications. Comparisons of the MDMA analogue, MDE, to hallucinogens and stimulants using the APZ Altered States of Consciousness scale (Dittrich 1998) and other measures suggest that putative entactogens produce a different drug effects syndrome than hallucinogens or psychostimulants (Gouzoulis-Mayfrank et al. 1999a; Gouzoulis-Mayfrank et al. 1999b). However, comparisons have been limited to single doses generally administered to different individuals. For now, the existence of this novel pharmacological class must be considered a “working hypothesis” rather than a fact until putative entactogenic effects are better characterized over a range of doses and these effects are compared, preferably in the same individuals, to those of a range of doses of hallucinogens and psychostimulants.

Table 2.5: Unaltered Neurocognitive Performance after Two MDMA Exposures

<table>
<thead>
<tr>
<th></th>
<th>PRE Score</th>
<th>POST Score</th>
<th>t</th>
<th>P (ns)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>11.0</td>
<td>11.5</td>
<td>-.90</td>
<td>.39</td>
</tr>
<tr>
<td><strong>Verbal Memory: Auditory Verbal Learning Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 5</td>
<td>12.6</td>
<td>12.5</td>
<td>.13</td>
<td>.90</td>
</tr>
<tr>
<td>Interference</td>
<td>10.6</td>
<td>9.9</td>
<td>.91</td>
<td>.38</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>9.9</td>
<td>9.7</td>
<td>.21</td>
<td>.84</td>
</tr>
<tr>
<td>Recognition</td>
<td>14.0</td>
<td>13.9</td>
<td>.19</td>
<td>.85</td>
</tr>
<tr>
<td><strong>Visual Memory: Continuous Visual Memory Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hits</td>
<td>38.8</td>
<td>37.7</td>
<td>.91</td>
<td>.38</td>
</tr>
<tr>
<td>False Alarms</td>
<td>15.3</td>
<td>15.1</td>
<td>.11</td>
<td>.92</td>
</tr>
<tr>
<td>d”prime</td>
<td>2.2</td>
<td>2.0</td>
<td>1.24</td>
<td>.24</td>
</tr>
<tr>
<td>Total</td>
<td>77.4</td>
<td>76.6</td>
<td>.48</td>
<td>.64</td>
</tr>
<tr>
<td>Recognition</td>
<td>3.5</td>
<td>4.1</td>
<td>-1.32</td>
<td>.21</td>
</tr>
<tr>
<td><strong>Executive/Frontal Lobe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consonant Tri.</td>
<td>50.9</td>
<td>49.7</td>
<td>.72</td>
<td>.48</td>
</tr>
<tr>
<td>FAS/CFL</td>
<td>43.1</td>
<td>46.1</td>
<td>-1.40</td>
<td>.18</td>
</tr>
</tbody>
</table>

Data are from Boone et al., in preparation, and are reproduced with permission.

**Neurocognitive and Psychomotor Performance Effects of MDMA**

MDMA appears to have modest acute effects on neurocognitive performance. The acute effects of MDMA have been measured using the digit symbol substitution task (Cami et al. 2000), a simple reaction time task (Cami et al. 2000), a continuous performance attention task (Gamma et al. 2000a), the Stroop task (Vollenweider et al. 1998a), and a prepulse inhibition measure of sensorimotor gating (Liechti et al. 2001b; Vollenweider et al. 1999b). Of these tasks, only the digit symbol substitution task and the prepulse inhibition task have detected MDMA-induced performance alterations. Performance on
the digit symbol substitution task was reduced when individuals were given 100 or 125 mg MDMA, but not 75 mg MDMA (Cami et al. 2000). Prepulse inhibition was increased after 1.5 or 1.7 mg/kg MDMA. A drug interaction study with the SSRI citalopram suggests that serotonin release is important for MDMA-induced prepulse inhibition increase (Liechti et al. 2001b). Dopamine D2 and 5HT2 receptors do not appear to be involved in this effect since it was not altered by pretreatment with either the D2 antagonist haloperidol or the 5HT2 antagonist ketanserin (Liechti et al. 2001b). In addition, Downing assessed 10 of his 21 volunteers using poorly described digit repetition, multiplication, memory, and finger-to-nose coordination tasks (Downing 1986). 3 of 10 volunteers had difficulty with the multiplication task. 4 volunteers gave idiosyncratic responses to the decision-making task, suggesting impaired judgment. Finally, 2 of 10 volunteers had difficulty with the finger-to-nose task. Thus, the acute effects of MDMA on neurocognitive performance are modest.

Studies of illicit ecstasy users have suggested that repeated MDMA use may be associated with lowered neurocognitive performance. In contrast, participation in clinical MDMA studies has not been associated with chronic alterations in neurocognitive performance. Table 2.5 shows neurocognitive data collected before and approximately 2 weeks after 14 volunteers were administered up to 2.5 mg/kg MDMA in the study partially described in Grob et al. (1996). Vollenweider also reports unchanged neurocognitive performance in his volunteers, many of whom were previously MDMA-naive (Dr. Franz Vollenweider, personal communication).

### Acute and Subacute Immunomodulating Effects of MDMA

Pacifici and colleagues carried out immunological testing on blood samples collected from volunteers administered 75 or 100 mg MDMA in studies of MDMA-ethanol interactions. Findings from this research are distributed throughout three publications. Four volunteers participated in a pilot study and six individuals took part in a second study (Pacifici et al. 1999; Pacifici et al. 2001), while samples drawn from an additional two individuals are described in a third publication (Pacifici et al. 2000). While total leukocyte count was unchanged, CD4 T-cell count (and therefore also the ratio of CD4 to CD8 T-cells) was decreased. This decrease was similar in magnitude to that produced by 0.8 g/kg ethanol (the equivalent of 4-5 drinks) in the same study. NK cell count was increased. In addition, phytohaemoagglutinin A-induced lymphocyte proliferation was decreased. This decrease was approximately twice that produced by ethanol and also appeared to last longer. Lymphocyte proliferation had only partially returned to baseline at 24 hours after drug administration. The concentrations of pro-inflammatory and anti-inflammatory cytokines were reported after MDMA in the later publication (Pacifici et al. 2001). MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon-Gamma and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 cytokines and increased the amount of Th2 cytokines measured in blood. The mechanism of this MDMA-induced immunomodulation is unclear but may involve MDMA-induced glucocorticoid release or sympathomimetic activity. Acute alterations in immune functioning after MDMA administration have also been noted in mice (House et al. 1995) and rats (Connor et al. 2000a; Connor et al. 2000b; Connor et al. 1998).
immunomodulation appears to be an acute pharmacological effect of MDMA and is not likely to persist. Nonetheless, these findings should be considered when evaluating the risks and benefits of administering MDMA to individuals with compromised immunocompetence.

Acute and Chronic Functional Cerebral Imaging Studies

MDMA acutely alters regional cerebral blood flow (rCBF). Gamma et al. (2000a) used [H$_2$\(^{15}$O]-Positron Emission Tomography (PET) to measure rCBF at 75 min after 1.7 mg/kg MDMA in 16 volunteers. They detected increases in prefrontal, inferior temporal, and cerebellar cortex rCBF. Decreased rCBF was detected in limbic, paralimbic, central frontal, and temporal areas.

These acute effects of MDMA on rCBF may be followed by long-lasting decreases in rCBF. Chang et al. (2000) assessed rCBF in 10 volunteers before and after participation in clinical MDMA research. MDMA-induced decreases in regional and global cerebral blood flow (CBF) occurred in a subset of eight volunteers assessed 10 to 21 days after last MDMA exposure. CBF was measured using [99mTc]-HMPAO SPECT co-registered with MRI and significant decreases were found bilaterally in the visual cortex, caudate, superior parietal, and dorsolateral frontal regions. Two additional volunteers showed evidence of possibly increased CBF at later time points (43 and 80 days after MDMA, respectively). This suggests that these changes are either a subacute drug effect of limited duration or part of a lasting biphasic effect (with decreases followed by increases). Because each volunteer was only assessed once after study participation, more research is needed to better understand the time course and possible significance of these changes. The authors suggest (but do not provide statistical results supporting) a possible relationship between time elapsed since last MDMA exposure and regional CBF and interpret this relationship as evidence of recovery. In addition, the authors did not find differences in regional or global CBF when 21 MDMA-experienced volunteers (with a reported 211 ± 340 exposures) were compared to 21 nonusers (data are presented in the same paper). Similarly, Gamma et al. (2001) saw no significant differences between 16 MDMA users (most of whom had used MDMA at least 100 times) and 17 nonusers when regional CBF was measured during a vigilance task using [H$_2$\(^{15}$O]-PET. Finally, it should also be pointed out that Gamma et al. reportedly did not detect changes in regional CBF using [H$_2$\(^{15}$O]-PET in a retrospective analysis of a study in which volunteers received 1.7 mg/kg MDMA (Dr. Alex Gamma, personal communication). It appears that two exposures to as little as 1.25 mg/kg MDMA may alter CBF at least 2 or 3 weeks after last drug exposure. The full time course of these changes is unclear.

Gender Differences in the Psychological and Physiological Effects of MDMA

Men and women may not experience the different psychological and physiological effects of MDMA with the same frequency or magnitude. A survey of Australian illicit ecstasy users found that being female was one of several factors that predicted an increase in experiencing side effects and adverse events after taking ecstasy (Topp et al. 1999). In studies of possible neurotoxicity, it has been suggested that female ecstasy
users may have a greater alterations of serotonergic function (McCann et al. 1994) but may be resistant to neurocognitive changes (Bolla, et al., 1998). An investigation relying on data pooled from three clinical studies found gender differences in the subjective and physiological effects of MDMA (Liechti, et al., 2000). Mood, alteration in consciousness, cardiovascular effects, body temperature and adverse events were measured in 74 individuals, most of them MDMA-naïve, who received 1.35 – 1.8 mg/kg MDMA in the course of three randomized, placebo-controlled clinical studies. Scores on all three scales on a measure of alterations in consciousness were higher in women than in men after MDMA.

When compared to men, women reported greater increases in positive mood, pleasant derealization, thought disorder, fear of loss of body control, alterations in perception, alterations in the meaning of objects, facilitated recall, and facilitated imagination. The gender difference in the intensity of the psychological effects of MDMA was most pronounced for its effects on perception and thought. Women specifically reported a greater increase in the “hallucinogen-like” effects of MDMA, including changes in thought and perception. While the authors failed to find a relationship between higher doses of MDMA and increases in positive mood or fear of ego dissolution in either gender, a relationship was found between higher doses (in mg/kg) and increased alteration of perception in women, but not in men. Men reported being more activated or energetic than women acutely after MDMA, and women reported more anxiety and dysphoric reactions. Anxiety was related to feelings of helplessness, defenselessness, and needing protection. More women than men reported experiencing the acute side effects measured in these studies, including commonly reported side effects, such as jaw-clenching, dry mouth, and loss of appetite. Sweating and nausea were the only side effects more frequently listed by men than women. When sub-acute effects were assessed 24 hours after the participants had received MDMA, women made up a greater percentage of the people reporting sub-acute effects, such as fatigue, dry mouth, and continued lack of appetite.

While women in this sample were more sensitive to some of the psychological effects of MDMA, men seemed to be more sensitive to the physiological effects of the drug. MDMA produced a significant increase in systolic blood pressure in both genders, but the increase was greater in men than in women. While MDMA elevated heart rate in both men and women, this elevation was only significantly different from heart rate at placebo for men. Lastly, it appeared that MDMA only significantly elevated body temperature in men. These findings suggest that men are more sensitive to the sympathomimetic effects of MDMA.

Drug Interaction Studies and the Neurotransmitter Systems Mediating the Effects of MDMA

Researchers in Switzerland have carried out drug interaction studies to investigate the neurotransmitter systems mediating the effects of MDMA in humans. In vitro and nonhuman animal studies have established that MDMA induces serotonin, dopamine, norepinephrine, and acetylcholine release (Battaglia et al. 1988a; Fischer et al. 2000;
Gudelsky and Nash 1996; Rudnick and Wall 1992) and can act directly on a number of receptors, including $\alpha_2$-adrenergic and 5HT$_2A$ receptors (Battaglia et al. 1988a; Lavelle et al. 1999; Nash et al. 1994). Clinical studies have further elucidated the roles of serotonergic and dopaminergic systems in the psychopharmacology of MDMA. Serotonin release appears to be either directly or indirectly responsible for a large number of the psychological and physiological effects of MDMA. When MDMA-induced serotonin release was attenuated by pretreatment with the SSRI citalopram, volunteers reported a reduction in MDMA-induced changes in mood, perception, and thought (Liechti et al. 2000a). Citalopram pretreatment also reduced the elevated blood pressure and heart rate usually produced by MDMA (Liechti and Vollenweider 2000b). However, serotonin release alone cannot account for all of the effects of MDMA, as volunteers who received MDMA after citalopram pretreatment still had elevated body temperature and increased scores on a measure of "emotional excitability," defined here as emotionality, excitability, and nervousness. Some of these effects seem to arise from stimulation of 5HT$_2$ receptors, since pretreatment with the 5HT$_2A$/2C antagonist ketanserin reduced subsequent MDMA effects on emotional excitability, changes in perception, diastolic blood pressure and body temperature (Liechti et al. 2000b). The hallucinogen-like effects of MDMA appear to be produced through 5HT$_2$ receptors (as would be expected), as ketanserin pretreatment reduced the changes in perception and thought, without greatly altering the increase in mood or anxiety over losing control produced by MDMA. Studies using the dopamine D$_2$ antagonist haloperidol indicate that the MDMA-induced increase in positive mood is due at least in part to dopaminergic mechanisms. When MDMA was given after haloperidol pretreatment, volunteers reported an increase in state anxiety, particularly as the effects of MDMA first began appearing, as well as difficulty concentrating and fatigue (Liechti and Vollenweider 2000a). Since pretreatment with haloperidol did not reduce MDMA's sympathomimetic effects in humans, it would appear that these are largely due to noradrenergic mechanisms. Although interpretation of these drug interaction studies is complicated by possible pharmacokinetic interactions and possible effects of the pharmacological blocking agents employed, these studies represent dramatic advances in our understanding of MDMA psychopharmacology. Further research is needed to investigate the role of other neurotransmitter systems and receptors, particularly the noradrenergic system and the 5HT$_{1A}$ receptor, in the human psychopharmacology of MDMA.

**Pharmacokinetics of MDMA**

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Basic pharmacokinetic parameters are summarized in Table 2.6. The fraction of MDMA bound to dog plasma proteins is approximately 0.4 and is concentration-independent over a wide range of concentrations (Garrett et al. 1991). Metabolites of MDMA which have been identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called alpha-methylidopamine), 3,4-methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997;
Ortuno et al. 1999). Additional metabolites have been identified in rodents (Chu et al. 1996; Lim and Foltz 1988; 1989; 1991; Yousif et al. 1990). Thus far, human plasma levels of MDMA and the metabolites HMMA, HMA, and MDA have been published. It appears that the dihydroxylated metabolites are short lived and de la Torre et al. (2000a) were unable to detect them in plasma. At higher doses (above approximately 100 mg), MDMA is excreted mainly as the unmetabolized drug, while at lower doses HMMA is the primary metabolite in urine (de la Torre et al. 2000a; Lanz et al. 1997). Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996).

The enzymes and pathways involved in MDMA metabolism have been examined through in vitro studies. The probable pathways of MDMA metabolism are summarized in Figure 2.3. The oxidation of the methylenedioxy group can take place via enzymes such as cytochrome p450 (Hiramatsu et al. 1990; Kumagai et al. 1991; Lim and Foltz 1988; Tucker et al. 1994) or by a nonenzymatic process involving the hydroxyl radical (Lin et al. 1992). The enzymes catalyzing this reaction have been examined in the rabbit

Table 2.6: MDMA Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>MDMA Dose</th>
<th>N</th>
<th>Cmax</th>
<th>Tmax</th>
<th>AUC 0-24</th>
<th>AUC/dose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 µg/l</td>
<td>2</td>
<td>19.8 and 82.8</td>
<td>2 and 3</td>
<td>100.1 and 813.9</td>
<td>2 and 16.3</td>
<td>de la Torre et al. 2000a</td>
</tr>
<tr>
<td>75 µg/l</td>
<td>8</td>
<td>130.9 ± 38.6</td>
<td>1.8 ± 0.38</td>
<td>1331.5 ± 646.03</td>
<td>17.8 ± 8.6</td>
<td>Mas et al. 1999</td>
</tr>
<tr>
<td>100 µg/l</td>
<td>8</td>
<td>222.5 ± 26.06</td>
<td>2.3 ± 1.1</td>
<td>2431.38 ± 766.52</td>
<td>30.5 ± 11.2</td>
<td>de la Torre et al. 2000b</td>
</tr>
<tr>
<td>125 µg/l</td>
<td>8</td>
<td>236.4 ± 57.97</td>
<td>2.4 ± 0.98</td>
<td>2623.7 ± 572.9</td>
<td>21 ± 4.6</td>
<td>Mas et al. 1999</td>
</tr>
<tr>
<td>150 µg/l</td>
<td>2</td>
<td>441.9 and 486.9</td>
<td>1.5 and 2</td>
<td>5132.8 and 5232</td>
<td>34.2 and 34.9</td>
<td>de la Torre et al. 2000a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MDMA Dose</th>
<th>N</th>
<th>ks</th>
<th>kc</th>
<th>T1/2</th>
<th>MDA T1/2a</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 µg/l</td>
<td>2</td>
<td>na</td>
<td>na</td>
<td>2.7 and 5.1</td>
<td>na</td>
<td>de la Torre et al. 2000b</td>
</tr>
<tr>
<td>75 µg/l</td>
<td>8</td>
<td>2.3835 ± 2.1362</td>
<td>0.1171 ± 0.0818</td>
<td>7.86 ± 3.58</td>
<td>0.42 ± 0.2</td>
<td>Mas et al. 1999</td>
</tr>
<tr>
<td>100 µg/l</td>
<td>8</td>
<td>2.70 ± 1.53</td>
<td>0.081 ± 0.018</td>
<td>8.96 ± 2.27</td>
<td>1.31 ± 0.55</td>
<td>De la Torre et al. 2000b</td>
</tr>
<tr>
<td>125 µg/l</td>
<td>8</td>
<td>2.1253 ± 1.1001</td>
<td>0.0923 ± 0.0428</td>
<td>8.73 ± 3.29</td>
<td>0.41 ± 0.22</td>
<td>Mas et al. 1999</td>
</tr>
<tr>
<td>150 µg/l</td>
<td>2</td>
<td>na</td>
<td>na</td>
<td>6.9 and 7.2</td>
<td>na</td>
<td>De la Torre et al. 2000a</td>
</tr>
</tbody>
</table>

(Kumagai et al. 1991), rat (Gollamudi et al. 1989; Hiramatsu and Cho 1990; Hiramatsu et al. 1990; Hiratsuka et al. 1995) and human (Kreth et al. 2000; Lin et al. 1997b; Maurer et al. 2000; Tucker et al. 1994; Wu et al. 1997). In human liver microsomes, Michaelis-Menten kinetics for formation of dihydroxylated metabolites are biphasic (Kreth et al. 2000). The low Km component for demethylation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher Km also contribute to MDMA demethylation, including CY1A2 and CYP3A4.

It has been hypothesized that genetic variations in CYP2D6 activity may influence risk of MDMA toxicity. CY2D6 activity is genetically determined and up to 10% of the Caucasian population has deficient CYP2D6 activity. It has therefore been suggested that individuals having this autosomal recessive trait may have increased plasma drug
concentrations and increased risk of acute adverse response to MDMA. The fact that CYP2D6 is apparently easily saturated makes this possible source of individual sensitivity appear less significant. In fact, there currently seems to be no evidence that the poor metabolizer genotype is by itself a major risk factor for acute MDMA toxicity. Schwab et al. (1999) found that three illicit MDMA users who developed MDMA-related hepatotoxicity all had extensive CYP2D6 activity. In addition, Kreth et al. (2000) reported that the poor metabolizer trait did not lead to significant alteration in maximal drug plasma concentrations in an individual participating in a clinical study of the MDMA analogue, MDE. Formation of the major demethylated metabolite (analogue to HMMA) was approximately 44% that of other volunteers, however. This provides further evidence that the role of CYP2D6 in MDMA metabolism is sufficiently limited that it is not a major risk factor in healthy individuals in a clinical setting.

Formation of HMMA and HMA from DHMA and DHA, respectively, has not been directly investigated, but may occur via catechol-o-methyl transferase (de la Torre et al. 2000a). It should be noted that thioether conjugates of DHA (and likely DHMA) have been hypothesized to play a role in MDMA neurotoxicity (Bai et al. 1999; Miller et al. 1996; 1997). The possible role of MDMA metabolites is discussed in Chapter 4.

Enzymes involved in the formation of MDA from MDMA in human liver microsomes have been investigated by two groups (Kreth et al. 2000; Maurer et al. 2000). Maurer et al. reported that formation of MDA was predominantly catalyzed by CYP1A2 (and to a lesser extent by CYP2D6), but did not present detailed results of their experiments. Kreth et al., in a publication focusing on MDE metabolism, reported high correlations between MDMA and MDE N-dealkylation (r=0.97, P<0.001) and MDE N-dealkylation and human liver microsome CYP2B6 content (r = 0.90, P<0.001). MDE N-dealkylation and CYP1A2 levels were also significantly correlated (r = 0.58, P<0.05). The role of CYP2B6 in human MDMA metabolism is consistent with rodent research (Gollamudi et al. 1989). Because Maurer et al. did not examine CYP2B6, there is no real discrepancy between the studies of Maurer and Kreth.

MDMA is a chiral compound and has been almost exclusively administered as a racemate. However, an early uncontrolled report suggests that the S-enantiomer is significantly more potent in humans than the R-enantiomer (Anderson et al. 1978). Studies in human volunteers (Fallon et al. 1999; Hensley and Cody 1999) and rodents (Cho et al. 1990; Fitzgerald et al. 1990; Matsushima et al. 1998) indicate that the disposition of MDMA is stereoselective, with the S-enantiomer having a shorter elimination half-life and greater excretion that the R-enantiomer.
For example, Fallon et al. (1999) reported that the area under the curve (AUC) of plasma concentrations was two to four times higher for the R-enantiomer than the S-enantiomer after 40 mg, p.o., in human volunteers. Moore et al. (1996) found greater levels of R-(-)-MDMA in blood, liver, vitreous and bile samples from an individual who died shortly after illicit MDMA use. Stereoselective analysis of biosamples in both an MDMA overdose and a traffic fatality had similar findings (Ramcharan, et al., 1998; Crifasi and Long, 1996).

The stereoselective pharmacokinetics of MDMA are reflected in formation of MDA enantiomers. In the first 24 hours after MDMA administration, greater plasma and urine concentrations of S-(+)-MDA than its R-enantiomer occur (Fallon et al. 1999; Moore et al. 1996). However, R-(-)-MDA becomes the more prevalent enantiomer in urine beginning 24 to 36 hours after MDMA administration (Hensley and Cody 1999). In a suicide attempt involving the ingestion of 90 ecstasy tablets, urine concentrations of S-(+)-MDA remained greater than R-(-)-MDA at 36 hrs, but relative prevalence had reversed at 60 hrs. Other reports have found stereoselective formation of HMMA and HMA although the lack of available standards precluded assignment of absolute enantiomeric identity (de Boer et al. 1997; Lanz et al. 1997).

MDMA kinetics are dose dependent within the range of commonly administered doses (de la Torre et al. 2000b). Thus, when dose is increased, exposure to MDMA (measured as AUC plasma) increases by a greater amount. This phenomenon is illustrated by the changes in the ratio of AUC to dose in Table 2.5. This increased exposure is particularly
dramatic when the AUC and Cmax for the two volunteers receiving 150 mg MDMA are compared to the 8 individuals receiving 125 mg MDMA.

These dose-dependent kinetics appear to be due to dose-dependent metabolism rather than changes in absorption or excretion. Mas et al. (1999) reported that 75 mg and 125 mg doses of MDMA had similar absorption constants and absorption half-lives. On the other hand, non-renal clearance for 125 mg MDMA was approximately half that of 75 mg MDMA.

The dose-dependent metabolism of MDMA is at least partially due to inhibition of some metabolic pathways. Several _in vitro_ studies have shown that MDMA is not just a substrate for CYP2D6 but also binds to it, forming an inhibitory complex (Brady et al. 1986; Delaforge et al. 1999; Wu et al. 1997). Compelling _in vivo_ evidence of enzyme inhibition was provided by de la Torre et al. (2000a) who showed that plasma levels and 24-hour urinary recovery of HMMA are dose-independent. This is likely the result of inhibition of CYP2D6-mediated DHMA formation.
Demographics and Self-Reported Effects of Illicit Ecstasy Use
Lisa Jerome, Ph.D., and Matthew Baggott, B.A.

Introduction and Overview

This chapter discusses surveys that examine the demographics of ecstasy use and the effects of ecstasy as retrospectively described by illicit ecstasy users. Findings from these retrospective studies are compared with findings from clinical studies. Throughout this report, the term “ecstasy” is used instead of “MDMA” whenever the identity of the consumed drug is in question.

Surveys of ecstasy users are useful for documenting patterns of drug use and common effects of ecstasy in uncontrolled settings. Yet they are limited by both the questions researchers ask and the participants, who may not have experienced the full range of rewarding and adverse drug effects. Therefore, the therapeutic potential of MDMA is better documented in reports of its use in psychotherapy, as described in Chapter 2. Similarly, adverse effects of ecstasy are more adequately documented in the case reports and studies described in Chapters 5 and 6.

Ecstasy use is highest among individuals between the ages of 16 and 25, with the drug most strongly associated with dance and “rave” sub-cultures. However, ecstasy use is not limited to one age group or sub-culture. In the United States, prevalence of ecstasy use in the last year was estimated to be 3.1% for eighth graders, and 8.2% for 12 graders in 2000, and estimated to be 5.5% for college students, and 3.6% for young adults (ages 19-28) in 1999.

In surveys of ecstasy users, commonly reported effects of ecstasy are generally consistent with effects seen in clinical MDMA studies, as described in Chapter 2. Commonly reported acute psychological effects of ecstasy include increases in positive mood, energy, feelings of closeness to others, anxiety, and difficulty concentrating as well as alterations in perception in several modalities. Jaw clenching, sweating, dry mouth, nausea, and insomnia are the most commonly reported acute physiological effects of ecstasy. Reported short-term sequelae, defined here as effects occurring from 24 hours to a week after using ecstasy, include reduced energy, depressed mood, irritability, and anxiety. However in some surveys, users of illicit ecstasy reported ecstasy-induced hallucinations and increases in sexual arousal, two effects either not reported or contradicted by descriptions appearing in other reports. Differences between clinical studies and retrospective surveys are probably due to a variety of factors, including differences in measurement techniques, differences in respondents’ understanding of terms used in measures, and the varying identity, potency, and purity of illicit ecstasy. Comparisons of the effects of ecstasy, amphetamines, and psychedelics/hallucinogens by experienced users support the hypothesis that MDMA has novel psychopharmacological effects.
Few of the reports reviewed in this chapter assessed possible long-term effects of ecstasy use and only a minority of volunteers in these reports described long-term benefits or difficulties. Most users of illicit ecstasy report decreased drug effects (short-term tolerance) when one dose of ecstasy is rapidly followed by another. However, lasting decrease of drug effects (long-term tolerance) has not been confirmed by all studies asking respondents about this phenomenon.

Two reports of co-administration of ecstasy with selective serotonin uptake inhibitors have somewhat conflicting findings, although both suggest that serotonin uptake inhibitors reduce many of the acute effects of ecstasy.

### Table 3.1: Estimated Prevalence of Ecstasy Use in the United States

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% Using at Least Once</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8th Grade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.4</td>
<td>3.2</td>
<td>2.7</td>
<td>2.7</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>10th Grade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.6</td>
<td>5.7</td>
<td>5.1</td>
<td>6.0</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>12th Grade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.1</td>
<td>6.9</td>
<td>5.8</td>
<td>8.0</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>College Students</td>
<td>2.0</td>
<td>2.9</td>
<td>2.3</td>
<td>2.1</td>
<td>3.1</td>
<td>4.3</td>
<td>4.7</td>
<td>6.8</td>
<td>8.4</td>
<td>-</td>
</tr>
<tr>
<td>Young Adults (19-28 yo)</td>
<td>3.2</td>
<td>3.9</td>
<td>3.8</td>
<td>3.8</td>
<td>4.5</td>
<td>5.2</td>
<td>5.1</td>
<td>7.2</td>
<td>7.1</td>
<td>-</td>
</tr>
<tr>
<td><strong>% Using in Last Year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8th Grade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.3</td>
<td>2.3</td>
<td>1.8</td>
<td>1.7</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>10th Grade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.6</td>
<td>3.9</td>
<td>3.3</td>
<td>4.4</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>12th Grade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.6</td>
<td>4.6</td>
<td>3.6</td>
<td>5.6</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>College Students</td>
<td>0.9</td>
<td>2</td>
<td>0.8</td>
<td>0.5</td>
<td>2.4</td>
<td>2.8</td>
<td>2.4</td>
<td>3.9</td>
<td>5.5</td>
<td>-</td>
</tr>
<tr>
<td>Young Adults (19-28 yo)</td>
<td>0.8</td>
<td>1</td>
<td>0.8</td>
<td>0.7</td>
<td>1.6</td>
<td>1.7</td>
<td>2.1</td>
<td>2.9</td>
<td>3.6</td>
<td>-</td>
</tr>
<tr>
<td><strong>% Using in Last 30-Days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8th Grade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.0</td>
<td>1.0</td>
<td>0.9</td>
<td>0.8</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>10th Grade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.8</td>
<td>1.3</td>
<td>1.3</td>
<td>1.8</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>12th Grade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.0</td>
<td>1.6</td>
<td>1.5</td>
<td>2.5</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>College Students</td>
<td>0.2</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
<td>0.8</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>Young Adults (19-28 yo)</td>
<td>0.1</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td>0.4</td>
<td>0.3</td>
<td>0.6</td>
<td>0.8</td>
<td>1.3</td>
<td>-</td>
</tr>
</tbody>
</table>

Data taken from the 2000 Monitoring the Future survey (Johnston et al. 2000a; Johnston, 2001)

### Demographics of Ecstasy Use: History and Current Trends

Non-medical use of MDMA apparently began in the early 1970s, sometimes under the name “MDM”. Seizures of MDMA were reported in Chicago in 1970 (Sreenivasan 1972) and 1972 (Gaston and Rasmussen 1972). However, MDMA use is only sporadically documented until about the mid-1970s. Around 1976, MDMA began to be used as an adjunct in psychotherapy and commercial manufacture of MDMA commenced in the Boston area. In 1983, a group based in Texas began to manufacture and distribute MDMA, aggressively promoting the drug and selling it openly at bars. Use of MDMA continued to spread in the United States until concerns about its widespread use and the neurotoxicity of a related drug led to its placement into Schedule I of the Controlled Substances Act.
Substances Act in 1985. In Europe, use of MDMA was closely associated with the “Acid House” dance sub-culture originating on the Spanish island of Ibiza circa 1985. Acid House evolved into the “rave” scene, which spread to the United States in the early 1990s.

Initially, ecstasy use was restricted to a few distinct sub-cultures. Early ecstasy-using groups described in the scientific literature include college students, young professionals engaged in the club or party circuit, aficionados of the Grateful Dead musical group, gay men, and the spiritually-minded people sometimes referred to as “New Age seekers” (Beck 1994; Lewis and Ross 1995; Peroutka et al. 1987; Solowij et al. 1992; Watson and Beck 1991). Later reports describe ecstasy use in “rave” sub-cultures (Boys 1997; Forsyth 1996; van de Wijngaart et al. 1999), high school students (Forsyth et al. 1997; Pedersen and Skrondal 1999; Schuster et al. 1998; Wright and Pearl 1990; 1995; 2000), college students (Conner et al. 1998; Meilman et al. 1990; Schuster et al. 1998; Webb et al. 1998; Webb et al. 1996), gay men (Klitzman et al. 2000), drug users (Robson and Bruce 1997; Schifano et al. 1998; Williamson et al. 1997), and central European prostitutes (Kurova 1998).

The most extensive data on ecstasy use in the United States are collected by the Monitoring the Future (MTF) survey, conducted by researchers at the University of Michigan (Johnston et al. 2000a; b). This annual survey of representative high school students and young adults has included questions on ecstasy use since 1991 for young adults and 1996 for high schools. Reported prevalence of ecstasy use in each annual MTF survey is summarized in Table 3.1. Demographic information on ecstasy users from the 1999 MTF survey is summarized in Table 3.2.

Several reports have focused on adolescents’ use of ecstasy. According to the 1999 Monitoring the Future survey of youth and young adults in the United States, 4.3% of 8th graders, 7.3% of 10th graders and 11% of 12th graders surveyed reported having used ecstasy at least once. While most U.S. high school students report using ecstasy only once or twice, some are regular users. Extent of ecstasy use by U.S. high school students is summarized in Table 3.3. The percentage of high school students who had reportedly tried ecstasy was lower (approximately 3%) in a sample of 10,812 Norwegian high school students (Pedersen and Skrondal 1999). In one survey, approximately 13% of 274 British high school students indicated that they knew someone who had used ecstasy (Pedersen and Skrondal 1999; Wright and Pearl 1995; 2000). In contrast, the 1999 MTF survey found that an estimated 26.7% of high school seniors in the United States reported having friends who took ecstasy and 2.7% reported that most or all of their friends took ecstasy.

Reported ecstasy use by university students varies from over a third of a sample of 369 undergraduates (Peroutka 1987) to 12% of a sample of 400 undergraduates attending a small private university in the U.S. (Meilman et al. 1990). As can be seen in Table 3.1, 8.4% of U.S. college students are estimated to have used ecstasy at least once. The ages of volunteers participating in the studies described in this document range from the early
teens to the mid-40s. However, a majority of participants are between the ages of 18 and 25, reflecting the demographics of ecstasy use.

**Table 3.2: Demographics of Ecstasy Users (Age 19-32) in the United States**

<table>
<thead>
<tr>
<th></th>
<th>Percent of Population Using:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Least Once</td>
<td>In Last Year</td>
</tr>
<tr>
<td>Total</td>
<td>6.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Female</td>
<td>5.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Modal Age:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-20</td>
<td>7.9</td>
<td>4.9</td>
</tr>
<tr>
<td>21-22</td>
<td>7.8</td>
<td>4.6</td>
</tr>
<tr>
<td>23-24</td>
<td>7.6</td>
<td>3.3</td>
</tr>
<tr>
<td>25-26</td>
<td>6.4</td>
<td>3.4</td>
</tr>
<tr>
<td>27-28</td>
<td>5.5</td>
<td>1.8</td>
</tr>
<tr>
<td>29-30</td>
<td>6.6</td>
<td>0.7</td>
</tr>
<tr>
<td>31-32</td>
<td>5.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Region:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>8.3</td>
<td>4.5</td>
</tr>
<tr>
<td>North Central</td>
<td>2.6</td>
<td>1.1</td>
</tr>
<tr>
<td>South</td>
<td>7.0</td>
<td>2.5</td>
</tr>
<tr>
<td>West</td>
<td>9.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Population Density:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farm/Country</td>
<td>4.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Small Town</td>
<td>5.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Medium City</td>
<td>6.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Large City</td>
<td>7.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Very Large City</td>
<td>10.5</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Data taken from the 1999 Monitoring the Future survey (Johnston et al. 2000b)
Most surveys of alcohol and drug use have found that males are more likely than females to use alcohol and other substances (Forsyth 1996; Forsyth et al. 1997; Pedersen and Skrondal 1999; Schuster et al. 1998; Williamson et al. 1997). The gender disparity in ecstasy use is less apparent than it is for most other substances (Boys et al. 1999; Boys 1997; Robson and Bruce 1997; Topp et al. 1999), though a survey of Norwegian high school students found the gender disparity to be greatest for ecstasy use (Pedersen and Skrondal 1999). A randomly selected sample of 3021 residents of the Munich area, ages 14 – 25, suggests that the prevalence of ecstasy use there increases with age for men, but not for women (Schuster et al. 1998). In studies in which ethnicity is reported, most illicit ecstasy users are found to be white or of European descent (Solowij et al. 1992; Topp et al. 1999; Webb et al. 1998; Williamson et al. 1997). Several researchers found that ecstasy users had attained slightly more formal education than users of other drugs (Boys 1997; Hammersley et al. 1999; Topp et al. 1999). The 1999 Monitoring the Future survey found that prevalence of ecstasy use in the last year among U.S. college students is now somewhat higher than among non-college-student peers (5.5% versus 3.9%).

Table 3.3: Estimated Frequency of Ecstasy Use by U.S. High School Students

<table>
<thead>
<tr>
<th>% Reporting Use At Least Once</th>
<th>8th</th>
<th>10th</th>
<th>12th</th>
</tr>
</thead>
<tbody>
<tr>
<td>No occasions</td>
<td>97.3</td>
<td>94.0</td>
<td>92.0</td>
</tr>
<tr>
<td>1-2 occasions</td>
<td>1.6</td>
<td>3.2</td>
<td>4.6</td>
</tr>
<tr>
<td>3-5 occasions</td>
<td>0.3</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>6-9 occasions</td>
<td>0.3</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>10-19 occasions</td>
<td>0.2</td>
<td>0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>20-39 occasions</td>
<td>0.1</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>40 or more</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

| % Reporting Use in Last Year |
|------------------------------|-----|------|------|
| No occasions                 | 98.3| 95.6 | 94.4 |
| 1-2 occasions                | 0.8 | 2.6  | 3.3  |
| 3-5 occasions                | 0.3 | 0.8  | 0.9  |
| 6-9 occasions                | 0.3 | 0.5  | 0.4  |
| 10-19 occasions              | 0.1 | 0.3  | 0.5  |
| 20-39 occasions              | 0.1 | 0.1  | 0.2  |
| 40 or more                   | 0.1 | 0.2  | 0.2  |

<table>
<thead>
<tr>
<th>% Reporting Use in Last 30-Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>No occasions</td>
</tr>
<tr>
<td>1-2 occasions</td>
</tr>
<tr>
<td>3-5 occasions</td>
</tr>
<tr>
<td>6-9 occasions</td>
</tr>
<tr>
<td>10-19 occasions</td>
</tr>
<tr>
<td>20-39 occasions</td>
</tr>
<tr>
<td>40 or more</td>
</tr>
</tbody>
</table>

Data taken from the 1999 Monitoring the Future survey (Johnston et al. 2000a)

While the reported frequency of ecstasy use varies, the most commonly reported rate of use is that of several times a month (Cohen 1995; Curran and Travill 1997; Davison and Parrott 1997; Forsyth 1996; Hammersley et al. 1999; Liester et al. 1992; Parrott and Lasky 1998; Peroutka et al. 1988; Schifano et al. 1998; Schuster et al. 1998; Siegel 1986; Solowij et al. 1992; Topp et al. 1999; Williamson et al. 1997). The typical interval between use reported by participants in some studies extended from once every few months to once a month (Hammersley et al. 1999; Liester et al. 1992; Solowij et al. 1992). However, respondents in other surveys reported using ecstasy from once a week to once every two weeks (Boys et al. 1999; Schifano et al. 1998; Williamson et al. 1997). It appears that longer intervals between use were more prevalent during the late 1980s and early 1990s, with intervals decreasing in length during the mid-1990s.

Most users of illicit ecstasy reported using approximately one tablet per occasion (Schifano et al. 1998; Solowij et al. 1992; Topp et al. 1999). Two early studies requesting estimated amount of MDMA contained per dose reported that the typical estimated amount of ecstasy used on each occasion ranged from 50 mg to 390 mg (Liester et al. 1992; Siegel 1986). The average dose was estimated to be between 100 mg and 150 mg (Liester et al. 1992; Siegel 1986). Some people used lower doses on occasion, while others used extremely high doses. When samples were formally assessed for contents in one study, it was found that the actual doses were usually smaller than estimated by volunteers (Siegel 1986). Many participants have combined ecstasy with other drugs on at least one occasion (Forsyth 1996; Parrott and Lasky 1998; Solowij et al. 1992; Topp et al. 1999). Cannabis, amphetamines, LSD and nitrates are the substances that were most commonly combined with ecstasy. At least two studies found that a large minority of respondents combined ecstasy with alcohol (Solowij et al. 1992; Topp et al. 1999), but other depressants were rarely, if ever, used along with ecstasy (Forsyth 1996; Topp et al. 1999). Cannabis is frequently smoked before and after using ecstasy at dance events (Forsyth 1996).

**An Overview of Retrospective or Uncontrolled Studies Addressing Drug Effects**

Researchers have sought to examine the acute and sub-acute effects of ecstasy through by conducting interviews or surveys with non-medical ecstasy users. Some reports were gathered from individuals who used MDMA non-medically before it was made a controlled substance (Buffum and Moser 1986; Siegel 1986; Watson and Beck 1991), but the majority rely on information gathered from presumably illicit ecstasy users (Cohen 1995; Curran and Travill 1997; Davison and Parrott 1997; Liester et al. 1992; Parrott and
Lasky 1998; Parrott and Stuart 1997; Peroutka 1989; Schifano et al. 1998; Solowij et al. 1992). A few researchers have gathered information from a specific group of individuals, such as psychiatrists (Liester et al. 1992), university students (Peroutka et al. 1988), in-treatment drug users (Parrott and Stuart 1997; Schifano et al. 1998), and rave attendees (van de Wijngaart et al. 1999). Individuals participating in these studies were either drawn from a randomly selected sample (Cohen 1995; Peroutka et al. 1988) or selected through “snowball sampling” (Curran and Travill 1997; Davison and Parrott 1997; Liester et al. 1992; Parrott and Lasky 1998; Parrott and Stuart 1997; Solowij et al. 1992). In one study, participants were drawn from consecutive admissions to a drug treatment clinic (Schifano et al. 1998).

There are some important limitations to retrospective and non-experimental investigations of the effects of ecstasy. These include self-selected samples of participants, uncontrolled settings of drug use, and the unknown identity, purity, and potency of illicit ecstasy. A sample of illicit ecstasy users is liable to be self-selected, raising the issue of whether people who choose to take ecstasy differ in their experience of the drug than people in general. Some authors have tried addressing this issue by comparing people who have only used the drug a few times with those who have used it more often (Peroutka et al. 1988; Solowij et al. 1992). While ecstasy is frequently taken at dance events, the settings where it is taken vary, possibly influencing the nature of the drug experience. Lastly, the identity, potency, and purity of illicit ecstasy tablets used by participants cannot be assessed in most retrospective studies. Some researchers attempt to gauge the identity of the material by requesting samples of the material (Siegel 1986) or conducting urine samples on selected participants (van de Wijngaart et al. 1999), but this can only confirm the identity of recently consumed ecstasy. In most cases, the identity of illicit ecstasy remains unknown. Hence the reported effects of ecstasy may be affected by variance in the identity, potency, and purity of illicit ecstasy.

Researchers investigating the reported effects of ecstasy in illicit or non-medical users have had different goals. Some researchers wished to measure the acute and sub-acute effects of ecstasy (Curran and Travill 1997; Davison and Parrott 1997; Liester et al. 1992; Parrott and Lasky 1998; Peroutka et al. 1988) while others sought to compare ecstasy with other drugs, such as amphetamine and LSD (Parrott and Stuart 1997; Siegel 1986; Solowij et al. 1992). Some researchers were seeking information about a specific drug effect (Buffum and Moser 1986; Watson and Beck 1991) or specific outcomes, such as adverse events that occurred subsequent to ecstasy use (Schifano et al. 1998; Topp et al. 1999). Since different researchers possessed different goals and sometimes interviewed or surveyed different populations, the measures used and the comparisons performed in each study are not identical.

Because of these considerations, the authors were unsuccessful in attempts to create a single table summarizing the effects attributed to ecstasy in all studies. However, Table 3.4 provides a summary of reported effects of ecstasy in one representative survey.
Acute Psychological Effects Reported in Retrospective Studies

Commonly reported acute subjective effects include euphoria, happiness, increased energy, increased peacefulness, feeling close to others, empathy, increased sociability, increased anxiety, confusion, difficulty concentrating, increased insight, changed perceptions of color, and visual hallucinations. Less commonly reported acute psychological effects of ecstasy are sensual feelings, agitation, depressed mood, and changed perception of time, being distant from others, and altered tactile perceptions. Feelings of euphoria and increased energy were the most commonly mentioned across studies, with each receiving mention in 6 out of 12 studies (Euphoria: Cohen 1995; Schifano et al. 1998; Siegel 1986; Solowij et al. 1992; van de Wijngaart et al. 1999; Watson and Beck 1991). Energy: Cohen 1995; Curran and Travill 1997; Davison and Parrott 1997; Parrott and Stuart 1997; Solowij et al. 1992; van de Wijngaart et al. 1999).

**Table 3.4: Effects of Ecstasy Reported by 100 Undergraduates**

<table>
<thead>
<tr>
<th>Acute Effects: Psychological</th>
<th>n / 100 Reporting Effect</th>
<th>Acute Effects: Physiological</th>
<th>n/100 Reporting Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sense of “closeness” with other people</td>
<td>90</td>
<td>Trismus</td>
<td>75</td>
</tr>
<tr>
<td>Increased alertness</td>
<td>50</td>
<td>Tachycardia</td>
<td>72</td>
</tr>
<tr>
<td>Luminescence of objects</td>
<td>42</td>
<td>Bruxism</td>
<td>65</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>38</td>
<td>Dry mouth</td>
<td>61</td>
</tr>
<tr>
<td>Parasthesias</td>
<td>35</td>
<td>Tremor</td>
<td>42</td>
</tr>
<tr>
<td>Hot or cold flashes</td>
<td>33</td>
<td>Palpitations</td>
<td>41</td>
</tr>
<tr>
<td>Increased sensitivity to cold</td>
<td>27</td>
<td>Diaphoresis (sweating)</td>
<td>38</td>
</tr>
<tr>
<td>Dizziness / Vertigo</td>
<td>24</td>
<td>Insomnia</td>
<td>31</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sub-Acute Effects: Psychological</th>
<th>n / 100 Reporting Effect</th>
<th>Sub-Acute Effects: Physiological</th>
<th>n/ 100 reporting Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>36</td>
<td>Muscle aches or fatigability</td>
<td>32</td>
</tr>
<tr>
<td>Sense of “closeness” with others</td>
<td>22</td>
<td>Tight jaw muscles</td>
<td>21</td>
</tr>
<tr>
<td>Depression</td>
<td>21</td>
<td>Headache</td>
<td>17</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>21</td>
<td>Dry mouth</td>
<td>14</td>
</tr>
<tr>
<td>Anxiety, worry or fear</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table adapted from Peroutka et al., 1988 and based on responses from 100 volunteers, ages 18-25, who had used ecstasy 1-38 times. Drug effects were selected by respondents from a list prepared by the researchers.
Anxiety was mentioned across 5 of 11 studies. Feeling social, feeling close to others, confusion, and visual hallucinations were mentioned in 4 of 12 studies. Feelings of dissociation, possibly similar to experiences produced by hallucinogens, were reported in two studies (Siegel 1986; van de Wijngaart et al. 1999). Users were more likely to report feelings of dissociation after very high doses of ecstasy (an estimated 500 mg and higher) (Siegel 1986).

Despite the potential for gathering inaccurate information in retrospective studies, the majority of the psychological effects reported by illicit ecstasy users are similar to those reported by participants in clinical MDMA studies (Cami et al. 2000; Grob et al. 1996; Vollenweider et al. 1998a). Increases in positive mood, energy, difficulty concentrating, and alterations in perception have been documented in both types of study. This suggests that while the identity of illicit ecstasy tablets is often uncertain, the effects of illicit ecstasy are fairly similar to those reported for MDMA.

To this date, controlled clinical studies have not formally measured increases in empathy or feelings of closeness to others associated with MDMA/ecstasy, although spontaneous remarks by volunteers about increased empathy or sociability have been noted (Cami et al. 2000; Grob et al. 1996; Vollenweider et al. 1998a; 1999a). Retrospective studies of illicit ecstasy users appear to offer stronger support for MDMA-induced increases in empathy, sociability, or feelings of closeness to others. Some researchers conducting retrospective surveys specifically requested information about empathy or closeness to others (Peroutka et al. 1988; Siegel 1986). Others asked volunteers to describe the effects of ecstasy within a structured interview (Liester et al. 1992). At least four studies found support for increased feelings of closeness to others, sociability, or empathy. Participants in at least one study reported feeling more friendly (Davison and Parrott 1997; Parrott and Stuart 1997), less aggressive (Liester et al. 1992), and less defensive (Liester et al. 1992) acutely after taking ecstasy. Illicit ecstasy users sampled from different populations reported increased empathy, friendliness, or sociability as acute effects of ecstasy, including psychiatrists (Liester et al. 1992), undergraduates (Peroutka et al. 1988) and people seeking treatment for substance abuse (Schifano et al. 1998). The reported increases in closeness to others, sociability and empathy appear to be unique to MDMA and a few structurally related analogues (Gouzoulis-Mayfrank et al. 1998; Nichols 1986) and support the proposed classification of MDMA as a member of a novel pharmacological class, called “entactogens” (Nichols 1986). Perhaps because of their training and focus on observing and analyzing thought and emotion, the psychiatrists surveyed seemed to be especially attentive to acute ecstasy-induced increases in insight and decreases in fear and defensiveness. Assuming that a majority of illicit ecstasy sold contains MDMA, it appears that the reputed entactogenic effects of MDMA occur across a variety of settings.

A surprisingly high number of individuals surveyed in these studies reported experiencing hallucinations, particularly visual hallucinations (Peroutka et al. 1988; Schifano et al. 1998; Siegel 1986; Solowij et al. 1992). The percentage of respondents reporting ecstasy-induced hallucinations varies from “rare” in the work of Solowij and Hall (1992) to 43% in the survey conducted by Siegel (1986). Participants in one survey
described most of these hallucinations as simple flashes of light or the appearance of an object in periphery vision that vanishes upon inspection (Peroutka et al. 1988). Sometimes volunteers reported seeing simple geometric forms, especially with closed eyes (Solowij et al. 1992). While these experiences were similar to those reported in clinical studies (Downing 1986; Vollenweider et al. 1998a), experiencing more complex forms, as reported among the ecstasy users in Siegel’s sample (1986) did not occur in any of the clinical studies. The high prevalence of visual hallucinations in retrospective surveys may be due to users purchasing other drugs sold as ecstasy. Differences in dose may also influence the frequency of hallucinations. Estimated doses taken by illicit ecstasy users are often higher than those employed in clinical MDMA studies (Liester et al. 1992; Siegel 1986). In addition, some surveys or interviews may not have presented participants with a clear definition of a hallucination. In these cases, respondents may have classified visual illusions or alterations in perception as hallucinations.

An investigation of sexual behavior after MDMA in men and women found that ecstasy reportedly increased receptivity to sexual behavior but decreased the occurrence of sexual behavior (Buffum and Moser 1986). Men’s sexual responses were reportedly particularly dampened by ecstasy. In contrast, a survey of 500 ecstasy users conducted five years later found that 83% of the respondents reported sexual arousal as an acute effect of ecstasy (Cohen 1995). Despite the larger number of respondents in the survey conducted by Cohen, the items contained in the survey designed by Buffum and Moser address specific sexual feelings and behaviors. Thus, it seems likely that the earlier study (Buffum and Moser 1986) is a more accurate reflection of the acute effects of ecstasy on sexual behavior. Acute decreases in libido have also been reported in uncontrolled and controlled clinical studies of MDMA (Greer and Tolbert 1986; Vollenweider et al. 1998a).

**Acute Physiological Effects of Ecstasy Reported in Retrospective Studies**

Retrospective surveys can only provide indirect documentation of the physiological effects of ecstasy and must rely on the possibly faulty perceptions and memories of volunteers. Furthermore, without objectively measuring certain parameters, such as heart rate and body temperature, it is impossible to ascertain the degree to which they are acutely altered by ecstasy. Despite these limitations, the reported physiological and somatic effects of ecstasy are similar to those documented in controlled clinical studies. These effects have been assessed in seven studies of ecstasy users (Cohen 1995; Curran and Travill 1997; Davison and Parrott 1997; Liester et al. 1992; Peroutka et al. 1988; Siegel 1986; Solowij et al. 1992) and one study of in-patient ecstasy-using substance abusers (Schifano et al. 1998). Jaw clenching, sweating, nausea, dry mouth, and insomnia are the most frequently reported physiological effects of illicit ecstasy. Other physiological effects reported in more than one study are increased heart rate, increased body temperature, dilated pupils, loss of appetite, tremor, headaches, and blurred vision. Most of the reported side effects of ecstasy are similar to those produced by psychostimulants, and nearly all are reported to be mild or moderate in nature.
The physiological effects of ecstasy most commonly reported in these studies also match those documented by medical personnel treating adverse events subsequent to ecstasy use. For example, tachycardia, dilated pupils, and hypertension were the most frequently cited physiological complaints, while agitation, excitement, and hallucinations were the most commonly reported psychological complaints in a series of consecutive cases contacting the National Poisons Information Center in Ireland (Cregg and Tracey 1993). A more complete review of medical reports of the adverse effects of ecstasy is presented in a separate document.

In summary, clinical MDMA studies offer a more accurate picture of the acute effects of MDMA in humans than retrospective studies. However, surveys of illicit users appear to be very consistent with the findings reported in clinical studies and reports of complaints brought to medical personnel. This suggests that the effects of MDMA in uncontrolled settings and in larger doses than those used in clinical studies are not dramatically different from the effects documented in clinical studies. While clinical MDMA studies have not yet formally measured ecstasy-induced increases in feelings of empathy, sociability, and closeness to others, surveys of illicit ecstasy users provide evidence for these effects.

**Sub-Acute and Long-term Effects of Ecstasy Reported in Retrospective Studies**

Surveys of ecstasy users have often included measures of effects that arise after the acute effects of ecstasy have subsided. Most studies focus on the effects appearing from up to a day after taking ecstasy to a week after use (Curran and Travill 1997; Davison and Parrott 1997; Liester et al. 1992; Parrott and Lasky 1998; Solowij et al. 1992; van de Wijngaart et al. 1999). Other researchers have focused specifically on long-term effects, defined as effects occurring from two weeks to years after ecstasy use (Schifano et al. 1998; Watson and Beck 1991). Information on sub-acute and long-term effects appears to be combined in some papers (Cohen 1995), and information on both types of effects has been reported separately by other researchers (Liester et al. 1992; Peroutka et al. 1988; Solowij et al. 1992).

Studies have varied in the methods and the time frame used for measuring drug effects occurring after the acute effects have subsided. Some researchers differentiate between effects occurring up to 24 hours after taking ecstasy and effects occurring a few days to a week later (Curran and Travill 1997; Parrott and Lasky 1998; Peroutka 1987). Some measures appear to be ambiguous in reference to time frame, but are likely to be interpreted as referring to effects appearing immediately after the acute effects have subsided (Davison and Parrott 1997). Effects occurring up to a week after use will be treated as sub-acute effects.

**Sub-acute Sequelae Reported After Ecstasy Use**

When short-term sequelae are defined as any effects that appear up to a week after the acute effects of ecstasy have subsided, the most commonly reported short-term sequelae in surveys of ecstasy users are depressed mood, insomnia, irritability, anxiety, being less
alert, and tight jaw. Fatigue, drowsiness, having a decreased appetite, continued feelings of closeness to others, and muscle aches were also reported in at least two of twelve studies. Short-term effects reported in only one study were headache, continued difficulty concentrating, continued decrease in anxiety, and a continued reduction in defensiveness. Psychiatrists who had taken MDMA / ecstasy seemed to experience the greatest number of positive short-term effects (Liester et al. 1992). They reported that the increased sociability and reduction in anxiety initiated by the drug continued after the acute effects had subsided. Several researchers wrote that residual effects disappeared from one to three days after ecstasy use (Peroutka et al. 1988; Siegel 1986; Solowij et al. 1992).

The sub-acute drug effects documented in clinical MDMA studies (Liechti et al. 2000a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; Vollenweider et al. 1998a) compare well with the short-term effects of ecstasy recalled by illicit ecstasy users. In clinical studies, decreased energy, decreased clear-headedness, moderately increased negative mood, and physiological effects such as decreased appetite, are reported after MDMA exposure. Some physical complaints appear to be more common in illicit ecstasy users than in volunteers in clinical MDMA studies. Illicit ecstasy users have reported muscle aches (Peroutka et al. 1988; van de Wijngaart et al. 1999) and back pain (Cohen 1995) shortly after using ecstasy, while these effects were not as commonly reported in clinical studies of the effects of MDMA. The muscle aches and back pain reported by illicit ecstasy users are probably at least partially due to physical activity, such as dancing, performed during the acute effects of ecstasy, and are probably not solely due to the effects of MDMA.

Long-term Sequelae Reported After Ecstasy Use

Some researchers define a long-term effect as any effect that either appears or persists a week after using ecstasy, while others define it as any effect that appears and persists many months after ecstasy use. Hence it is not clear whether all of the long-term effects reported in retrospective studies have occurred at the same point in time. Comparing across studies, the most commonly reported long-term effects of using ecstasy were increases in anxiety and dysphoric mood, increased sensitivity to emotion, changes in spiritual practices or increased spirituality and changes in life values, all reported in two out of 12 studies. While increased impulsivity is listed as a long-term effect in two different studies (Liester et al. 1992; Schifano et al. 1998), the percentage in one study (Liester et al. 1992) is very small (5%, or one individual). Long-term sequelae reported in only one study include a persistent increase in social function and reduction in defenses in the sample of psychiatrists (Liester et al. 1992), jaw clenching when anxious in one individual in a sample of undergraduates (Peroutka et al. 1988), flashbacks, frequent headaches and stomach aches in a sample of 500 ecstasy users (Cohen 1995) and psychotic symptoms in 28% of a sample of drug users consecutively admitted to a drug treatment program (Schifano et al. 1998).

Schifano and colleagues sought to discover the number of psychiatric conditions that occurred after ecstasy use (Schifano et al. 1998). After interviewing 150 ecstasy-using
patients admitted to a drug treatment program, Schifano and colleagues found that 12% of individuals had anxiety disorders, 32% had mood disorders and 28% had psychotic disorders, with time between last use and diagnosis varying across the sample. However, due to the retrospective nature of the study and to non-random sampling, it is not possible to conclude that these diagnoses have any relation to ecstasy use. Individuals in this study are not necessarily representative of ecstasy users in general. Instead, they represent a segment of the drug-using population that desires medical or psychiatric help in relation to their drug use. A second study (Curran and Travill 1997), using a different design, also reported an increase in anxiety and depressed mood after ecstasy use. Five days after taking ecstasy at a club, participants had higher anxiety and depression scores than they had when assessed at the club or one day after taking ecstasy. These same ecstasy users had higher anxiety or depression scores at five days after the first assessment than people who had used alcohol at the first assessment. None of the participants in this study were diagnosed with an affective disorder, although their scores on the Beck Depression Inventory scores were comparable to those occurring in mild to moderate clinical depression. It should also be noted that other researchers categorize effects occurring five days after ecstasy use as short-term effects, (Liester et al. 1992; Peroutka et al. 1988).

Because of a hypothesized association with serotonergic function, mood is often measured in studies comparing illicit ecstasy users with people who have not used ecstasy (Gamma et al. 2000b; Gerra et al. 2000; Morgan 1998; Parrott and Lasky 1998). An increase in depressed mood or dysthymia after ecstasy use has been reported in some studies that compare ecstasy users with individuals who have not used ecstasy (Gamma et al. 2000b; Gerra et al. 1998). However, other studies have not found an association between depressed mood or depression and ecstasy use (Morgan 1998; Parrott and Lasky 1998). Likewise, studies that have sought to detect decreases in cognitive or emotional function in ecstasy users have also failed to find an association between depressed mood and ecstasy use (Dafters et al. 1999; Krystal et al. 1992). It appears that retrospective studies are more consistent in reporting depressed mood after ecstasy use than are studies that compare illicit ecstasy users with non-users. Decreases in positive mood or increases in depressed mood may be time-limited effects of ecstasy use, a hypothesis supported by the findings of Parrott and Lasky (1998). Ecstasy users in this study felt more depressed two days after having used ecstasy than did people who had not used ecstasy, but both groups reported relatively similar moods seven days after ecstasy administration and at baseline. Depressed mood appears to be a commonly reported sub-acute effect of ecstasy use, but only one retrospective study has found a relationship between ecstasy use and affective disorders diagnosed after ecstasy use (Schifano et al. 1998). Researchers wishing to draw stronger conclusions about the presence of persistent depressed mood after ecstasy use may need to employ more specific measures of depression and larger samples or prospective study designs.

In contrast to studies focusing on possible long-term adverse effects of ecstasy, Watson and Beck sought to study the link between spirituality, religious behavior and ecstasy / MDMA use by conducting qualitative interviews with 100 ecstasy users (Watson and Beck 1991). Although they found that some individuals used ecstasy in their spiritual
practices, the authors do not provide figures indicating the percentage of their sample engaged in spiritual practices involving ecstasy/MDMA. Because their study is retrospective, the link between ecstasy use and increased or changed spiritual beliefs or activity can only be considered an association. As is the case with the study of Schifano and colleagues, it is unclear as to whether ecstasy use is directly related to long-term changes in spiritual activities or whether this is an artifact of self-selected sampling. However, a retrospective study of 20 psychiatrists who had used ecstasy indicated that 46% changed their religious or spiritual practices for over a week after taking ecstasy (Liester et al, 1992).

Comparisons between these studies and clinical MDMA trials are difficult to make. To date, only one uncontrolled clinical study has described long-term psychological effects of MDMA. In this study, long-term effects were defined as those occurring two weeks to two years after MDMA administration, which took place in the context of psychotherapy (Greer and Tolbert 1986). There are some similarities between the findings in this study and the findings of retrospective studies. A little over half of the participants in the clinical study reported changes in life goals subsequent to MDMA-assisted psychotherapy, and a little under half reported that they had changed their spiritual or physical practices subsequent to MDMA-assisted therapy. Most of these changes were viewed positively. However, one of the participants experienced intensified anxiety subsequent to MDMA-assisted psychotherapy, but he viewed this as a necessary development and did not regret having been part of the study. Since MDMA was administered in the course of psychotherapy, both reported benefits and reported problems occurring after MDMA administration may also relate to the therapeutic session or preexisting issues rather than to the direct effects of MDMA.

In summary, commonly reported short-term sequelae after ecstasy use include depressed mood, insomnia, irritability, anxiety, decreased alertness, and jaw tension. Because of the lack of a clear definition as to what constitutes a long-term effect and because few clinical studies have measured long-term effects after MDMA administration, only tenuous conclusions can be made about long-term effects occurring after taking ecstasy or MDMA. While problems and benefits have been reported to persist for more than a week after taking ecstasy, it is not clear whether the drug was directly involved in producing these effects. However, studies of illicit ecstasy users suggest that at least some individuals may experience changes in interpersonal relations or life goals that they perceive to be positive or beneficial and other individuals may experience increases in anxiety or depression. Further research is needed to address the issue of potential long-term effects occurring after use of ecstasy or MDMA. Researchers should clearly define the onset times and durations that qualify effects as “long-term”. Prospective studies of potential ecstasy or MDMA users are needed as well. Researchers may then be able to identify and assess any long-term benefits or problems seen after ecstasy use.

**Comparisons Between Ecstasy, Hallucinogens and Psychostimulants**

Individuals familiar with the effects of amphetamines, hallucinogens, and ecstasy were asked to compare the effects of each of the three drug classes with the others in two
Table 3.5: Frequently Reported Effects of Ecstasy, Amphetamines, and Hallucinogens

<table>
<thead>
<tr>
<th>‘MAIN’ EFFECTS</th>
<th>Ecstasy</th>
<th>Amphetamines</th>
<th>Hallucinogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talkative</td>
<td>Energetic</td>
<td>Talkative</td>
<td>Strange thoughts*</td>
</tr>
<tr>
<td>Open minded</td>
<td>Alert*</td>
<td>Confident</td>
<td>Open minded</td>
</tr>
<tr>
<td>Closeness to others*</td>
<td>Clear thinking</td>
<td>Attentive</td>
<td>Enlightened</td>
</tr>
<tr>
<td>Happiness *</td>
<td>Confident</td>
<td>Clear thinking</td>
<td>Insightful</td>
</tr>
<tr>
<td>Easy going*</td>
<td>Clear thinking</td>
<td>Increased self esteem</td>
<td>Restless</td>
</tr>
<tr>
<td>Accepting*</td>
<td>Attentive</td>
<td>Accepting</td>
<td>Energetic</td>
</tr>
<tr>
<td>Sensual*</td>
<td>Increased self esteem</td>
<td>Attentive</td>
<td>Accepting</td>
</tr>
<tr>
<td>Euphoria*</td>
<td>Open minded</td>
<td>Easy going</td>
<td>Easy going</td>
</tr>
<tr>
<td>Confident</td>
<td>Easy going</td>
<td>Accepting</td>
<td>Talkative</td>
</tr>
<tr>
<td>Carefree</td>
<td>Accepting</td>
<td>Happiness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>‘SIDE’ EFFECTS</th>
<th>Ecstasy</th>
<th>Amphetamines</th>
<th>Hallucinogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of appetite</td>
<td>Loss of appetite</td>
<td>Visual illusions</td>
<td>Visual hallucinations</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Rapid heartbeat</td>
<td>Insomnia</td>
<td>Loss of appetite</td>
</tr>
<tr>
<td>Rapid heartbeat</td>
<td>Jaw tension</td>
<td>Insomnia</td>
<td>Confusion</td>
</tr>
<tr>
<td>Jaw tension</td>
<td>Grinding teeth</td>
<td>Poor concentration</td>
<td>Auditory hallucinations</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Sedation</td>
<td>Anxiety</td>
<td>Mental instability</td>
</tr>
<tr>
<td>Grinding teeth</td>
<td>Palpitations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot and cold flushes</td>
<td>Irritability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating / sweaty palms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor concentration</td>
<td>Desire to urinate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desire to urinate</td>
<td>Tremors</td>
<td>Rapid heartbeat</td>
<td></td>
</tr>
</tbody>
</table>

Table adapted from Solowij & Hall, 1992 and based on responses from 46 / 100
volunteers experienced with all three drug classes. Drug effects were selected by
respondents from a list prepared by the researchers. Asterisks indicate those main
effects that distinguished each drug category from the rest, significant at P ≤ .001.

surveys of illicit ecstasy users (Parrott and Stuart 1997; Solowij et al. 1992). MDMA
shares structural and pharmacological characteristics with both amphetamines and
hallucinogenic phenethylamines, such as mescaline. Amphetamine produces most of its
effects through acting on the dopaminergic and noradrenergic systems, whereas classical
hallucinogens share an affinity for 5HT2A receptors. Because MDMA possesses both
dopaminergic and noradrenergic effects and has an affinity for the 5HT2A receptor
(Battaglia and De Souza 1989), researchers have sought to compare the effects of ecstasy,
psychostimulants, and hallucinogens (Parrott and Stuart 1997; Solowij et al. 1992). Comparisons from one of these studies are summarized in Table 3.5.

Participants in both drug comparison studies reported that ecstasy shared some similarities with psychostimulants (Parrott and Stuart 1997; Solowij et al. 1992). Like amphetamines, ecstasy was reported to make users talkative, and many of the acute physiological effects, such as loss of appetite and jaw tension, were reported for both ecstasy and amphetamines (Solowij et al. 1992). Both ecstasy and amphetamines reportedly produce increases in energy, confidence, and elation (Parrott and Stuart 1997). While ecstasy apparently produces greater feelings of emotional composure than amphetamine or LSD, the degree of composure associated with ecstasy is closer to that of amphetamine than LSD (Parrott and Stuart 1997). Illicit ecstasy users reported that ecstasy and hallucinogens also produce some similar effects (Parrott and Stuart 1997; Solowij et al. 1992). Both ecstasy and hallucinogens reportedly produce difficulties in concentration and increases in open-mindedness and feelings of acceptance (Solowij et al. 1992). When compared with each other and with amphetamine, both ecstasy and LSD were associated with decreased clear-headedness (Parrott and Stuart 1997).

Unlike psychostimulants or hallucinogens, ecstasy was reported to produce increases in agreeableness (Parrott and Stuart 1997), feelings of closeness to others, happiness, feeling easy going, and sensual feelings (Solowij et al. 1992). Ecstasy alone is highly rated along these dimensions. Thus, ecstasy is rated as being similar to amphetamines and hallucinogens by experienced drug users, but it is also reported to possess some distinguishing features as well.

The adverse effects of ecstasy have been compared with those of amphetamine and cocaine powder. Experienced drug users familiar with all three drugs rated ecstasy as producing effects that were more severe than those associated with cocaine but less severe than those associated with amphetamine (Williamson et al. 1997). Volunteers in this study and that of Solowij and Hall (1992) rated the adverse effects associated with ecstasy as mild to moderate in severity.

Decline in Drug Effects After Repeated Use or “Loss of Magic”

Four studies addressed the issue of changes in the effects of ecstasy arising after repeated use (Davison and Parrott 1997; Liester et al. 1992; Peroutka et al. 1988; Solowij et al. 1992). In some cases, items referring to changes in effects after repeated use were only posed to individuals who had used ecstasy more than three (Solowij et al. 1992) or five times (Peroutka et al. 1988). Participants indicated whether the effects of ecstasy grew more intense or less intense over time. All studies that requested information about tolerance reported that participants had found that taking another dose immediately after the first dose produced fewer positive effects and greater negative effects (Davison and Parrott 1997; Peroutka et al. 1988; Solowij et al. 1992).

These studies also investigated the possibility of a general decline in the effects of ecstasy with each successive use, sometimes referred to as “loss of magic.” Scientific evidence
for a decrease in the intensity of effects with repeated use of ecstasy is currently inconclusive and may depend upon at least two factors. Volunteers in two of the four studies listed above reported that the effects of ecstasy decreased with repeated use (Peroutka et al. 1988; Solowij et al. 1992). Volunteers in one of the four studies reported no decline in the intensity of drug effects over time (Liester et al. 1992). People participating in another one of the four studies reported that any decline in the effects of ecstasy experienced over repeated use was related more to growing familiarity with the effects of the drug than to an actual decline in effects (Davison and Parrott 1997). Participants reporting a decline in drug effects with repeated use attributed this decline to the effects of the drug itself, to the quality of ecstasy, and to familiarity with the effects (Peroutka et al. 1988; Solowij et al. 1992). Participants in the study that did not find a decline in drug effects after repeated use also had the longest reported average interval between each use (Liester et al. 1992), with the minimum interval between instances of use being “several weeks.” The reduction in the effects of ecstasy over successive uses may be due in part to frequency of use, with a decline in drug effects associated with more frequent use. It is also possible that expectations about drug effects play a role in the reported decline in drug effects, with novelty-seeking users growing disappointed with ecstasy once they become familiar with the drug’s effects (Davison and Parrott 1997; Solowij et al. 1992).

Coadministration of Ecstasy with SSRIs in Illicit Ecstasy Users

Several researchers have collected cases of individuals who have taken MDMA or ecstasy in combination with a selective serotonin reuptake inhibitor, or SSRI. Two retrospective studies discuss the effects of coadministration of SSRIs along with ecstasy in illicit users. One collection of case reports (McCann and Ricaurte 1993) found that four individuals who took fluoxetine (Prozac) before taking ecstasy experienced less negative effects with only minor attenuation of the positive effects of ecstasy. Subsequent publications suggest that this report is incorrect (Liechti et al. 2000a; Liechti and Vollenweider 2000b; Stein and Rink 1999). A later case report found that both the positive and the negative effects of ecstasy were greatly reduced in two individuals who took citalopram (Celexa) and ecstasy (Stein and Rink 1999). The findings in the second report are confirmed by a controlled clinical study that compared the effects of MDMA given alone with the effects produced after pre-treatment with citalopram (Liechti et al. 2000a; Liechti and Vollenweider 2000b). Taken together, the two reports and the definitive clinical study suggest that serotonin release is involved in producing many of the subjectively experienced effects of MDMA.

Other Avenues of Investigating the Effects of Ecstasy / MDMA

A few researchers and therapists have attempted to reproduce some or all of the effects of hallucinogenic drugs through post-hypnotic suggestion (Greer and Tolbert 1990; Masters and Houston 1972). Self-hypnosis was used to reproduce the analgesic effects of MDMA in a cancer patient (Greer and Tolbert 1990). Currently, there are no controlled studies using hypnotically induced re-creations of the effects of MDMA, but there is one published report of an attempt to recreate the subjective effects of MDMA through
hypnotic induction. Hastings (1994) sought to reproduce the effects of ecstasy via post-hypnotic suggestion, with four individuals who had previous experience with MDMA or ecstasy serving as volunteers in this study. Volunteers were asked to report what they experienced during the period of post-hypnotic suggestion and to compare it with their experience with ecstasy, though statistical comparisons were not used to test the strength of these comparisons. It appears that Hastings was partially successful in reproducing the effects of ecstasy in his volunteers, particularly in the realms of “bodily experience” and “energy.” Three of the four participants reported that their experience was nearly identical to their last experience with ecstasy, while one of the participants reported that the effects were different from his or her last experience with ecstasy, but pleasant nonetheless.
MDMA Neurotoxicity: Studies in Nonhuman animals
Matthew Baggott, BA

Introduction and Overview

Numerous studies have examined nonhuman animals and tissue cultures for evidence of MDMA-induced neurotoxicity. These studies are important because they allow controlled investigation of toxic changes that may occur in humans. These studies can be divided into three areas of neurochemical investigation: (1) monoaminergic neurotoxicity; (2) non-monoaminergic neurotoxicity; and (3) in vitro decreases in neural cell viability. The possible damage identified in each of these areas cannot always be equated. Nonetheless, any study of functioning in intact MDMA-exposed animals implicitly investigates all types of neurotoxicity.

High or repeated-dose MDMA regimens can produce long-term changes in indices of monoaminergic and axonal functioning in animals. Increasing evidence indicates that these changes are at least partially the result of damage. The magnitude of these changes varies with dose, species, and route of administration. Rodent studies have shown that changes in the core temperature of animals can increase or decrease MDMA neurotoxicity, although this finding has not been confirmed in primates. While some recovery does occur, a study in squirrel monkeys suggests that there may be permanent changes in axonal distribution. Oxidative stress appears to play an important role in MDMA neurotoxicity, but the exact mechanisms are poorly understood. The sustained acute pharmacological effects of MDMA may exhaust neuronal energy sources and antioxidant defenses, leading to damage. Metabolites of MDMA are another possible source of oxidative stress. The risks of monoaminergic neurotoxicity in humans are controversial and are discussed in the next chapter.

Research has also uncovered MDMA-induced non-monoaminergic neurotoxicity in rats. Measures of neural cell injury indicate that MDMA, like methamphetamine, can damage non-monoaminergic cell bodies in the somatosensory cortex. Another area of research uses cultured cell lines and has suggested that sustained exposure to MDMA can decrease neural cell viability and trigger programmed cell death. These neural cell changes have only been detected after high MDMA exposures that are unlikely to occur in clinical settings.

Few behavioral correlates of neurotoxic MDMA exposure have been found in drug-free nonhuman animals, despite dramatic serotonergic changes, alterations in neurofunctioning, and changes in response to drugs. Changes in MDMA-exposed animals include thermoregulatory impairment, decreased locomotor activity, and neurocognitive impairment. Lasting thermoregulatory impairment has been demonstrated in MDMA-exposed animals by two research groups. Rats exposed to a neurotoxic MDMA regimen showed reductions in diurnal and nocturnal locomotor activity at 7 to 14 days after drug treatment. Two studies have suggested that neurotoxic MDMA exposure may cause neurocognitive impairment in rats. The first study used adult animals and the second study used newborn rats. In contrast, at least 9 other studies failed to find evidence of neurocognitive impairment in MDMA-exposed animals.
These studies indicate that neurotoxic MDMA exposures can cause behavioral changes. These changes have been difficult to detect and it is not known whether they are temporary or permanent.

This section will discuss: (1) the nature and interpretation of MDMA-induced serotonergic changes; (2) the possible mechanisms of these changes; (3) factors influencing the magnitude of these changes (such as dose, route of administration, species and animal strain, and environment); (4) the time course of these changes and recovery; (5) evidence of non-monoaminergic damage; (6) in vitro cell viability studies; and (7) the behavioral and functional correlates of MDMA-induced long-term changes in animals.

Definitions

Before discussing MDMA-induced changes and their interpretation, it is necessary to define a few terms. In this document, drug doses and dosing patterns that produce these long-term serotonergic changes will be referred to as “neurotoxic regimens.” Neurotoxic regimens often consist of four to eight injections of MDMA given over the course of one to four days. However, a single injection of MDMA can also produce these changes. In this document, any changes noted at 7 or more days after drug administration will be considered “long-term.” Enough studies have also examined the brains of animals at longer time periods (often at 2, 4, or 8 weeks) to establish that the MDMA-induced serotonergic changes at 7 days are primarily long-term in nature.

The reader will note that the term “neurotoxicity” has not been defined. There are, unfortunately, no universally accepted definitions of this term and most definitions are broad enough to encompass short-term alcohol-induced headaches as well as the permanent nerve cell damage and parkinsonism caused by the neurotoxic meperidine analogue N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). A useful approach to the question of whether MDMA is neurotoxic may be to describe the nature and mechanisms of the long-term changes it can cause. When this is done, it can be seen that the serotonergic changes induced by at least some neurotoxic MDMA regimens are accompanied by loss of axons and that the acute events that trigger these changes involve damage to the brain by free radicals. This suggests that MDMA neurotoxicity is a type of drug-induced damage, even though the consequences of this damage are elusive. It must be noted that some scientists disagree with this interpretation and argue that MDMA-induced serotonergic changes should not be considered neurotoxic. This matter will be discussed below.

MDMA Can Induce Long-term Serotonergic Changes

At some, but not all, active doses, MDMA produces long-lasting changes to the serotonergic system. These long-term changes include decreases in brain concentrations of the neurotransmitter serotonin (5HT) and its metabolite 5-hydroxyindoleacetic acid (5HIAA). Tryptophan hydroxylase (TPH), the rate-limiting enzyme within the serotonergic neuron that begins the synthesis of 5HT, is decreased. There are also decreases in the density of the
serotonin reuptake transporter (SERT). SERT is a protein on the membrane of serotonergic neurons that functions to “recycle” released 5HT by transferring it back into the serotonergic neuron. Most studies suggest that MDMA primarily causes long-term changes in serotonergic neurons that have their cell bodies in an area of the brainstem called the dorsal raphe nucleus.

Long-lasting decreases in these serotonergic markers suggest that either (a) some type of “down-regulation” has occurred and the nerve cell is making and maintaining fewer of the markers or (b) that there are fewer serotonergic nerve terminals and axons in the region being measured. This issue has been important to the question of whether MDMA is truly neurotoxic. Down-regulation suggests an active adaptation to drug effects, while axonal loss suggests damage may have occurred. Deciding between these possibilities can be difficult. SERT density can be regulated in response to drugs, although this has been difficult to consistently demonstrate experimentally (Le Poul et al. 2000; Ramamoorthy et al. 1998). Similarly, 5HT levels can be influenced by diet and other factors. Because MDMA has been shown to rapidly inactivate the enzyme TPH, decreased 5HT levels would be expected until TPH activity returns to normal. Thus, decreased 5HT synthesis and subsequent SERT down-regulation initially appear to be a plausible explanation for MDMA-induced serotonergic changes. Ultimately, however, it is clear that MDMA can cause axonal loss. To demonstrate this, it is necessary to examine the structure of serotonergic axons and terminals in MDMA-exposed animals.

**Serotonergic Changes are Accompanied by Structural Changes to Axons**

An important approach to understanding MDMA-induced serotonergic changes involves staining brain slices from MDMA-exposed animals. Most commonly, immunocytochemistry techniques are used to stain 5HT, allowing serotonergic axons and terminals to be seen. When this is done, irregular swelling and what appears to be fragmentation of fine serotonergic axons is visible shortly after a neurotoxic regimen of MDMA or MDA (Kalia et al. 2000; O’Hearn et al. 1988; Scallet et al. 1988). Later immunocytochemistry measurements, at 2 or 4 weeks after neurotoxic MDMA regimens, also show a persistent decrease in stained axons (O’Hearn et al. 1988; Scallet et al. 1988; Slikker et al. 1988; Wilson et al. 1989). The initial swelling suggests some type of axonal damage, while the later decrease in stained axons suggests a loss of axons. However, some have argued that immunocytochemistry cannot reliably distinguish between true changes in 5HT-containing axons and changes in 5HT that are unaccompanied by axonal change. Because of this limitation, it is necessary to confirm the apparent loss of axons using techniques that do not rely on serotonergic markers.

Transport of materials within axons is crucial for maintaining cell structure and function. Lasting reductions in axonal transport suggest a drastic impairment of axonal functioning and, more likely, loss of axons. One can assess axonal transport by measuring transport of compounds between brain regions that serotonergic axons should connect. For example, if injected into the cortex, the fluorescent dye Fluoro-Gold should be transported along serotonergic axons into cell bodies in the brainstem. Axonal transport studies have been carried out after neurotoxic MDMA (Callahan et al. 2001; Ricaurte et al. 2000) and...
parachloroamphetamine (Fritschy et al. 1988; Haring et al. 1992) regimens. Their results suggest that a loss of axons occurs after at least some neurotoxic regimens of MDMA and related drugs.

Another method of assessing loss of nerve terminals involves measuring the vesicular monoamine transporter type II (VMAT2). This is a protein on the storage vesicles inside serotonergic (and other monoaminergic) nerve terminals. Because the amount of VMAT2 does not appear to be adjusted in response to drug exposure (Vander Borght et al. 1995), it is sometimes used as an indirect measure of nerve terminals in research on neurodegenerative disorders such as Parkinson’s disease. In the case of neurotoxic MDMA exposure, decreased VMAT2 would suggest that nerve terminals and axons have been lost. In fact, neurotoxic regimens of MDMA (Ricaurte et al. 2000) or methamphetamine (Frey et al. 1997) can decrease VMAT2. Therefore, at least some neurotoxic regimens of MDMA are associated with structural changes to cells. Examining the dorsal raphe nucleus leads to the conclusion that cell bodies of these affected axons do not die despite axon loss (Fischer et al. 1995; Hatzidimitriou et al. 1999; O’Hearn et al. 1988).

The data presented so far consistently indicate that MDMA can cause serotonergic axons to degenerate and that this explains at least some of the MDMA-induced decrease in serotonergic markers. Further evidence of axonal degeneration comes from studies in which recovery from MDMA neurotoxicity is associated with apparent sprouting and regrowth of axons (discussed in more detail below). At this point the reader may be wondering why MDMA neurotoxicity has been controversial. There are probably three reasons. First, research on axonal transport and VMAT2 has only recently been carried out with MDMA. Second, MDMA neurotoxicity initially seemed to be without any behavioral correlates. Third, techniques that normally detect neural cell damage yield ambiguous results after MDMA regimens. This point is discussed below.

Non-serotonergic Indicators of Cell Damage are Inconsistently Affected by MDMA

In general, neural cell damage can be detected using silver staining and/or by measuring expression of glial fibrillary acidic protein (GFAP) (O’Callaghan et al. 1995). These techniques seem to detect MDMA-induced alterations at higher doses than those needed to affect serotonergic indices (Commins et al. 1987b; O’Callaghan and Miller 1993). In one study, very high neurotoxic MDMA exposures resulted in increased GFAP but produced less SHT depletion than lower MDMA exposures (O’Callaghan and Miller 1993). Furthermore, the MDMA-induced cell damage detected by silver staining appears to occur in nonserotonergic cells (Commins et al. 1987b; Jensen et al. 1993) as well as in what are likely serotonergic axons (Scallet et al. 1988). These inconsistencies are difficult to interpret. Some have interpreted them as evidence that MDMA-induced serotonergic changes are the result of down-regulation of the serotonergic system rather than damage (e.g., O’Callaghan and Miller in press). Others have argued that the techniques for measuring cell damage are simply insensitive to selective serotonergic damage (Axt et al. 1994; Bendotti et al. 1994; Wilson and Molliver 1994). MDMA-induced damage to non-serotonergic cells is discussed in more detail in a subsequent section.
Because studies of axonal transport and VMAT2 changes have provided strong evidence of MDMA-induced axonal degeneration, it appears that serotonergic down-regulation can no longer fully explain the long-term effects of MDMA. Structural changes to serotonergic axons must also be explained. Although we are not aware that this hypothesis has been advanced, one could argue that loss of axons represents a non-neurotoxic form of neuroplasticity. In fact, non-neurotoxic (though not necessarily beneficial) morphological changes can occur in the CNS as the result of alterations in serotonin levels (reviewed in Azmitia 1999). However, as we better understand the mechanisms of these MDMA-induced serotonergic changes, it appears more likely that these changes are, in fact, the result of damage, specifically damage involving oxidative stress.

The Role of Oxidative Stress in MDMA neurotoxicity

Neurotoxic regimens of MDMA increase oxidative stress in the brain. In this document, the term "oxidative stress" will be used to refer to both the increase in free radicals and other reactive chemical species and the burden these species place on cellular functioning. Free radicals are highly reactive chemical species that contain one or more unpaired electrons and exist separately. Free radicals can damage neural macromolecules through reduction and oxidation reactions, altering the ability of these molecules to carry out their normal cellular function.

MDMA-induced oxidative stress has been measured in two ways. First, researchers have examined the brains of MDMA-treated animals for substances that react with thiobarbituric acid (Colado et al. 1997a; Jayanthi et al. 1999; Sprague and Nichols 1995b). Increases in these substances suggest that neural lipids have been oxidized. Second, researchers have perfused the brains of live animals with either salicylate or d-phenylalanine. These substances react with hydroxyl radicals to form 2,3-dihydroxybenzoic acid and d-tyrosine, respectively. By measuring formation of these compounds, researchers have demonstrated that neurotoxic MDMA regimens increase the amount of extracellular hydroxyl radicals of the striatum (Shankaran et al. 2001; Shankaran et al. 1999a; b) and hippocampus (Colado et al. 1999b; Colado et al. 1997b).

There is strong evidence that this oxidative stress is involved in the mechanisms of MDMA neurotoxicity. The antioxidants, ascorbate and cysteine, each reduce MDMA neurotoxicity in rats without altering striatal levels of MDMA or MDMA-stimulated dopamine release (Gudelsky 1996; Schmidt and Kehne 1990; Shankaran et al. 2001; Shankaran et al. 1999a; b). Ascorbate also decreases the acute MDMA-induced oxidation of endogenous vitamin E in the striatum and hippocampus (Shankaran et al. 2001). The free radical scavenger N-tert-butyl-alpha-phenylnitronone decreases both MDMA-induced hydroxyl formation and MDMA neurotoxicity in rats, although this may be partially due to an attenuation of MDMA-induced hyperthermia (Che et al. 1995; Colado et al. 1998; Colado and Green 1995; Yeh 1999). Pretreatment with the antioxidant alpha-lipoic acid blocks both MDMA-induced serotonergic neurotoxicity and increased GFAP expression in the rat hippocampus without altering MDMA-induced hyperthermia (Aguirre et al. 1999). Mice that have been genetically altered to have large amounts of the human antioxidant enzyme, copper/zinc superoxide dismutase, are protected from MDMA-induced dopamine depletions, probably because of the increased trapping of superoxide
radicals (Cadet et al. 1994; Cadet et al. 1995; Jayanthi et al. 1999). At the same time, these genetically modified mice are protected from the acute inactivation of antioxidant enzymes and increases in neural lipid peroxidation seen in normal mice after a neurotoxic MDMA regimen (Cadet et al. 1994; Cadet et al. 1995; Jayanthi et al. 1999).

Early evidence that MDMA caused significant oxidative stress (Stone et al. 1989a) showed that TPH that had been inactivated in rats at 3 hrs after high dose MDMA could be reactivated in vitro using sulphhydryl-reducing conditions. This demonstrated that the acute inactivation of TPH by MDMA was due to intracellular oxidative stress. Intracellular oxidative stress appears to be an effect of MDMA that requires sustained brain concentrations of MDMA (or a centrally formed metabolite). While a single injection of MDMA into the brain (intracerebroventricularly) had no effect on TPH activity, slow infusion of 1 mg/kg MDMA into the brain over 1 hr produced enough oxidative stress to acutely reduce TPH activity (Schmidt and Taylor 1988). The acute decrease in TPH activity is an early effect of MDMA and can be measured at post 15 min (Stone et al. 1989b). TPH inactivation can also be produced by non-neurotoxic MDMA doses (Schmidt and Taylor 1988; Stone et al. 1989a; Stone et al. 1989b). It therefore appears that MDMA rapidly induces oxidative stress but only produces neurotoxicity when endogenous free radical scavenging systems are overwhelmed.

In summary, MDMA neurotoxicity involves an initial period of oxidative damage, with increases in free radicals and damage to neural lipids occurring. It appears difficult to argue that dramatic MDMA-induced increases in free radicals and resulting oxidation of neural lipids and proteins are not damage. This damage seems to be part of the sequence of events producing serotonergic neurotoxicity since treatments that decrease MDMA-induced oxidative stress also decrease the long-term serotonergic changes (e.g., Aguirre et al. 1999). While MDMA can cause loss of axons, some simultaneous serotonergic down-regulation cannot be ruled out. Research on methamphetamine-induced dopaminergic neurotoxicity has led some to conclude that long-term dopaminergic changes can occur without significant axonal loss (Harvey et al. 2000; Wilson et al. 1996). Whether this is also the case with MDMA is unknown. For now, it seems reasonable to consider long-term serotonergic alterations after MDMA exposure as indicating that some degree of damage has occurred, while remembering that one is also measuring the response of the serotonergic system to acute drug effects and loss of axons.

**Proposed Sources of Oxidative Stress**

Several possible sources of neurotoxic oxidative stress have been proposed. First, the sustained pharmacological effects of MDMA may deplete neuronal energy sources and/or impair energy metabolism within the neuron (Huether et al. 1997). Second, both MDMA and dopamine can be metabolized to highly reactive quinone-like molecules. Quinones are molecules with two carbonyl groups either adjacent or separated by two carbons on an unsaturated six-membered ring. They are often very reactive and can form free radicals, potentially reacting with and damaging neural macromolecules. There is not yet conclusive evidence to implicate any of these possible causes and some (perhaps regionally specific) combination of mechanisms is possible. The possible roles of energy exhaustion or impairment, MDMA metabolites, and dopamine...
metabolites are discussed below. It has also been proposed that 5HT metabolites, increased intracellular Ca2+, nitric oxide, or glutamate may contribute to MDMA neurotoxicity. However, current evidence provides little support for these theories and their discussion will be brief.

**Energy Exhaustion or Impairment as a Source of Oxidative Stress**

Energy exhaustion or impairment may cause MDMA neurotoxicity. The normal activities of the neuron cause a certain degree of oxidative stress. A sustained increase in neuronal activity would therefore be expected to increase oxidative stress. More importantly, increased neuronal activity is accompanied by increased energy consumption that could eventually lead to a depletion of neuronal energy sources. This can impair the energy-requiring mechanisms that maintain and repair neurons. Furthermore, the most important source of cellular energy, mitochondria, can be impaired by oxidative stress (Crompton et al. 1999). Mitochondria produce adenosine triphosphate (ATP), the source of energy for most cellular processes. Insufficient ATP will lead to cell damage or death.

Whether energy exhaustion or impairment actually plays a role in MDMA neurotoxicity is not yet clear. MDMA has been shown to increase neuronal energy consumption. In rats, doses of 5 to 30 mg/kg intraperitoneal MDMA were found to acutely (post 50 min) increase cerebral glucose utilization in 12 of 60 examined regions, while decreasing utilization in 8 regions (Wilkerson and London 1989). The measurement time used in this study was likely too early to detect possible neurotoxicity-related energy depletion. MDMA also increases glycogen phosphorylase activity in vitro (Poblete and Azmitia 1995), which suggests that MDMA could decrease glial stores of glycogen, an important source of energy in the brain.

MDMA-induced alterations in mitochondria functioning have been reported (Burrows et al. 2000), but it is not yet clear these alterations are sufficient to impair mitochondria and damage cells. Burrows, Gudelsky, and Yamamoto (2000) reported that a neurotoxic regimen of MDMA transiently inhibited by 10 to 20% the activity of cytochrome oxidase, one of the protein complexes catalyzing oxidative phosphorylation. It is not clear if this degree of inhibition significantly impairs mitochondrial functioning. In another study, brain ATP levels were unchanged at 1 to 3 hours after a neurotoxic dose of MDMA to rats (Hervias et al. 2000). This shows that the ability of mitochondria to produce ATP is not impaired at these times, although later times were not examined. In the same report, nicotinamide increased MDMA neurotoxicity. Nicotinamide is the precursor molecule for the electron carrier NAD. It should therefore have enhanced ATP production and reduced neurotoxicity if mitochondrial impairment is truly involved. However, the authors suggest that nicotinamide may also alter MDMA metabolism, increasing formation of neurotoxic metabolites. At this point, evidence that MDMA neurotoxicity involves mitochondrial impairment must be considered inconclusive.

**MDMA Metabolites as a Source of Oxidative Stress**

MDMA metabolites may also play a role in MDMA neurotoxicity. However, it is difficult to investigate this possible role. Hypothetically, a given metabolite may only be toxic in the
Table 4.1. Studies of the Neurotoxicity of Putative MDMA Metabolites

<table>
<thead>
<tr>
<th>PUTATIVE METABOLITE</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>5HT</th>
<th>5HIAA</th>
<th>TPH</th>
<th>DA</th>
<th>TH</th>
<th>DOPAC/HVA</th>
<th>OTHER CHANGES</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,5-bis(glutathion-S-yl)-alphamethyldopamine</td>
<td>150 nmol X 4, every 12 hrs</td>
<td>intracortical</td>
<td>Decreased in STR and CORT. No significant change in HIP, MID/DI/TEL and PONS.</td>
<td>No significant change in CORT, STR, HIP, MID/DI/TEL and PONS</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP</td>
<td>NA</td>
<td>NA</td>
<td>No significant changes in NE in CORT, STR, or HIP</td>
<td>Bai et al., 1999</td>
</tr>
<tr>
<td>2,5-bis(glutathion-S-yl)-alphamethyldopamine</td>
<td>300 nmol X 4, every 12 hrs</td>
<td>intracortical</td>
<td>Decreased in CORT and STR. No significant change in HIP, midbrain/diencephalon/teiencephalon, and PONS.</td>
<td>No significant change in CORT, STR, HIP, MID/DI/TEL and PONS.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP</td>
<td>NA</td>
<td>NA</td>
<td>No significant changes in NE in CORT, STR, or HIP</td>
<td>Bai et al., 1999</td>
</tr>
<tr>
<td>2,5-bis(glutathion-S-yl)-alphamethyldopamine</td>
<td>150 nmol X 4, every 12 hrs</td>
<td>intrastriatal</td>
<td>Decrease in CORT. No significant changes in STR, HIP, MID/DI/TEL and PONS.</td>
<td>Decrease in CORT. No significant changes in STR, HIP, MID/DI/TEL and PONS.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP</td>
<td>NA</td>
<td>NA</td>
<td>No significant changes in NE in CORT, STR, or HIP</td>
<td>Bai et al., 1999</td>
</tr>
<tr>
<td>2,5-bis(glutathion-S-yl)-alphamethyldopamine</td>
<td>300 nmol X 4, every 12 hrs</td>
<td>intrastriatal</td>
<td>Decreased in CORT and STR. No significant change in HIP, MID/DI/TEL, and PONS.</td>
<td>Decreased in CORT and STR; Increased in HIP. No significant change in HIP, MID/DI/TEL and PONS.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP</td>
<td>NA</td>
<td>NA</td>
<td>No significant changes in NE in CORT, STR, or HIP</td>
<td>Bai et al., 1999</td>
</tr>
<tr>
<td>5-(glutathion-S-yl)-alphamethyldopamine</td>
<td>200 nmol X 4, every 12 hrs</td>
<td>intracortical</td>
<td>Decreased in CORT. No significant changes in STR, HIP, MID/DI/TEL, and PONS.</td>
<td>Decreased in CORT and STR. No significant change in STR, CORT, HIP, MID/DI/TEL, and PONS.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP</td>
<td>NA</td>
<td>NA</td>
<td>No significant changes in NE in CORT, STR, or HIP</td>
<td>Bai et al., 1999</td>
</tr>
</tbody>
</table>
Table 4.1 (continued). Studies of the Neurotoxicity of Putative MDMA Metabolites

<table>
<thead>
<tr>
<th>PUTATIVE METABOLITE</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>5HT</th>
<th>5HIAA</th>
<th>TPH</th>
<th>DA</th>
<th>TH</th>
<th>DOPAC/HVA</th>
<th>OTHER CHANGES</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-(glutathion-S-yl)-alphamethyldopamine</td>
<td>400 nmol X 4, every 12 hrs</td>
<td>intracortical</td>
<td>Decreased in CORT and STR. No significant change in HIP, MID/DI/TEL and PONS.</td>
<td>No significant change in CORT, STR, HIP, MID/DI/TEL and PONS.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>Bai et al., 1999</td>
<td></td>
</tr>
<tr>
<td>5-(glutathion-S-yl) alphamethyldopamine</td>
<td>200 nmol X 4, every 12 hrs</td>
<td>intrastriatal</td>
<td>Decreased in CORT and STR. No significant change in HIP, MID/DI/TEL and PONS.</td>
<td>No significant change in CORT, STR, HIP, MID/DI/TEL and PONS.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>Bai et al., 1999</td>
<td></td>
</tr>
<tr>
<td>5-(N-acetylcystein-S-yl) alphamethyldopamine</td>
<td>400 nmol X 4, every 12 hrs</td>
<td>intrastriatal</td>
<td>Decreased in STR. No significant change in CORT, HIP, MID/DI/TEL and PONS.</td>
<td>Increase in STR. No significant change in CORT, STR, HIP, MID/DI/TEL and PONS.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>Bai et al., 1999</td>
<td></td>
</tr>
<tr>
<td>5-(N-acetylcystein-S-yl) alphamethyldopamine</td>
<td>7 &amp; 20 nmol X 4, every 12 hrs</td>
<td>intracortical</td>
<td>Decreased in STR. No significant change in CORT, HIP, MID/DI/TEL, PONS.</td>
<td>Decreased in STR. No significant change in CORT, HIP, MID/DI/TEL and PONS.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>Bai et al., 1999</td>
<td></td>
</tr>
<tr>
<td>5-(N-acetylcystein-S-yl) alphamethyldopamine</td>
<td>7 &amp; 20 nmol X 4, every 12 hrs</td>
<td>intracortical</td>
<td>Decreased in CORT. No significant change in STR, HIP, MID/DI/TEL, and PONS.</td>
<td>Decreased in CORT. No significant change in STR, HIP, MID/DI/TEL and PONS.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>Bai et al., 1999</td>
<td></td>
</tr>
</tbody>
</table>
Table 4.1 (continued). Studies of the Neurotoxicity of Putative MDMA Metabolites

<table>
<thead>
<tr>
<th>PUTATIVE METABOLITE</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>5HT</th>
<th>5HIAA</th>
<th>TPH</th>
<th>DA</th>
<th>TH</th>
<th>DOPAC/HVA</th>
<th>OTHER CHANGES</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-(N-acetylcystein-S-yl)-alphamethyldopamine</td>
<td>7 &amp; 20 nmol X 4, every 12 hrs</td>
<td>intrahippocampal</td>
<td>For HIP, no significant change with dose of 7 nmol, but a decrease at dose of 20 nmol. No significant change in CORT, STR, MDI/TEL, and PONS.</td>
<td>No change in CORT, STR, MDI/TEL, and PONS. In an apparent oversight by the authors, there is no mention of whether or not there is a change in the HIP.</td>
<td>NA</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>NA</td>
<td>NA</td>
<td>No significant change in NE in CORT, STR, or HIP.</td>
<td>Bai et al., 1999</td>
</tr>
<tr>
<td>5-(glutathion-S-yl)-alphamethyldopamine</td>
<td>720 nmol X 4, every 12 hrs</td>
<td>ICV</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Miller et al., 1997</td>
</tr>
<tr>
<td>5-(N-acetylcystein-S-yl)-alphamethyldopamine</td>
<td>100 nmol X 4, every 12 hrs</td>
<td>ICV</td>
<td>No significant changes in CORT, STR, or HIP.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Miller et al., 1997</td>
</tr>
<tr>
<td>2,5-bis(glutathion-S-yl)-alphamethyldopamine</td>
<td>475 nmol X 4, every 12 hrs</td>
<td>ICV</td>
<td>Decreased in ipsilateral CORT and HIP not STR. Decreased in contralateral CORT not STR or HIP. No change in PONS and midbrain.</td>
<td>Decreased in ipsilateral HIP not STR and CORT. No change in contralateral CORT, STR, or HIP.</td>
<td>NA</td>
<td>No change in STR.</td>
<td>NA</td>
<td>No change in DOPAC or HVA in STR.</td>
<td>NA</td>
<td>Miller et al., 1997</td>
</tr>
<tr>
<td>5-(glutathion-S-yl)-alphamethyldopamine</td>
<td>720 nmol X 4, every 12 hrs</td>
<td>ICV</td>
<td>No significant change in MDI/TEL, CORT, STR, HIP.</td>
<td>No significant change in MDI/TEL, CORT, STR, HIP.</td>
<td>NA</td>
<td>No significant change in STR, MDI/TEL, PONS/MED, or HYPO.</td>
<td>NA</td>
<td>No change in DOPAC or HVA in STR, MDI/TEL, PONS/MED, or HYPO.</td>
<td>Miller et al., 1996</td>
<td></td>
</tr>
<tr>
<td>PUTATIVE METABOLITE</td>
<td>DOSE</td>
<td>ROUTE</td>
<td>5HT</td>
<td>5HIAA</td>
<td>TPH</td>
<td>DA</td>
<td>TH</td>
<td>DOPAC/HVA</td>
<td>OTHER CHANGES</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>-----------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>2,4,5-trihydroxylamphetamine</td>
<td>0.25 umol</td>
<td>ICV</td>
<td>Decreased in HIP not STR.</td>
<td>Decreased in HIP not STR.</td>
<td>Decreased in HIP and STR.</td>
<td>Decreased in STR.</td>
<td>Decreased DOPAC in STR.</td>
<td>Decreased DOPAC and HVA in STR.</td>
<td>Decreased NE in HIP.</td>
<td>Elayan et al., 1992</td>
</tr>
<tr>
<td>2,4,5-trihydroxylamphetamine</td>
<td>0.5 umol</td>
<td>ICV</td>
<td>Decreased in HIP not STR.</td>
<td>Decreased in HIP not STR.</td>
<td>Decreased in HIP and STR.</td>
<td>Decreased in STR.</td>
<td>Decreased NE in HIP.</td>
<td>Decreased DOPAC and HVA in STR.</td>
<td>Decreased NE in HIP.</td>
<td>Elayan et al., 1992</td>
</tr>
<tr>
<td>6-hydroxy-MDMA</td>
<td>1 umol</td>
<td>ICV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No changes in HIP and STR.</td>
<td>No changes in HIP and STR.</td>
<td>Elayan et al., 1992</td>
</tr>
<tr>
<td>6-hydroxy-MDA</td>
<td>1 umol</td>
<td>ICV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Increased in HIP.</td>
<td>NA</td>
<td>Elayan et al., 1992</td>
</tr>
<tr>
<td>3,4-dihydroxymethamphetamine (alpha-methylepinine)</td>
<td>135 ug</td>
<td>ICV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No change in HIP.</td>
<td>Increased in STR.</td>
<td>Elayan et al., 1992</td>
</tr>
<tr>
<td>3,4-dihydroxymethamphetamine (alpha-methylepinine)</td>
<td>300 ug</td>
<td>ICV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No changes in HIP.</td>
<td>No changes in HIP.</td>
<td>Steele et al., 1991</td>
</tr>
<tr>
<td>3,4-dihydroxymethamphetamine (alpha-methylepinine)</td>
<td>600 ug</td>
<td>ICV</td>
<td>No change in HYPO, CORT, HIP, or STR.</td>
<td>Increase in HIP.</td>
<td>No change in HYPO, CORT, HIP, or STR.</td>
<td>No change in HYPO, CORT, or STR.</td>
<td>No change in HYPO, CORT, HIP, or STR.</td>
<td>No changes in NE in HYPO, CORT, HIP, or STR.</td>
<td>Steele et al., 1991</td>
<td></td>
</tr>
<tr>
<td>PUTATIVE METABOLITE</td>
<td>DOSE</td>
<td>ROUTE</td>
<td>5HT</td>
<td>5HIAA</td>
<td>TPH</td>
<td>DA</td>
<td>TH</td>
<td>DOPAC/HVA</td>
<td>OTHER CHANGES</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>--------</td>
<td>------</td>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>-----------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>2,4,5-trihydroxymethamphetamine</td>
<td>100 ug</td>
<td>ICV</td>
<td>Decreased in HIP, not STR or FCx.</td>
<td>No change in FCx, HIP, or STR.</td>
<td>Decreased in HIP, STR. Increased in DR. No change in FCx or MR.</td>
<td>Decreased in STR.</td>
<td>Decreased in STR not SN.</td>
<td>Decreased DOPAC and HVA in STR.</td>
<td>NA</td>
<td>Johnson et al., 1992</td>
</tr>
<tr>
<td>2,4,5-trihydroxymethamphetamine</td>
<td>200 ug</td>
<td>ICV</td>
<td>Decreased in HIP, STR, and FCx.</td>
<td>No change in FCx, HIP, or STR.</td>
<td>Decreased in HIP, STR. Increased in DR. No change in FCx or MR.</td>
<td>Decreased in STR.</td>
<td>Decreased in STR not SN.</td>
<td>Decreased DOPAC and HVA in STR.</td>
<td>NA</td>
<td>Johnson et al., 1992</td>
</tr>
<tr>
<td>6-hydroxy-MDMA</td>
<td>10 mg/kg</td>
<td>IP</td>
<td>No change in HIP or CORT.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zhao et al., 1992</td>
</tr>
<tr>
<td>6-hydroxy-MDMA</td>
<td>20 mg/kg</td>
<td>IP</td>
<td>No change in HIP or CORT.</td>
<td>NA</td>
<td>NA</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zhao et al., 1992</td>
</tr>
<tr>
<td>6-hydroxy-MDMA</td>
<td>100 ug</td>
<td>ICV</td>
<td>No change in HIP or CORT.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zhao et al., 1992</td>
</tr>
<tr>
<td>6-hydroxy-MDMA</td>
<td>400 ug</td>
<td>ICV</td>
<td>No change in HIP or CORT.</td>
<td>NA</td>
<td>NA</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zhao et al., 1992</td>
</tr>
<tr>
<td>6-hydroxy-MDMA</td>
<td>?</td>
<td>intrastratal</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zhao et al., 1992</td>
</tr>
<tr>
<td>2,4,5-trihydroxymethamphetamine</td>
<td>100 ug</td>
<td>ICV</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>Decreased in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zhao et al., 1992</td>
</tr>
<tr>
<td>trihydroxymethamphetamine</td>
<td>50 ug</td>
<td>intrastratal</td>
<td>Decreased in STR.</td>
<td>NA</td>
<td>NA</td>
<td>Decreased in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zhao et al., 1992</td>
</tr>
<tr>
<td>PUTATIVE METABOLITE</td>
<td>DOSE</td>
<td>ROUTE</td>
<td>5HT</td>
<td>5HIAA</td>
<td>TPH</td>
<td>DA</td>
<td>TH</td>
<td>DOPAC/HVA</td>
<td>OTHER CHANGES</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>-------</td>
<td>-----</td>
<td>-------</td>
<td>-----</td>
<td>----</td>
<td>----</td>
<td>-----------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>2,4,5-trihydroxymethamphetamine</td>
<td>100 ug</td>
<td>intrastriatal</td>
<td>Decreased in STR.</td>
<td>NA</td>
<td>NA</td>
<td>Decreased in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zhao et al., 1992</td>
</tr>
<tr>
<td>2,4,5-trihydroxymethamphetamine</td>
<td>100 ug</td>
<td>intracortical</td>
<td>No change in CORT.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zhao et al., 1992</td>
</tr>
<tr>
<td>2,4,5-trihydroxymethamphetamine</td>
<td>400 ug</td>
<td>intracortical</td>
<td>Decreased in CORT.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zhao et al., 1992</td>
</tr>
<tr>
<td>alpha-methyldopamine</td>
<td>400 ug</td>
<td>intrastriatal</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>McCann &amp; Ricaurte, 1991</td>
</tr>
<tr>
<td>alpha-methyldopamine (50 mg/kg pargyline ip pretreatment 30-45 min pre)</td>
<td>400 ug</td>
<td>ICV</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>McCann &amp; Ricaurte, 1991</td>
</tr>
<tr>
<td>3-methoxy-4-hydroxyamphetamine (50 mg/kg pargyline ip pretreatment 30-45 min pre)</td>
<td>400 ug</td>
<td>ICV</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>McCann &amp; Ricaurte, 1991</td>
</tr>
<tr>
<td>alpha-methyl-dopa (25 mg/kg carbidopa pretreatment)</td>
<td>200 mg/kg, twice daily for 4 days</td>
<td>sc</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>McCann &amp; Ricaurte, 1991</td>
</tr>
<tr>
<td>3-O-methyl-alpha-methyl-dopa (25 mg/kg carbidopa pretreatment)</td>
<td>200 mg/kg, twice daily for 4 days</td>
<td>sc</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>McCann &amp; Ricaurte, 1991</td>
</tr>
<tr>
<td>simultaneous 3-O-methyl-alpha-methyl-dopa and alpha-methyl-dopa (25 mg/kg carbidopa pretreatment)</td>
<td>200 mg/kg each drug, twice daily for 4 days</td>
<td>sc</td>
<td>No change in STR.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>McCann &amp; Ricaurte, 1991</td>
</tr>
</tbody>
</table>
presence of MDMA, when the metabolite has high concentrations in the brain for several hours, or when certain acute effects of MDMA have already occurred. In such situations, administering the toxic metabolite on its own would not necessarily lead to toxicity. Thus, it is hard to interpret the many studies in which an MDMA metabolite was administered and no evidence of neurotoxicity was found (Elayan et al. 1992; Johnson et al. 1992a; McCann and Ricaurte 1991; Steele et al. 1991; Zhao et al. 1992). One can also investigate the potential role of metabolites by altering the MDMA metabolism and determining whether that alters neurotoxicity. Thus far, attempts to alter MDMA metabolism in rats with SKF-525A or phenobarbital have not provided evidence that MDMA metabolites are important in neurotoxicity (Gollamudi et al. 1989). Studies examining the neurotoxicity of centrally administered MDMA metabolites are summarized in Table 4.1.

A number of studies have focused on the MDMA metabolites, 3,4-dihydroxymethamphetamine (DHMA, also called alpha-methylepinine) and 3,4-dihydroxyamphetamine (DHA, also called alpha-methyldopamine). These metabolites are readily oxidized to quinones. Spontaneous oxidation of these quinones could generate hydrogen peroxide and superoxide radicals (Horton and Fairhurst 1987). Neither DHA nor DHMA has been found to produce long-term 5HT depletions when infused into the brains of rats (Johnson et al. 1992a; McCann and Ricaurte 1991; Miller et al. 1996; Steele et al. 1991). However, DHA (and likely DHMA) may become neurotoxic after forming thioether conjugates. Conjugation is considered the second phase of drug metabolism and can be seen as an attempt by the body to make foreign compounds more polar and thus more easily excreted in urine and bile. This is accomplished by adding functional groups to foreign compounds, forming products such as sulfates, glucuronides, and peptides. In some cases, this “detoxifying” process fails and conjugates of foreign compounds can have increased toxicity in comparison to the unconjugated compounds.

Several thioether metabolites of DHA can produce selective long-term (7 day) decreases in 5HT levels when infused into rat brains (Bai et al. 1999; Miller et al. 1996; 1997; Monks et al. 1999). These 5HT depleting metabolites include 2,5-bis-(Glutathion-S-yl)-alpha-methyldopamine, 5-(Glutathion-S-yl)-alpha-methyldopamine, and 5-(N-acetylcystein-S-yl)-alpha-methyldopamine. While DHA and DHMA are likely too polar to cross the blood-brain barrier, their conjugates are transported across by specialized pumps. The doses of conjugated metabolites required to deplete 5HT are relatively low. If only two percent of a systemic neurotoxic dose is converted to these metabolites and reaches the brain, this may be sufficient to produce 5HT depletions (Bai et al. 1999). It remains to be seen if the 5HT depletions produced by these conjugated metabolites are accompanied by the other features of MDMA neurotoxicity, such as axonal changes and SERT decreases. If the effects of these conjugated metabolites fully mimic MDMA neurotoxicity, this would provide strong evidence that they play a significant role in this toxicity.

**Dopamine Metabolites as a Source of Oxidative Stress**

It has also been suggested that some of the dopamine released by MDMA may be transported by SERT into serotonergic axons (Faraj et al. 1994) and subsequently oxidized (Nash 1990; Schmidt and Kehne 1990; Sprague and Nichols 1995b). The oxidation of dopamine can form
hydrogen peroxide, which, in turn, may produce hydroxyl radicals. A quinone-like dopamine metabolite may also be formed with potential to generate further free radicals (Cadet and Brannock 1998; Graham et al. 1978). Among many other potential toxic effects on cells, dopamine oxidation products have been shown to impair mitochondrial functioning (Berman and Hastings 1999).

There is some evidence for dopaminergic involvement in MDMA neurotoxicity. Previous dopaminergic neurotoxicity in the substantia nigra reduces subsequent MDMA neurotoxicity (Schmidt et al. 1990c; Stone et al. 1988). Coadministration of the dopamine reuptake inhibitor, mazindol, reduces MDMA-induced striatal dopamine release and hydroxyl radical formation as well as the long-term serotonin depletion (Nash and Brodkin 1991; Shankaran et al. 1999b). This attenuation of the effects of MDMA takes place without altering the acute hyperthermic response to MDMA. The neuroprotective effect of mazindol is consistent with reports that MDMA neurotoxicity is inhibited by drugs that suppress MDMA-induced dopamine release, such as GBR-12909 (Stone et al. 1988).

Over the last few years, some of the evidence for dopaminergic involvement in MDMA neurotoxicity has been reinterpreted. A number of dopaminergic drugs that modify MDMA neurotoxicity probably act by modulating body temperature rather than through a specifically dopaminergic mechanism, as previously thought. These drugs include alpha-methyl-paratyrosine (Malberg et al. 1996) and haloperidol (Colado et al. 1999c). The mechanism by which L-dopa increases neurotoxicity is currently unclear with conflicting findings from two groups (Colado et al. 1999c; Schmidt et al. 1991). Although the monoamine oxidase-B (MAO-B) inhibitors, L-Deprenyl (selegiline) and MDL-72974, each attenuate MDMA neurotoxicity (Sprague and Nichols 1995a; b), they may act by scavenging free radicals since blockade of MAO-B gene expression with antisense oligonucleotides is not neuroprotective (Sprague et al. 1999).

If dopamine plays a central role in MDMA neurotoxicity, one might expect a correlation between dopamine release and MDMA neurotoxicity. Nichols and colleagues found a linear correlation between the acute striatal dopamine release produced by a series of different substituted amphetamines and subsequent long-term 5HT depletions (Johnson et al. 1991; Nash and Nichols 1991). However, another group (Colado et al. 1999c) reported that non-neurotoxic and neurotoxic doses of MDMA produced comparable amounts of dopamine release in rats. Furthermore, some brain areas with relatively little dopamine such as the hippocampus show profound 5HT depletions after MDMA. In fact, Shankaran and Gudelsky (1998) reported that blocking MDMA-induced acute dopamine release in the hippocampus (using the norepinephrine uptake inhibitor, desipramine) did not prevent long-term 5HT depletions in that region. The same report suggested that the mechanism of MDMA neurotoxicity may vary between brain regions.

In conclusion, dopamine release seems to play a role in MDMA neurotoxicity, but there is currently no direct evidence that a metabolite of dopamine acts as a toxin after MDMA administration.
There is Currently Little Evidence that 5HT Metabolites Act as Toxins

Berger et al. (1992a) suggested that 5HT metabolites may be responsible for phenethylamine-induced neurotoxicity. Indeed, hydroxylated metabolites of 5HT such as 5,6- and 5,7-dihydroxytryptamine are selective serotonergic neurotoxins. More recently, Dryhurst and colleagues have demonstrated that oxidation of 5HT by superoxide anion radical can lead to tryptamine-4,5-dione, a mitochondrial toxin (Jiang et al. 1999; Wrona and Dryhurst 1998).

Although such 5HT metabolites can be neurotoxic, there is currently no evidence to suggest these specific metabolites contribute to MDMA neurotoxicity. Toxic 5HT metabolites have not yet been reported in brains of MDMA-treated animals. Although a molecule resembling 5,6-dihydroxytryptamine was reported by Commins et al. (1987a) in rat brains after neurotoxic regimens of both parachloroamphetamine and methamphetamine, this has not been confirmed. On the contrary, a more stable product of hydroxyl-mediated 5HT oxidation, 5-(hydroxyindoyl)-3-(ethylamino)-2-oxindole, is not elevated in rat brains after neurotoxic regimens of methamphetamine (Yang et al. 1997). As evidence against the possibility of neurotoxic 5HT metabolites, Sprague et al. (1994) found that pretreatment with the 5HT precursors, tryptophan or 5-hydroxytryptophan, decreased MDMA neurotoxicity. This finding is somewhat unexpected given that 5-hydroxytryptophan pretreatment enhances MDMA-induced 5HT and dopamine release in the striatum (Gudelsky and Nash 1996). In addition, prior depletion of 5HT with parachlorophenylalanine does not decrease neurotoxicity (Brodkin et al. 1993). Thus, increasing 5HT is protective, while decreasing 5HT is not. It is difficult to reconcile these findings with the possibility of neurotoxic 5HT metabolites.

Glutamate Does Not Appear to Play a Major Role in MDMA neurotoxicity

Excitatory amino acids such as glutamate have well-established potential to damage neurons (Choi 1992; Olney 1994). A role for glutamate in MDMA neurotoxicity was suggested by a report that the N-methyl-D-aspartate (NMDA) antagonist, dextrorphan, inhibited MDMA-induced 5HT depletions in the rat striatum (Finnegan et al. 1990). Subsequent studies employing other NMDA antagonists, such as dizocilpine (also called MK-801), have not supported this conclusion. Although it is neuroprotective, dizocilpine appears to protect against MDMA neurotoxicity through a thermoregulatory mechanism (Farfel and Seiden 1995). Glutamate antagonists that do not block MDMA-induced hyperthermia are not neuroprotective (Colado et al. 1998; Farfel and Seiden 1995). As further evidence against a role for glutamate in MDMA neurotoxicity, Nash and Yamamoto (1992) reported that a neurotoxic MDMA regimen had no effect on acute glutamate efflux in the striatum of rats. Finally, excitotoxicity does not usually produce selective axon loss. Thus, there currently appears to be no strong evidence that glutamate plays in role in the mechanism of MDMA neurotoxicity.
A Possible Role for Ca$^{2+}$ in MDMA Neurotoxicity

Despite the lack of evidence that glutamate plays a role in MDMA neurotoxicity, there may be similarities in the intracellular mechanisms of excitotoxicity and MDMA neurotoxicity. Excitotoxicity involves increases in Ca$^{2+}$ influx into the cell. MDMA may also disturb the cellular homeostasis of serotonergic axons by increasing intracellular Ca$^{2+}$ concentrations. Kramer, Poblete, and Azmitia (1998) reported that MDMA produces a Ca$^{2+}$ dependent protein kinase C translocation through its interactions with the SERT. They suggested that sustained interaction of MDMA with the SERT may therefore increase intracellular Ca$^{2+}$ concentrations. High intracellular Ca$^{2+}$ concentrations could impair cellular functioning in a number of ways. Increased intracellular Ca$^{2+}$ may impair mitochondrial activity since elevated levels of Ca$^{2+}$ have been found to increase free radical production in isolated cerebellar and cerebral mitochondria (Dykens 1994).

Studies employing calcium channel blockers have found mixed evidence that Ca$^{2+}$ mediates MDMA neurotoxicity. The calcium channel blocker, flunarazine, protects against the MDMA-induced 5HT depletions (Finnegan et al. 1993) and reductions in cortical and nigrostriatal TPH activity (Johnson et al. 1992b). However, other L-type calcium channel antagonists, such as nimodipine, are not protective (Johnson et al. 1992b). These studies did not control for possible effects of drug treatment on body temperature.

Increased intracellular Ca$^{2+}$ could activate Ca$^{2+}$/calmodulin-dependent nitric oxide synthase (NOS). Resulting nitric oxide (NO) can react with the superoxide anion to form peroxynitrite, a highly reactive free radical. NO also impairs mitochondrial activity through poorly understood mechanisms (Brorson et al. 1999). Increased NOS activity and resulting excessive NO levels may therefore participate in MDMA neurotoxicity, although evidence for this is ambiguous. The NO donor nitroprusside increased MDMA-induced cytotoxicity in an in vitro study using cultured human serotonergic cells (Simantov and Tauber 1997). Brain NOS activity is increased in the frontal and parietal cortices 6 hrs after a neurotoxic regimen of MDMA in rats (Zheng and Laverty 1998). Pretreatment with the NOS inhibitor N$^{G}$-nitro-L-arginine methyl ester (L-NAME) decreases MDMA neurotoxicity in those areas. On the other hand, L-NAME also induces hypothermia and other NOS inhibitors lacking this hypothermic effect are not protective (Taraska and Finnegan 1997).

Extent of Neurotoxicity Depends on Dose, Route of Administration, Animal Age, and Species.

Neurotoxicity is dose-dependent. Long-term changes occur in rats at doses approximately 5 to 10 times higher than those known to be psychoactive. A study using male Dark Agouti rats (O'Shea et al. 1998), found that, seven days after drug exposure, 4 mg/kg intraperitoneally injected MDMA did not affect hippocampal 5HT levels. 10 mg/kg MDMA decreased hippocampal 5HT to about 65% of control levels, while 15 mg/kg MDMA lowered levels to about 40% of controls. Cortical SERT density was similarly decreased, showing that changes were not just due to altered synthesis of 5HT. The 5HT-depleting effects of 0, 20, or 40 mg/kg
subcutaneous MDMA were compared at two and eight weeks after drug administration in Sprague-Dawley rats (Commins et al. 1987b). Interestingly, doubling the dose from 20 to 40 mg/kg only moderately increased the extent of 5HT depletions. For example, 5HT levels in the hippocampus at post 8 weeks were reduced to 70% of control levels by 20 mg/kg MDMA and 60% of control levels by 40 mg/kg MDMA.

**Single vs. Multiple Dose Exposures.** Most MDMA neurotoxicity studies have used multiple dose regimens. These studies show that "binge" use of MDMA carries greater risk of neurotoxicity than single doses. When administered repeatedly, a non-neurotoxic dose of MDMA can become neurotoxic (Battaglia et al. 1988a; O'Shea et al. 1998). Multiple dose neurotoxic regimens appear able to produce more profound and possibly more lasting serotonergic changes than single MDMA administration (Battaglia et al. 1988b). The results of multiple dose studies are difficult to compare across species since the same interdosing interval can have very different effects in two species with different clearance rates of MDMA.

**Route of Administration.** The importance of route of administration in altering long-term serotonergic changes has been investigated. In the rat, subcutaneous injection and oral administration of MDMA produce comparable 5HT depletions in the hippocampus (Finnegan et al. 1988). Studies with nonhuman primates have yielded less consistent results. In the squirrel monkey, repeated oral administration of MDMA resulted in only one-half to two-thirds as much 5HT depletion as the equivalent subcutaneous dose (Ricaurte et al. 1988a). In the rhesus monkey, in contrast, repeated oral administration of MDMA produced twice the decrease in hippocampal SERT activity as was produced by repeated subcutaneous injection (Kleven et al. 1989). These apparent differences between nonhuman primate species increase the difficulty of assessing the risk of oral MDMA administration in humans.

**Age of Animal.** Although young rats undergo MDMA-induced acute serotonergic effects (Broening et al. 1994), they are insensitive to both MDMA-induced hyperthermia (Broening et al. 1995) and MDMA neurotoxicity. Rats appear to become vulnerable to MDMA neurotoxicity at about 35 days after birth, possibly due to changes in the dopaminergic system (Aguirre et al. 1998b). However, Broening et al. (2001) were able to produce small serotonin depletions in newborn rats using 5 mg/kg MDMA subcutaneously injected twice daily for 10 days. This shows that newborn rats are resistant, but not invulnerable, to MDMA neurotoxicity. Few studies have examined whether aged animals have increased vulnerability to MDMA neurotoxicity. Young adult (3 month old) and aged (24 months old) mice undergo comparable dopaminergic neurotoxicity, but display age-specific differences in accompanying changes in neurotransmitter turnover and cell signaling activity (Slotkin et al. 2000). These differences were interpreted by the researchers as indicating that aged mice were less able to compensate on the cellular level for loss of dopaminergic axons.

**Species and Strain Differences in Vulnerability**
A variety of species have been used MDMA neurotoxicity research. These species include mice, rats, guinea pigs (Battaglia et al. 1988b; Commins et al. 1987b), cynomolgus monkeys (Ricaurte et al. 1988c; Wilson et al. 1989), baboons (Scheffè & et al. 1998), squirrel monkeys (Fischer et al. 1987b).
1995; Hatzidimitriou et al. 1999; Kleven et al. 1989; Ricaurte 1989; Ricaurte et al. 1988a; Ricaurte et al. 1988b; Ricaurte et al. 1988c; Ricaurte et al. 1992), and rhesus monkeys (Ali et al. 1993; Beardsley et al. 1986; De Souza et al. 1990; Frederick et al. 1998; Frederick et al. 1995; Insel et al. 1989; Jagust et al. 1996; Ricaurte et al. 1988c; Slikker et al. 1988; Slikker et al. 1989; Taffe et al. 2001; Wilson et al. 1989). All species tested are vulnerable to MDMA neurotoxicity. However, mice are unusual in that they primarily undergo long-term dopaminergic, rather than serotonergic, changes. There appear to be species differences in the MDMA exposure required to produce neurotoxicity and the extent of depletions produced. However, there are insufficient data from most species to indicate the species-specific dose-response function.

**Strain Differences in Vulnerability.** Rat strains differ in sensitivity to MDMA neurotoxicity. For example, neurotoxicity could not be detected when 25 mg/kg MDMA was intraperitoneally administered to randomly bred albino rats (Logan et al. 1988). In contrast, Dark Agouti rats have a threshold between 4 and 10 mg/kg intraperitoneally injected MDMA for undergoing 5HT depletions (O'Shea et al. 1998). These apparent strain differences may also be influenced by differences in ambient temperature and animal housing (Dafters 1995; Gordon and Fogelson 1994).

**Primates are More Vulnerable than Rats.** In comparison to rats, nonhuman primates seem to have a lower threshold dose for MDMA neurotoxicity and generally undergo more extensive decreases in serotonergic markers (Ali et al. 1993; Fischer et al. 1995; Insel et al. 1989; Ricaurte et al. 1992; Ricaurte and McCann 1992; but see also De Souza et al. 1990 for slightly different results). This has suggested to some that humans may be even more sensitive than nonhuman primates. Possible reasons for the increased vulnerability of nonhuman primates compared to rodents include the increased length of serotonergic axons in primates, the increased degree of axonal myelination in primates, and expected pharmacokinetic differences between species (Campbell 1995; Fischer et al. 1995). Research with fenfluramine suggests that species differences in fenfluramine-induced serotonergic neurotoxicity may be largely due to pharmacokinetic differences (Mennini et al. 1996). However, no published studies have documented the pharmacokinetics of MDMA in nonhuman primates.

**Squirrel Monkey Research.** Many MDMA neurotoxicity studies have used squirrel monkeys as subjects (Fischer et al. 1995; Hatzidimitriou et al. 1999; Kleven et al. 1989; Ricaurte 1989; Ricaurte et al. 1988a; Ricaurte et al. 1988b; Ricaurte et al. 1988c; Ricaurte et al. 1992). The threshold dose for producing long-term 5HT depletions in squirrel monkeys is between 2.5 and 5 mg/kg oral MDMA. Two weeks after a single 5.0 mg/kg oral MDMA dose to this species, 5HT levels were decreased to 83% of control levels in the hypothalamus and 79% of controls in the thalamus but were not changed in other examined brain regions (Ricaurte et al. 1988a). SERT density was not reported in this study. In contrast, no long-term serotonergic changes occurred after 2.5 mg/kg MDMA was given orally every two weeks for four months to squirrel monkeys (Ricaurte, unpublished, cited in Vollenweider et al. 1999a).

**Rhesus Monkey Research.** Another commonly studied nonhuman primate species is the rhesus monkey (Ali et al. 1993; De Souza et al. 1990; Frederick et al. 1998; Frederick et al. 1995; Insel
et al. 1989; Jagust et al. 1996; Ricaurte et al. 1988c; Slikker et al. 1988; Slikker et al. 1989; Taffe et al. 2001; Wilson et al. 1989). Determining the threshold dose for 5HT depletions in this species is difficult since all published studies using rhesus monkeys have employed multiple dose neurotoxic regimens. In one study, 1.25 mg/kg oral MDMA did not produce any long-term serotonergic changes when given twice daily for 4 consecutive days. Similarly repeated doses of 2.5 mg/kg MDMA lowered hippocampal 5HT (to about 80% of controls) but did not affect levels in 6 other brain regions at post 1 month (Ali et al. 1993). Another experiment (Insel et al. 1989) found that 2.5 mg/kg MDMA given intramuscularly twice daily for 4 days to rhesus monkeys produced extensive (possibly short term) 5HT depletions but did not alter SERT density at 16 to 18 hours after the last drug exposure. Since SERT was unaffected, the researchers concluded that axonal loss had not occurred, despite the (possibly short-term) 5HT depletions. One study, which raised interesting questions about possible tolerance to MDMA neurotoxicity, investigated the long-term effects of escalating doses of MDMA (Frederick et al. 1995). Intramuscular MDMA (0.10-20.0 mg/kg) was given twice daily for 14 consecutive days at each dose level and followed by three dose-response regimens using single MDMA doses up to 5.6 mg/kg. One month after the final dose-response determination and 21 months after the initial escalating dose regimen, animals were sacrificed. Few significant serotonergic effects were found. MDMA exposure did not produce significant 5HT depletions in any brain region and decreased SERT to about 60% of control levels only in the hippocampus (and not two other brain regions). Because escalating dose regimens of d-fenfluramine (Caccia et al. 1992) or d-amphetamine (Robinson and Camp 1987) provide protection against the neurotoxicity of these drugs, it seems likely that the same poorly-understood phenomenon is being detected here. Thus, data on rhesus monkeys are complex and perhaps all that can be said with certainty is that the threshold dose for long-term 5HT depletions appears to be above 1.25 mg/kg oral MDMA in this species.

Why Are Such High Doses Used In Neurotoxicity Research?

Research on MDMA neurotoxicity has sometimes been criticized for the high, repeated dose regimens that are commonly used. Some have questioned whether repeated injections of 20 mg/kg MDMA in rodents can provide useful information about the toxicity of single oral doses of 1.7 to 2.0 mg/kg MDMA in humans. It is true that many of the neurotoxic regimens are not designed to be clinically relevant but were intended to maximize the serotonergic neurotoxicity of MDMA in order to better understand its mechanisms and consequences.

However, comparing dose on the basis on body weight can be misleading. In general, smaller species excrete drugs more quickly and form metabolites in greater amounts than larger species. This is due to many factors including the proportionally larger livers and kidneys and faster blood circulation times in smaller mammals (Lin 1998; Mordenti and Chappell 1989). As a result of such factors, the time it takes to lower the plasma levels of MDMA by half is about 1.5 hours in a rat (Cho et al. 1990) and about 8 hours in a human (Mas et al. 1999). This suggests that small species may require higher doses (in mg/kg) to achieve drug exposures comparable to those seen in larger species. These considerations at least partially justify the apparently high doses commonly used in rodent toxicity studies. Unfortunately, higher doses tend to alter the character of the drug exposure. While they lengthen the time smaller animals are exposed to the
drug, they also tend the produce higher peak blood concentrations of drug and greater acute effects than occur in larger species at lower doses.

A number of techniques have been developed for estimating equivalent drug doses in different species (useful articles from this large literature include Ings 1990; Lin 1998; Mahmood 1999; Mordenti and Chappell 1989). One of the most commonly used techniques, allometric interspecies scaling, involves administering a drug to different species and measuring resulting blood concentrations of drug. These measurements are then used to empirically determine the relationships between species weight, drug exposure, and dose. Drug exposure in humans can be estimated from these relationships. In these estimates, equivalent drug exposures are assumed to produce equivalent drug effects, including neurotoxicity. Ricaurte and colleagues (2000) recently estimated that as little as 1.28 mg/kg MDMA may produce long-term 5HT depletions in humans if interspecies dose conversions for MDMA follow a pattern that is common for drugs that are not extensively metabolized. Estimates of this sort are useful for emphasizing that the MDMA dose required to produce neurotoxicity in humans may be within the range of commonly administered doses, despite the seemingly higher doses used in rodent studies.

However, such estimates require making assumptions about the mechanisms of neurotoxicity. For example, it is necessary to assume that the different species experience comparable drug effects when blood concentrations of drug are the same. This may not be true of neurotoxicity. Neuronal responses to focal ischemic/reperfusion injury show temporal differences between rats and baboons (Tagaya et al. 1997). Several other possible reasons for species differences in MDMA neurotoxicity have already been given in the paragraph on differences in vulnerabilities between the primate and the rat. In addition, species may differ in the brain concentration of drug produced by a given blood concentration. It is not known if this is the case with MDMA, although it does seem to be true for fenfluramine (Campbell 1995). In rats, MDMA concentrations in the brain are 7 to 10 times higher than in plasma (Chu et al. 1996). In a human fatality, postmortem MDMA concentrations were about 6 times higher in the brain than in the plasma (Rohrig and Prouty 1992), although postmortem drug redistribution may have occurred. If these data are reliable, rats may have similar peak brain levels to humans when plasma levels are the same.

Furthermore, if MDMA neurotoxicity is caused by a toxic metabolite, as some have suggested, then the more extensive metabolism of MDMA expected in smaller animals will lead to increased neurotoxicity. Formation of specific drug metabolites in different species is difficult to predict and few data are available on MDMA. Research on species differences in fenfluramine metabolism have led some to conclude that no nonhuman species provides a good model of possible human fenfluramine neurotoxicity (Caccia et al. 1995; Marchant et al. 1992). Because current data suggest that both MDMA and metabolite exposure may mediate neurotoxicity, more data are needed from more species before interspecies dose conversions can be made with any confidence.

Data from clinical MDMA studies show that there is a complex relationship between MDMA dose and blood levels of the drug and its metabolites (de la Torre et al. 2000a; Mas et al. 1999).
It appears that MDMA inactivates one of the enzymes that is important to its metabolism (an enzyme known as cytochrome p450 isozyme 2D6 or ‘CYP 2D6’) (Brady et al. 1986; Wu et al. 1997). As a result, small increases in dose can lead to large increases in drug exposure. When dose was increased from 125 mg to 150 mg, drug exposure (measured as area under the MDMA plasma concentration verses time curve) almost doubled in human volunteers (de la Torre et al. 2000a). At the same time, formation of some metabolites remained approximately constant. These complex dose-dependent pharmacokinetics in humans further increase the difficulty of estimating dose conversions between species. Nonetheless, these human studies with MDMA do suggest that doses above 125 mg may be associated with unexpectedly increased drug exposure and risks of acute toxicity.

**Extent of Neurotoxicity in Rats is Influenced by Environment, Especially Ambient Temperature**

A number of studies have explored the relationships between environmental temperature, animal core temperature, and neurotoxicity. In rats, MDMA can dose-dependently induce thermoregulatory impairment (Broening et al. 1995; Colado and Green 1995; Dafters 1994; 1995; Gordon et al. 1991) perhaps through alterations in hypothalamic functioning and drug-induced impairment in thermoregulatory behaviors. Resulting changes in animal temperature can alter neurotoxicity with hyperthermia increasing and hypothermia decreasing serotonergic depletions. Thus, degree of hyperthermia has been found to correlate with both long-term 5HT depletions in adult rats (Broening et al. 1995; Colado and Green 1995; Colado et al. 1993; Malberg and Seiden 1998) and long-term dopamine depletions in mice (Miller and O'Callaghan 1994). In addition to the ambient temperature, the degree of hyperthermia is influenced by the thermal conductivity of animal housing and animal hydration status (Dafters 1995; Gordon and Fogelson 1994).

The mechanisms by which temperature affects MDMA neurotoxicity are unclear. Plasma levels of MDMA in rats (Colado and Green 1995) and brain levels of MDMA in mice (Campbell 1996) do not appear to be influenced by changes in animal core temperature. MDMA-induced neurotransmitter release may be temperature sensitive (Sabol and Seiden 1998), although studies examining the temperature dependence of methamphetamine-induced DA release have reported conflicting findings (Bowyer et al. 1993; LaVoie and Hastings 1999). It may also be that increased temperature nonspecifically increases the rate of reactions and contributes to oxidative stress, as occurs in ischemic neurotoxicity (Globus et al. 1995). Prolonged hyperthermia has been shown to decrease mitochondrial immunoreactivity in some brain regions, suggesting decreased energy stores (Burrows and Meshul 1999). However, hyperthermia on its own does not selectively damage the serotonergic system.

Although hyperthermia increases neurotoxicity and hypothermia decreases it, MDMA neurotoxicity can occur without hyperthermia (Broening et al. 1995). In addition, the link between temperature and neurotoxicity has primarily been investigated in rodents. One study examining methamphetamine-induced neurotoxicity in vervet monkeys reported that hypothermia (induced by the NMDA antagonist dizocilpine) failed to protect against
Table 4.2. Studies of Drugs Modifying MDMA Neurotoxicity and Hyperthermia

<table>
<thead>
<tr>
<th>MDMA REGIMEN (dose, route)</th>
<th>OTHER INTERVENTION</th>
<th>CATEGORY OF OTHER INTERVENTION</th>
<th>OUTCOME OF MDMA + OTHER INTERVENTION</th>
<th>HYPER-THERMIA?</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/kg sc, twice daily for 4 d</td>
<td>1-tryptophan 400 mg/kg ip twice daily for 4 d, 30 min pre MDMA</td>
<td>5HT precursor</td>
<td>Some protection</td>
<td>NA</td>
<td>(Sprague et al. 1994)</td>
</tr>
<tr>
<td>20 mg/kg sc, twice daily for 4 d</td>
<td>5-hydroxytryptophan 50 mg/kg ip (with RO 4-4602 50 mg/kg) twice daily for 4 d, 30 min pre MDMA</td>
<td>5HT precursor with a peripheral decarboxylase inhibitor</td>
<td>Some protection</td>
<td>NA</td>
<td>(Sprague et al. 1994)</td>
</tr>
<tr>
<td>20 mg/kg d-MDMA sc, four times, every 2 hrs</td>
<td>d-fenfluramine 25 mg/kg sc, 20 min before 1st and 3rd injection MDMA</td>
<td>5HT releaser</td>
<td>Some protection</td>
<td>Attenuated hyperthermia</td>
<td>(Miller and O’Callaghan 1994)</td>
</tr>
<tr>
<td>40 mg/kg sc</td>
<td>fluoxetine (10 mg/kg ip), 1 hr pre MDMA</td>
<td>5HT reuptake inhibitor</td>
<td>Protection</td>
<td>Hyperthermia</td>
<td>(Malberg et al. 1996)</td>
</tr>
<tr>
<td>10 mg/kg sc</td>
<td>DOI 2 mg/kg ip, 15 min pre MDMA</td>
<td>5HT₂ agonist</td>
<td>Exacerbated toxicity (5HT decrease in STR)</td>
<td>NA</td>
<td>(Gudelsky et al. 1994)</td>
</tr>
<tr>
<td>30 mg/kg MDMA HCl sc</td>
<td>ketanserin 5 mg/kg sc, 15 min pre MDMA</td>
<td>5HT₂ antagonist</td>
<td>Protection</td>
<td>Attenuated hyperthermia</td>
<td>(Aguirre et al. 1998a)</td>
</tr>
<tr>
<td>40 mg/kg sc</td>
<td>ketanserin (6 mg/kg ip), 1 hr pre MDMA</td>
<td>5HT₂ antagonist</td>
<td>Protection</td>
<td>Hypothermia occurred and manual warming blocked protection</td>
<td>(Malberg et al. 1996)</td>
</tr>
<tr>
<td>30 mg/kg sc</td>
<td>MDL-28133A 0.03, 0.1, 0.3, 1.0 mg/kg sc, along with MDMA</td>
<td>5HT₂ antagonist</td>
<td>Some protection by 0.1, 0.3, or 1.0 mg/kg but not by 0.03 mg/kg</td>
<td>NA</td>
<td>(Schmidt et al. 1992a)</td>
</tr>
<tr>
<td>30 mg/kg sc</td>
<td>MDL-28133A 1 mg/kg sc, along with MDMA</td>
<td>5HT₂ antagonist</td>
<td>Some protection</td>
<td>NA</td>
<td>(Schmidt et al. 1992a)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>(±)-MDL 11,939 5 mg/kg sc, along with MDMA</td>
<td>5HT₂ antagonist</td>
<td>Some protection</td>
<td>NA</td>
<td>(Schmidt et al. 1991) also Schmidt and Kehne 1990)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>R-(+)-MDL 11,939 5 mg/kg sc, along with MDMA</td>
<td>5HT₂ antagonist</td>
<td>Some protection</td>
<td>NA</td>
<td>(Schmidt et al. 1991)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>S-(−)-MDL 11,939 5 mg/kg sc, along with MDMA</td>
<td>5HT₂ antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Schmidt et al. 1991)</td>
</tr>
</tbody>
</table>
Table 4.2. Studies of Drugs Modifying MDMA Neurotoxicity and Hyperthermia

<table>
<thead>
<tr>
<th>MDMA REGIMEN (dose, route)</th>
<th>OTHER INTERVENTION</th>
<th>CATEGORY OF OTHER INTERVENTION</th>
<th>OUTCOME OF MDMA + OTHER INTERVENTION</th>
<th>HYPER-THERMIA?</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/kg sc</td>
<td>ritanserin 5 mg/kg sc, along with MDMA</td>
<td>5HT2 antagonist</td>
<td>Some protection</td>
<td>NA</td>
<td>(Schmidt et al. 1991)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>MDL 11,939 5 mg/kg sc, post 3 hr MDMA</td>
<td>5HT2 antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Schmidt et al. 1991)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>MDL 11,939 5 mg/kg sc, along with MDMA</td>
<td>5HT2 antagonist</td>
<td>Protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990a)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>MDL 11,939 5 mg/kg sc, post 1 hr MDMA</td>
<td>5HT2 antagonist</td>
<td>Less protection than earlier intervention</td>
<td>NA</td>
<td>(Schmidt et al. 1990a)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>MDL 11,939 5 mg/kg sc, post 3 hr MDMA</td>
<td>5HT2 antagonist</td>
<td>Less protection than earlier intervention</td>
<td>NA</td>
<td>(Schmidt et al. 1990a)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>MDL 11,939 5 mg/kg sc, post 6 hr MDMA</td>
<td>5HT2 antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990a)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>MDL 11,939 5 mg/kg sc, along with MDMA</td>
<td>5HT2 antagonist</td>
<td>Some protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990a)</td>
</tr>
<tr>
<td>20 or 30 mg/kg sc</td>
<td>MDL 11,939 5 mg/kg sc, along with MDMA</td>
<td>5HT2 antagonist</td>
<td>Protection</td>
<td>Attenuated hyperthermia</td>
<td>(Schmidt et al. 1990b)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>MDL 26,508 5 mg/kg, along with MDMA</td>
<td>5HT2 antagonist</td>
<td>Protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990c)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>MDL 11,939 5 mg/kg, along with MDMA</td>
<td>5HT2 antagonist</td>
<td>Protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990c)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>ritanserin 1, 5 mg/kg sc, 15 m pre MDMA</td>
<td>5HT2 antagonist</td>
<td>Protection</td>
<td>NA</td>
<td>(Johnson et al. 1993)</td>
</tr>
<tr>
<td>30 mg/kg sc</td>
<td>MDL 100,907 0.01, 0.03, 0.1, 0.3, and 1 mg/kg sc, along with MDMA</td>
<td>5HT2 antagonist</td>
<td>Dose-dependent protection</td>
<td>NA</td>
<td>(Schmidt et al. 1992b)</td>
</tr>
<tr>
<td>30 mg/kg sc</td>
<td>MDL-28133A 1 mg/kg sc and L-Dopa 100 mg/kg ip (with carbidopa 25 mg/kg ip), along with (carbidopa was 30 m pre) MDMA</td>
<td>5HT2 antagonist and DA precursor and peripheral Dopa decarboxylase inhibitor</td>
<td>No protection</td>
<td>NA</td>
<td>(Schmidt et al. 1992a)</td>
</tr>
<tr>
<td>MDMA REGIMEN (dose, route)</td>
<td>OTHER INTERVENTION</td>
<td>CATEGORY OF OTHER INTERVENTION</td>
<td>OUTCOME OF MDMA + OTHER INTERVENTION</td>
<td>HYPER-THERMIA?</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>20 mg/kg ip</td>
<td>ondansetron 0.5 mg/kg ip, 5 m pre and 55 m post MDMA</td>
<td>5HT3 antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Colado and Green 1994)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>MDL 73,147 5 mg/kg, along with MDMA</td>
<td>5HT3 antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990c)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>prazosin 3 mg/kg, along with MDMA</td>
<td>Alpha-1 antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990c)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>chloral hydrate 400 mg/kg ip followed by 30-100 mg/kg supplements to maintain anesthesia through 3 hr post, 30 m pre MDMA</td>
<td>Anesthetic</td>
<td>Protection</td>
<td>Attenuated hyperthermia; high ambient temperature did not alter protection</td>
<td>(Schmidt et al. 1990b)</td>
</tr>
<tr>
<td>20 mg/kg sc twice, 7 hr apart</td>
<td>tripelemamine 20 mg/kg ip twice 7 hr apart, along with MDMA</td>
<td>Antihistamine; but also &quot;moderate&quot; hydroxyl radical scavenger.</td>
<td>Some protection</td>
<td>Attenuated hyperthermia</td>
<td>(Yeh et al. 1999)</td>
</tr>
<tr>
<td>20 mg/kg sc twice, 7 hr apart</td>
<td>pyrilamine, 20 mg/kg ip twice 7 hr apart, along with MDMA</td>
<td>Antihistamine; but also &quot;potent&quot; hydroxyl radical scavenger, SSRI, and &quot;moderate&quot; DA reuptake inhibitor.</td>
<td>Exacerbated toxicity</td>
<td>Enhanced hyperthermia</td>
<td>(Yeh et al. 1999)</td>
</tr>
<tr>
<td>20 mg/kg sc twice, 7 hr apart</td>
<td>diphenhydramine 20 mg/kg ip twice 7 hr apart, along with MDMA</td>
<td>Antihistamine; but also inhibits p450 and is &quot;moderate&quot; DA uptake inhibitor.</td>
<td>Some protection</td>
<td>Hyperthermia</td>
<td>(Yeh et al. 1999)</td>
</tr>
</tbody>
</table>
### Table 4.2. Studies of Drugs Modifying MDMA Neurotoxicity and Hyperthermia

<table>
<thead>
<tr>
<th>MDMA REGIMEN (dose, route)</th>
<th>OTHER INTERVENTION</th>
<th>CATEGORY OF OTHER INTERVENTION</th>
<th>OUTCOME OF MDMA + OTHER INTERVENTION</th>
<th>HYPER- THERMIA?</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/kg sc twice, 6 hr apart</td>
<td>chlorpheniramine 10 or 25 mg/kg ip twice, 6 hr apart, along with MDMA</td>
<td>Antihistamine; but also inhibits 5HT uptake, inhibits p450; hydroxyl scavenger; &quot;moderate&quot; DA uptake inhibitor.</td>
<td>Protection</td>
<td>Hypothermia</td>
<td>(Yeh et al. 1999)</td>
</tr>
<tr>
<td>20 mg/kg sc twice, 7 hr apart</td>
<td>chlorpheniramine 20 mg/kg ip twice, 7 hr apart, along with MDMA</td>
<td>Antihistamine; but also inhibits 5HT uptake, inhibits p450; hydroxyl scavenger; &quot;moderate&quot; DA uptake inhibitor.</td>
<td>Protection</td>
<td>Hypothermia</td>
<td>(Yeh et al. 1999)</td>
</tr>
<tr>
<td>20 mg/kg sc twice, 7 hr apart</td>
<td>chlorpheniramine 20 mg/kg ip twice, 7 hr apart, 3 hrs post MDMA</td>
<td>Antihistamine; but also inhibits 5HT uptake, inhibits p450; hydroxyl scavenger; &quot;moderate&quot; DA uptake inhibitor.</td>
<td>Protection</td>
<td>Hypothermia</td>
<td>(Yeh et al. 1999)</td>
</tr>
<tr>
<td>20 mg/kg sc twice, 7 hr apart</td>
<td>chlorpheniramine 20 mg/kg ip twice, 7 hr apart, 6 hrs post MDMA</td>
<td>Antihistamine; but also inhibits 5HT uptake, inhibits p450; hydroxyl scavenger; &quot;moderate&quot; DA uptake inhibitor.</td>
<td>Protection</td>
<td>Hypothermia until 6 hr then hypothermia</td>
<td>(Yeh et al. 1999)</td>
</tr>
<tr>
<td>20 mg/kg ip</td>
<td>alpha-lipoic acid, 100 mg/kg ip twice daily for 2 days, last injection was 30 m pre MDMA</td>
<td>Antioxidant</td>
<td>&quot;Full&quot; protection</td>
<td>Unchanged</td>
<td>(Aguirre et al. 1999)</td>
</tr>
<tr>
<td>10 mg/kg ip, every 2 hr for 4 injections</td>
<td>ascorbic acid, 100 mg/kg ip, every 2 hr for 5 injections</td>
<td>Antioxidant</td>
<td>Protection</td>
<td>Unchanged</td>
<td>(Shankaran et al. 2001)</td>
</tr>
<tr>
<td>MDMA REGIMEN (dose, route)</td>
<td>OTHER INTERVENTION</td>
<td>CATEGORY OF OTHER INTERVENTION</td>
<td>OUTCOME OF MDMA + OTHER INTERVENTION</td>
<td>HYPER-THERMIA?</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------</td>
<td>-------------------------------</td>
<td>-------------------------------------</td>
<td>----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>sodium ascorbate 250 mg/kg ip twice 5.5 hr apart, 30 m pre, 5 hr post MDMA</td>
<td>Antioxidant</td>
<td>Protection</td>
<td>NA</td>
<td>(Gudelsky 1996)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>cysteine 500 mg/kg ip twice 5.5 hr apart, 30 m pre, 5 hr post MDMA</td>
<td>Antioxidant</td>
<td>Protection</td>
<td>NA</td>
<td>(Gudelsky 1996)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>cysteine 1 g/kg, along with MDMA</td>
<td>Antioxidant</td>
<td>Protection</td>
<td>NA</td>
<td>(Schmidt and Kehne 1990)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>1-benzyl-piperazine 10 mg/kg ip twice daily for 3 d, along with MDMA</td>
<td>Benzylpiperazine derivative</td>
<td>No protection</td>
<td>NA</td>
<td>(Hashimoto et al. 1992b)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>1-piperonyl-piperazine 10 mg/kg ip twice daily for 3 d, along with MDMA</td>
<td>Benzylpiperazine derivative</td>
<td>Some protection</td>
<td>NA</td>
<td>(Hashimoto et al. 1992b)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>p-chlorobenzyl-piperazine 10 mg/kg ip twice daily for 3 d, along with MDMA</td>
<td>Benzylpiperazine derivative</td>
<td>Some protection</td>
<td>NA</td>
<td>(Hashimoto et al. 1992b)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>p-methoxy-benzyl-piperazine 10 mg/kg ip twice daily for 3 d, along with MDMA</td>
<td>Benzylpiperazine derivative</td>
<td>No protection</td>
<td>NA</td>
<td>(Hashimoto et al. 1992b)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>p-nitro-benzyl-piperazine 10 mg/kg ip twice daily for 3 d, along with MDMA</td>
<td>Benzylpiperazine derivative</td>
<td>Some protection</td>
<td>NA</td>
<td>(Hashimoto et al. 1992b)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>desipramine 10 mg/kg ip twice daily for 3 d, along with MDMA</td>
<td>Benzylpiperazine derivative</td>
<td>No protection</td>
<td>NA</td>
<td>(Hashimoto et al. 1992b)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>l-piperonyl-piperazine 20 mg/kg ip twice daily for 3 d, along with MDMA</td>
<td>Benzylpiperazine derivative, compound with 3,4-methylenedioxyphenyl group</td>
<td>Some protection</td>
<td>NA</td>
<td>(Hashimoto et al. 1992b)</td>
</tr>
<tr>
<td>MDMA REGIMEN (dose, route)</td>
<td>OTHER INTERVENTION</td>
<td>CATEGORY OF OTHER INTERVENTION</td>
<td>OUTCOME OF MDMA + OTHER INTERVENTION</td>
<td>HYPER-THERMIA?</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------</td>
<td>--------------------------------</td>
<td>--------------------------------------</td>
<td>----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>pindolol 5 mg/kg, along with MDMA</td>
<td>Beta-adrenoceptor antagonist and nonselective 5HT1 antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990c)</td>
</tr>
<tr>
<td>10 mg/kg sc, five times, every 6 hr</td>
<td>Flunarizine 30 mg/kg ip, 15 m pre each dose MDMA</td>
<td>Calcium channel blocker</td>
<td>Protection</td>
<td>NA</td>
<td>(Johnson et al. 1992b)</td>
</tr>
<tr>
<td>15 mg/kg ip</td>
<td>2-Deoxy-D-Glucose (2-DG) 500 mg/kg sc, 4.5, 2.5, 0.5 hr pre and 1.5, 3.5 hr post MDMA</td>
<td>Competitive inhibitor of glucose uptake and metabolism</td>
<td>Protection</td>
<td>Hypothermia occurred and manual warming blocked protection</td>
<td>(Hervias et al. 2000)</td>
</tr>
<tr>
<td>40 mg/kg sc</td>
<td>CGS-19755 25 or 50 mg/kg twice, 15 m pre, 40 m post MDMA</td>
<td>Competitive NMDA (AMPA) antagonist</td>
<td>Protection</td>
<td>Hypothermia</td>
<td>(Farfel and Seiden 1995)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>alpha-methyl-para-tyrosine 100 mg/kg twice, 3 h pre and along with MDMA</td>
<td>Competitive tyrosine hydroxylase inhibitor</td>
<td>Protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990c); also (Schmidt and Kehne 1990)</td>
</tr>
<tr>
<td>20 mg/kg sc twice, 6 hr apart</td>
<td>ethanol 0.5 g/kg IP twice, 6 hr apart, along with MDMA</td>
<td>Complex</td>
<td>No protection</td>
<td>Unchanged</td>
<td>(Yeh 1999)</td>
</tr>
<tr>
<td>20 mg/kg sc twice, 6 hr apart</td>
<td>ethanol 1.0 g/kg IP twice, 6 hr apart, along with MDMA</td>
<td>Complex</td>
<td>No protection</td>
<td>Hypothermia</td>
<td>(Yeh 1999)</td>
</tr>
<tr>
<td>20 mg/kg sc twice, 6 hr apart</td>
<td>ethanol 2.0 g/kg IP twice, 6 hr apart, along with MDMA</td>
<td>Complex</td>
<td>No protection</td>
<td>Hypothermia</td>
<td>(Yeh 1999)</td>
</tr>
<tr>
<td>20 mg/kg ip</td>
<td>gamma-butyrolactone 400 mg/kg ip, 5 m pre and 55 m post MDMA</td>
<td>Complex, GHB analog/precursor</td>
<td>Some protection</td>
<td>NA</td>
<td>(Colado and Green 1994)</td>
</tr>
<tr>
<td>MDMA REGIMEN (dose, route)</td>
<td>OTHER INTERVENTION</td>
<td>CATEGORY OF OTHER INTERVENTION</td>
<td>OUTCOME OF MDMA + OTHER INTERVENTION</td>
<td>HYPER-THERMIA?</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------</td>
<td>--------------------------------</td>
<td>-------------------------------------</td>
<td>----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>N-alpha-dimethylpiperonylamine 20 mg/kg ip twice daily for 3 d, along with MDMA</td>
<td>Compound with 3,4-methylenedioxyphenyl group</td>
<td>No protection</td>
<td>NA</td>
<td>(Hashimoto et al. 1992a)</td>
</tr>
<tr>
<td>15 mg/kg ip</td>
<td>haloperidol, 2 mg/kg ip, 5 m pre and 55 m post MDMA</td>
<td>DA antagonist</td>
<td>Some protection</td>
<td>Normothermia; protection lost in high ambient temperature</td>
<td>(Colado et al. 1999c)</td>
</tr>
<tr>
<td>30 mg/kg MDMA HCl sc</td>
<td>haloperidol, 2 mg/kg ip, 15 min pre MDMA</td>
<td>DA antagonist</td>
<td>Protection</td>
<td>Hypothermia</td>
<td>(Aguirre et al. 1998a)</td>
</tr>
<tr>
<td>20 mg/kg ip twice, 6 hr apart</td>
<td>haloperidol 2 mg/kg ip, 10 m pre each MDMA injection MDMA</td>
<td>DA antagonist</td>
<td>Some protection</td>
<td>Attenuated hyperthermia</td>
<td>(Hewitt and Green 1994)</td>
</tr>
<tr>
<td>7.5 mg/kg sc every 2 hr x 4</td>
<td>haloperidol 1 mg/kg ip every 2 hr x 4, 30 m pre each MDMA injection MDMA</td>
<td>DA antagonist</td>
<td>Some protection</td>
<td>NA</td>
<td>(Finnegan et al. 1993)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>haloperidol 1 mg/kg sc, post 3 hr MDMA</td>
<td>DA antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990a)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>haloperidol 2 mg/kg ip, along with MDMA</td>
<td>DA antagonist</td>
<td>Some protection</td>
<td>Unchanged</td>
<td>(Schmidt et al. 1990b)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>haloperidol 2 mg/kg ip, along with MDMA</td>
<td>DA antagonist</td>
<td>Protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990c)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>alpha-methyl-para-tyrosine 120 mg/kg ip, 90 m pre MDMA</td>
<td>DA depletor</td>
<td>Moderate protection</td>
<td>NA</td>
<td>(Stone et al. 1988)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>unilateral 8-OHDA 12 ug in substantia niagra, 7 d pre MDMA</td>
<td>DA neurotoxin</td>
<td>No protection on both lesioned and unlesioned sides</td>
<td>NA</td>
<td>(Schmidt et al. 1990c)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>bilateral 8-OHDA 12 ug in substantia niagra, 7 d pre MDMA</td>
<td>DA neurotoxin</td>
<td>Some protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990c)</td>
</tr>
</tbody>
</table>
Table 4.2. Studies of Drugs Modifying MDMA Neurotoxicity and Hyperthermia

<table>
<thead>
<tr>
<th>MDMA REGIMEN (dose, route)</th>
<th>OTHER INTERVENTION</th>
<th>CATEGORY OF OTHER INTERVENTION</th>
<th>OUTCOME OF MDMA + OTHER INTERVENTION</th>
<th>HYPER-THERMIA?</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg/kg ip</td>
<td>L-Dopa 25 mg/kg and benserazide 6.25 mg/kg ip, 2 hr post MDMA</td>
<td>DA precursor and peripheral Dopa decarboxylase inhibitor</td>
<td>No protection or exacerbation</td>
<td>Prolonged hyperthermia</td>
<td>(Colado et al. 1999c)</td>
</tr>
<tr>
<td>20 mg/kg d-MDMA sc, four times, every 2 hrs</td>
<td>cocaine HCl 100 mg/kg sc, 20 m before 1st and 3rd injection MDMA</td>
<td>DA reuptake blocker</td>
<td>No protection</td>
<td>Attenuated hyperthermia</td>
<td>(Miller and O'Callaghan 1994)</td>
</tr>
<tr>
<td>10 mg/kg ip every 2 hrs x 4</td>
<td>mazindol 5 mg/kg ip repeated 4 times, 30 min pre MDMA</td>
<td>DA uptake inhibitor</td>
<td>Protection</td>
<td>Unchanged</td>
<td>(Shankaran et al. 1999b)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>GBR 12909 20 mg/kg ip, 12 m pre MDMA</td>
<td>DA uptake inhibitor</td>
<td>Moderate protection</td>
<td>NA</td>
<td>(Stone et al. 1988)</td>
</tr>
<tr>
<td>15 mg/kg ip</td>
<td>N-tert-Butyl-alpha-Phenylnitrone 120 mg/kg route??? twice, 125 m apart, 10 m pre, 120 m post MDMA</td>
<td>Free radical scavenger</td>
<td>Some protection</td>
<td>Unchanged</td>
<td>(Colado et al. 1997b)</td>
</tr>
<tr>
<td>10 mg/kg ip</td>
<td>N-tert-Butyl-alpha-Phenylnitrone 150 mg/kg IP twice, 10 m pre, 120 m post MDMA</td>
<td>Free radical scavenger</td>
<td>Some protection</td>
<td>Attenuated hyperthermia</td>
<td>(Colado and Green 1995)</td>
</tr>
<tr>
<td>10 mg/kg sc, twice daily for 4 days</td>
<td>sodium salicylate (3.1 - 100 mg/kg ip, repeated), 1 hr pre MDMA</td>
<td>Free radical trapper, but also antipyretic</td>
<td>No protection</td>
<td>Hyperthermia</td>
<td>(Yeh 1997)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>sodium salicylate (12.5 - 400 mg/kg ip), 1 hr pre MDMA</td>
<td>Free radical trapper, but also antipyretic</td>
<td>Exacerbated toxicity (5HT decrease)</td>
<td>Increased</td>
<td>(Yeh 1997)</td>
</tr>
<tr>
<td>20 mg/kg sc twice, 6 hr apart</td>
<td>N-tert-Butyl-alpha-Phenylnitrone (50, 100, 200, or 400mg/kg IP and ethanol 0.5 or 1.0 g/kg IP) twice, 6 hr apart, along with MDMA</td>
<td>Free radical trapping agent</td>
<td>Protection</td>
<td>Hypothermia</td>
<td>(Yeh 1997)</td>
</tr>
<tr>
<td>15 mg/kg ip</td>
<td>pentobarbitone 25 mg/kg ip twice, 5 min pre, 55 min post MDMA</td>
<td>GABA enhancer</td>
<td>No protection</td>
<td>&quot;Brief&quot; hypothermia</td>
<td>(Colado et al. 1999a)</td>
</tr>
<tr>
<td>MDMA REGIMEN (dose, route)</td>
<td>OTHER INTERVENTION</td>
<td>CATEGORY OF OTHER INTERVENTION</td>
<td>OUTCOME OF MDMA + OTHER INTERVENTION</td>
<td>HYPER-THERMIA?</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------</td>
<td>----------------</td>
<td>----------</td>
</tr>
<tr>
<td>15 mg/kg ip</td>
<td>pentobarbitone 40 mg/kg ip twice, 5 min pre, 55 min post MDMA</td>
<td>GABA enhancer</td>
<td>Protection</td>
<td>&quot;Sustained hypothermia; protection abolished by induced hyperthermia&quot;</td>
<td>(Colado et al. 1999a)</td>
</tr>
<tr>
<td>20 mg/kg ip</td>
<td>pentobarbitone na (25 mg/kg ip), 5 min pre and 55 min post MDMA</td>
<td>GABA enhancer</td>
<td>Some protection</td>
<td>NA</td>
<td>(Colado and Green 1994)</td>
</tr>
<tr>
<td>20 mg/kg ip, twice, 6 hr apart</td>
<td>chlormethiazole 100 mg/kg ip, 10 min pre each MDMA injection MDMA</td>
<td>GABA enhancer</td>
<td>Some protection</td>
<td>Normothermia</td>
<td>(Hewitt and Green 1994)</td>
</tr>
<tr>
<td>15 mg/kg ip</td>
<td>chlormethiazole 50 mg/kg ip, 5 min pre, 55 min post MDMA</td>
<td>GABA potentiator</td>
<td>Protection</td>
<td>Modest hypothermia; protection reduced by high ambient temperature</td>
<td>(Colado et al. 1998)</td>
</tr>
<tr>
<td>40 mg/kg sc</td>
<td>Dizocilpine (MK-801) 2.5 mg/kg and hot ambient temperature, 15 min pre MDMA</td>
<td>Glutamate receptor antagonist; Heat</td>
<td>No protection</td>
<td>Hyperthermia due to ambient temperature</td>
<td>(Farfel and Seiden 1995)</td>
</tr>
<tr>
<td>50 mg/kg ip, daily for 3 d</td>
<td>Human SOD expression, - MDMA</td>
<td>Increased endogenous antioxidant enzymes</td>
<td>-</td>
<td>-</td>
<td>(Cadet et al. 1995)</td>
</tr>
<tr>
<td>50 mg/kg ip, daily for 3 d</td>
<td>Human SOD expression, - MDMA</td>
<td>Increased endogenous antioxidant enzymes</td>
<td>-</td>
<td>-</td>
<td>(Cadet et al. 1995)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>reserpine 5 mg/kg sc, 18 hr pre MDMA</td>
<td>Inhibits vesicular storage of monoamines</td>
<td>Some protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990c); also (Schmidt and Kehne 1990)</td>
</tr>
<tr>
<td>30 mg/kg ip</td>
<td>reserpine 5 mg/kg ip, 24 hr pre MDMA</td>
<td>Inhibits vesicular storage of monoamines</td>
<td>No protection</td>
<td>NA</td>
<td>(Hekmatpanah et al. 1989)</td>
</tr>
</tbody>
</table>
Table 4.2. Studies of Drugs Modifying MDMA Neurotoxicity and Hyperthermia

<table>
<thead>
<tr>
<th>MDMA REGIMEN (dose, route)</th>
<th>OTHER INTERVENTION</th>
<th>CATEGORY OF OTHER INTERVENTION</th>
<th>OUTCOME OF MDMA + OTHER INTERVENTION</th>
<th>HYPER-THERMIA?</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/kg sc</td>
<td>reserpine 5 mg/kg, 12 hr pre MDMA</td>
<td>Inhibits vesicular storage of monoamines</td>
<td>Protection</td>
<td>NA</td>
<td>(Stone et al. 1988)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>monofluoromethyl DOPA 100 mg/kg IP daily for 3 d, 3, 2 and 1 d pre MDMA</td>
<td>Irreversible l- aromatic amino acid decarboxylase inhibitor</td>
<td>Some protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990c); also (Schmidt and Kehne 1990)</td>
</tr>
<tr>
<td>15 mg/kg ip</td>
<td>AR-B15896AR 20 mg/kg ip twice, 5 m pre, 55 m post MDMA</td>
<td>Low affinity NMDA channel blocker</td>
<td>No protection</td>
<td>Unchanged</td>
<td>(Colado et al. 1998)</td>
</tr>
<tr>
<td>7.5 mg/kg sc every 2 hr x 4</td>
<td>flunarizine 15 mg/kg ip every 2 hr x 4, 30 m pre each MDMA injection MDMA</td>
<td>L-type calcium channel antagonist</td>
<td>Moderate Protection</td>
<td>NA</td>
<td>(Finnegan et al. 1993)</td>
</tr>
<tr>
<td>7.5 mg/kg sc every 2 hr x 4</td>
<td>flunarizine 20 mg/kg ip every 2 hr x 4, 30 m pre each MDMA injection MDMA</td>
<td>L-type calcium channel antagonist</td>
<td>Protection</td>
<td>NA</td>
<td>(Finnegan et al. 1993)</td>
</tr>
<tr>
<td>7.5 mg/kg sc every 2 hr x 4</td>
<td>haloperidol 1 mg/kg ip every 2 hr x 4, 30 m pre each MDMA injection MDMA</td>
<td>L-type calcium channel antagonist</td>
<td>Some protection</td>
<td>NA</td>
<td>(Finnegan et al. 1993)</td>
</tr>
<tr>
<td>7.5 mg/kg sc every 2 hr x 4</td>
<td>nifedipine 25 or 30 mg/kg ip three times, 30 m pre 1st, 2nd, and 4th MDMA injections MDMA</td>
<td>L-type calcium channel antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Finnegan et al. 1993)</td>
</tr>
<tr>
<td>7.5 mg/kg sc every 2 hr x 4</td>
<td>verapamil 20 mg/kg ip three times, 30 m pre 1st, 2nd, and 4th MDMA injections MDMA</td>
<td>L-type calcium channel antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Finnegan et al. 1993)</td>
</tr>
<tr>
<td>7.5 mg/kg sc every 2 hr x 4</td>
<td>verapamil 50 mg/kg ip three times, 30 m pre 1st, 2nd, and 4th MDMA injections MDMA</td>
<td>L-type calcium channel antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Finnegan et al. 1993)</td>
</tr>
<tr>
<td>40 mg/kg sc</td>
<td>L-deprenyl (2 mg/kg IP), 30 m pre MDMA</td>
<td>MAO-B inhibitor</td>
<td>Some protection</td>
<td>NA</td>
<td>(Sprague and Nichols 1995a)</td>
</tr>
</tbody>
</table>
### Table 4.2. Studies of Drugs Modifying MDMA Neurotoxicity and Hyperthermia

<table>
<thead>
<tr>
<th>MDMA REGIMEN (dose, route)</th>
<th>OTHER INTERVENTION</th>
<th>CATEGORY OF OTHER INTERVENTION</th>
<th>OUTCOME OF MDMA + OTHER INTERVENTION</th>
<th>HYPER-</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg/kg sc MDL-72974 (1.25 mg/kg ip), 30 min pre MDMA</td>
<td>MAO-B inhibitor</td>
<td>Some protection</td>
<td>NA</td>
<td>(Sprague and Nichols 1995a)</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg sc desipramine 10 mg/kg ip, 60 min pre MDMA</td>
<td>NE reuptake inhibitor</td>
<td>Protection</td>
<td>NA</td>
<td>(Shankaran and Gudelsky 1998)</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg ip chlormethiazole 50 mg/kg ip twice, 5 m pre, 55 m post MDMA</td>
<td>Neuroprotective</td>
<td>Protection</td>
<td>NA</td>
<td>(Colado et al. 1993)</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg ip chlormethiazole 100 mg/kg ip, 20 m post MDMA</td>
<td>Neuroprotective</td>
<td>Some protection</td>
<td>Attenuated hyperthermia</td>
<td>(Colado et al. 1993)</td>
<td></td>
</tr>
<tr>
<td>40 mg/kg ip Nω-nitro-L-arginine (10 mg/kg x 2), 30 m pre, 16 h post MDMA</td>
<td>Nitric oxide synthase inhibitor</td>
<td>Partial protection of 5HT in 2 of 6 regions</td>
<td>Unchanged</td>
<td>(Zheng and Laverty 1998)</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg sc, every 2 hr x 4 L-NAME (150 mg/kg ip, twice), 30 min prior to 1st and 4th MDMA doses MDMA</td>
<td>Nitric oxide synthase inhibitor</td>
<td>Some protection</td>
<td>NA</td>
<td>(Finnegan and Taraska 1997)</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg sc, every 2 hr x 4 NG-nitro-L-arginine (50 mg/kg ip, twice daily for 4 days), last injection was 14 hr pre MDMA MDMA</td>
<td>Nitric oxide synthase inhibitor</td>
<td>No protection</td>
<td>NA</td>
<td>(Finnegan and Taraska 1997)</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg sc every 2 hrs x 4 Dizocilpine (MK-801) 2 mg/kg sc every 2 hrs x 4, along with MDMA</td>
<td>NMDA antagonist</td>
<td>Moderate Protection</td>
<td>NA</td>
<td>(Finnegan and Taraska 1996)</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg sc, d-MDMA, every 2 hr x 4 Dizocilpine (MK-801) (1.0 mg/kg sc, twice), 30 min pre 1st and 3rd dose MDMA</td>
<td>NMDA antagonist</td>
<td>Protection</td>
<td>Hypothermia noted</td>
<td>(Miller and O'Callaghan 1995)</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg sc, d-MDMA, every 2 hr x 4 Dizocilpine (MK-801) (1.0 mg/kg sc, twice) 30 min pre 1st and 3rd dose MDMA</td>
<td>NMDA antagonist</td>
<td>Protection</td>
<td>Normothermia</td>
<td>(Miller and O'Callaghan 1995)</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg sc, d-MDMA, every 2 hr x 4 Dizocilpine (MK-801) (1.0 mg/kg sc, twice), 30 min pre 1st and 3rd dose MDMA</td>
<td>NMDA antagonist</td>
<td>Protection</td>
<td>Hypothermia noted</td>
<td>(Miller and O'Callaghan 1995)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4.2. Studies of Drugs Modifying MDMA Neurotoxicity and Hyperthermia

<table>
<thead>
<tr>
<th>MDMA REGIMEN (dose, route)</th>
<th>OTHER INTERVENTION</th>
<th>CATEGORY OF OTHER INTERVENTION</th>
<th>OUTCOME OF MDMA + OTHER INTERVENTION</th>
<th>HYPERTERMIA?</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/kg ip twice, 6 hr apart</td>
<td>Dizocilpine (MK-801) 1 mg/kg, 10 m pre each MDMA injection MDMA</td>
<td>NMDA antagonist</td>
<td>Some protection</td>
<td>Attenuated hyperthermia</td>
<td>(Hewitt and Green 1994)</td>
</tr>
<tr>
<td>20 mg/kg d-MDMA sc, four times, every 2 hrs</td>
<td>Dizocilpine (MK0801) 1.0 mg/kg sc, 20 m before 1st and 3rd injection MDMA</td>
<td>NMDA antagonist</td>
<td>Some protection</td>
<td>Hypothermia occurred and high ambient temperature blocked protection</td>
<td>(Miller and O'Callaghan 1994)</td>
</tr>
<tr>
<td>20 mg/kg d-MDMA sc, four times, every 2 hrs</td>
<td>Dizocilpine (MK-801) (1.0 mg/kg sc, twice), 20 m before 1st and 3rd injection MDMA</td>
<td>NMDA antagonist</td>
<td>Protection</td>
<td>NA</td>
<td>(O'Callaghan and Miller 1994)</td>
</tr>
<tr>
<td>20 mg/kg ip twice, 5 m pre, 55 m post MDMA</td>
<td>Dizocilpine (MK-801) 1 mg/kg ip twice, 5 m pre, 55 m post MDMA</td>
<td>NMDA antagonist</td>
<td>Some protection</td>
<td>NA</td>
<td>(Colado et al. 1993)</td>
</tr>
<tr>
<td>25 mg/kg d-MDMA sc, every 2 hr x 4</td>
<td>Dizocilpine (MK-801) 1.0 mg/kg sc, 30 m pre 1st and 3rd MDMA injections MDMA</td>
<td>NMDA antagonist</td>
<td>NA</td>
<td>NA</td>
<td>(Miller and O'Callaghan 1993)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>Dizocilpine (MK-801) 2.5 mg/kg, 15 m pre MDMA</td>
<td>NMDA antagonist</td>
<td>Some protection</td>
<td>NA</td>
<td>(Farfel et al. 1992)</td>
</tr>
<tr>
<td>40 mg/kg sc</td>
<td>Dizocilpine (MK-801) 0.5 mg/kg, 15 m pre MDMA</td>
<td>NMDA antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Farfel et al. 1992)</td>
</tr>
<tr>
<td>40 mg/kg sc</td>
<td>Dizocilpine (MK-801) 1.0 mg/kg, 15 m pre MDMA</td>
<td>NMDA antagonist</td>
<td>No protection</td>
<td>NA</td>
<td>(Farfel et al. 1992)</td>
</tr>
<tr>
<td>40 mg/kg sc</td>
<td>Dizocilpine (MK-801) 2.5 mg/kg, 15 m pre MDMA</td>
<td>NMDA antagonist</td>
<td>Some protection</td>
<td>NA</td>
<td>(Farfel et al. 1992)</td>
</tr>
<tr>
<td>10 mg/kg sc five times, every 6 hr</td>
<td>Dextrophan 7.5-45.0 m/kg five times, every 6 hr, 20 m pre each injection MDMA</td>
<td>NMDA antagonist</td>
<td>Protection (dose-dependent)</td>
<td>NA</td>
<td>(Finnegan et al. 1990)</td>
</tr>
</tbody>
</table>
### Table 4.2. Studies of Drugs Modifying MDMA Neurotoxicity and Hyperthermia

<table>
<thead>
<tr>
<th>MDMA REGIMEN (dose, route)</th>
<th>OTHER INTERVENTION</th>
<th>CATEGORY OF OTHER INTERVENTION</th>
<th>OUTCOME OF MDMA + OTHER INTERVENTION</th>
<th>HYPER-THERMIA?</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/kg twice daily for 2 d</td>
<td>Dizocilpine (MK-801) 10 mg/kg, 30 m pre each dose MDMA</td>
<td>NMDA antagonist</td>
<td>Protection (&quot;virtually eliminated silver staining&quot;)</td>
<td>NA</td>
<td>(Jensen et al. 1993)</td>
</tr>
<tr>
<td>20 mg/kg d-MDMA sc, four times, every 2 hrs</td>
<td>diethylthiocarbamate HCl 400 mg/kg sc, 20 m before 1st and 3rd injection MDMA</td>
<td>NO trapping agent, SOD inhibitor, metal chelator</td>
<td>Some protection</td>
<td>Hypothermia</td>
<td>(Miller and O'Callaghan 1995)</td>
</tr>
<tr>
<td>40 mg/kg sc</td>
<td>NBQX 55 mg/kg three injections 15 m apart, 15 m pre, along with, 15 m post MDMA</td>
<td>Noncompetitive NMDA antagonist</td>
<td>No protection</td>
<td>Hyperthermia or Normothermia</td>
<td>(Farfel and Seiden 1995)</td>
</tr>
<tr>
<td>15 mg/kg ip</td>
<td>Nicotinamide 200 mg/kg ip, 0.5 hr pre, along with, 2, 4 hr post MDMA</td>
<td>Precursor for the electron carrier NAD, potentially improving mitochondrial energy production but also possibly altering MDMA metabolism</td>
<td>Exacerbated</td>
<td>Hyperthermia</td>
<td>(Hervias et al. 2000)</td>
</tr>
<tr>
<td>30 mg/kg MDMA HCl sc</td>
<td>fluoxetine, 5 mg/kg sc, 15 min pre MDMA</td>
<td>SSRI</td>
<td>Protection</td>
<td>Hyperthermia</td>
<td>(Aguirre et al. 1998a)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>paroxetine 10 mg/kg ip twice daily for 3 d, along with MDMA</td>
<td>SSRI</td>
<td>Some protection</td>
<td>NA</td>
<td>(Hashimoto et al. 1992a)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>6-nitroquipazine 10 mg/kg ip twice daily for 3 d, along with MDMA</td>
<td>SSRI</td>
<td>Protection</td>
<td>NA</td>
<td>(Hashimoto et al. 1992a)</td>
</tr>
</tbody>
</table>
Table 4.2. Studies of Drugs Modifying MDMA Neurotoxicity and Hyperthermia

<table>
<thead>
<tr>
<th>MDMA REGIMEN (dose, route)</th>
<th>OTHER INTERVENTION</th>
<th>CATEGORY OF OTHER INTERVENTION</th>
<th>OUTCOME OF MDMA + OTHER INTERVENTION</th>
<th>HYPER- THERMIA?</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/kg sc</td>
<td>MDL 27,777 5 mg/kg sc, post 3 hr MDMA</td>
<td>SSRI</td>
<td>Some protection</td>
<td>NA</td>
<td>(Schmidt et al. 1990a)</td>
</tr>
<tr>
<td>10 mg/kg sc</td>
<td>MDL 27,777 5 mg/kg sc, along with MDMA</td>
<td>SSRI</td>
<td>&quot;Full&quot; protection</td>
<td>Attenuated hyperthermia</td>
<td>(Schmidt et al. 1990b)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>fluoxetine 5 mg/kg sc, along with MDMA</td>
<td>SSRI</td>
<td>Protection</td>
<td>NA</td>
<td>(Schmidt 1987)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>fluoxetine 5 mg/kg sc, post 3 hr MDMA</td>
<td>SSRI</td>
<td>Protection</td>
<td>NA</td>
<td>(Schmidt 1987)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>fluoxetine 5 mg/kg sc, post 6 hr MDMA</td>
<td>SSRI</td>
<td>Possible protection</td>
<td>NA</td>
<td>(Schmidt 1987)</td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>fluoxetine 5 mg/kg sc, post 12 hr MDMA</td>
<td>SSRI</td>
<td>No protection</td>
<td>NA</td>
<td>(Schmidt 1987)</td>
</tr>
<tr>
<td>100 mg/kg twice daily for 2 d</td>
<td>fluoxetine 5 mg/kg twice daily for 2 d, 30 min pre each dose MDMA</td>
<td>SSRI</td>
<td>Protection (decreased vol and intensity of silver stained tissue in frontalparietal cortex)</td>
<td>NA</td>
<td>(Jensen et al. 1993)</td>
</tr>
<tr>
<td>10 mg/kg ip twice daily for 3 d</td>
<td>6-nitroquipazine 5 mg/kg ip, along with MDMA</td>
<td>SSRI</td>
<td>Protection</td>
<td>NA</td>
<td>(Hashimoto and Goromaru 1990)</td>
</tr>
<tr>
<td>20 mg/kg sc, d-MDMA, every 2 hr x 4 restraint, from 30 min pre to 30 min post MDMA</td>
<td>Stressor</td>
<td>Some protection</td>
<td>Hypothermia noted</td>
<td>(Miller and O'Callaghan 1995)</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>adrenalectomy, before MDMA</td>
<td>Surgical removal of glucocorticoid source</td>
<td>Some protection</td>
<td>NA</td>
<td>(Johnson et al. 1989)</td>
</tr>
<tr>
<td>20 mg/kg ip</td>
<td>p-chlorophenylalanine (PCPA) 150 mg/kg ip daily for 3 d, daily for 3 d, ending 1 d pre MDMA</td>
<td>Tryptophan hydroxylase inhibitor</td>
<td>No protection</td>
<td>NA</td>
<td>(Brodkin et al. 1993)</td>
</tr>
<tr>
<td>MDMA REGIMEN (dose, route)</td>
<td>CATEGORY OF OTHER INTERVENTION</td>
<td>OUTCOME OF MDMA + OTHER INTERVENTION</td>
<td>HYPER- THERMIA?</td>
<td>REFERENCE</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------</td>
<td>-------------------------------------</td>
<td>-----------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg sc</td>
<td>adrenalectomy AND corticosterone 10 mg sc, 24 hr and 15 min pre, 24 h post MDMA</td>
<td>Surgical removal of glucocorticoid source and injection of corticosterone</td>
<td>Exacerbated toxicity compared to adrenalectomy alone</td>
<td>NA</td>
<td>(Johnson et al. 1989)</td>
</tr>
<tr>
<td>40 mg/kg sc</td>
<td>alpha-methyl-para-tyrosine (75 mg/kg ip, twice), 5 and 1 hr pre MDMA</td>
<td>Tyrosine hydroxylase inhibitor (DA depleter)</td>
<td>Protection</td>
<td>Hypothermia occurred and manual warming blocked protection</td>
<td>(Malberg et al. 1996)</td>
</tr>
<tr>
<td>20 mg/kg ip</td>
<td>alpha-methyl-para-tyrosine, 250 mg/kg ip, 2 hr pre MDMA</td>
<td>Tyrosine hydroxylase inhibitor (DA depleter)</td>
<td>Protection</td>
<td>NA</td>
<td>(Brodkin et al. 1993)</td>
</tr>
</tbody>
</table>

The following papers have not been obtained and are therefore not included in this table: (Gibb et al. 1997; Murray et al. 1996; Vorhees 1997)
Drug Modifying MDMA Neurotoxicity

Many studies have coadministered another drug in order to investigate the neurochemical mechanisms that produce MDMA neurotoxicity. However, the recognition that animal core temperature influences MDMA neurotoxicity has forced researchers to re-evaluate many of these studies. Drug interaction studies investigating MDMA neurotoxicity are summarized in Table 4.2. As can be seen, the role of temperature in many of these studies is still unclear.

Time Course of Changes and Extent of Recovery

High doses of MDMA have a biphasic effect on indices of serotonergic functioning, causing acute decreases, then partial recovery, and then chronic decreases in these indices. For example, after a single dose of 10 mg/kg MDMA to a rat, release of 5HT leads to depletion of tissue levels of 5HT and its metabolite 5HIAA within 3 hrs of dosing (Schmidt 1987; Stone et al. 1987b). At approximately post 6 hrs, levels begin to return to normal, but this recovery is not sustained. About 24 hr after dosing, 5HT levels begin a second, sustained decrease and remain significantly lower than baseline 2 weeks later. This sustained decrease is thought to be associated with axonal degeneration.

The intracellular enzyme TPH follows a similar time course, with decreased activity occurring within 15 min of drug administration. However, there is less short-term recovery of TPH activity in comparison to 5HT. This recovery of TPH activity appears to involve regeneration of oxidatively inactivated enzyme rather than synthesis of new enzyme. SERT functioning is also altered. Uptake of radiolabelled 5HT is decreased to 80% of control levels in tissue prepared from striata of rats sacrificed at one hour after 15 mg/kg subcutaneous MDMA (Fleckenstein et al. 1999). It should be noted that significant acute 5HT depletions are not necessarily produced by all active doses of MDMA. In Sprague Dawley rats, 2.5 mg/kg MDMA did not produce an acute decrease in 5HT or 5HIAA at 3 hours after injection (Schmidt et al. 1986). Striatal 5HT depletions were found in a chronic MDMA user who died shortly after MDMA ingestion (Kish et al. 2000). This suggests that at least some of the doses administered by illicit users are sufficient to produce 5HT depletions.

The above description focuses on serotonergic changes because these are used to measure toxicity. Many other acute neurochemical changes occur after MDMA exposure. For example, dopamine is released (Stone et al. 1986) and dopamine transporter reuptake activity is decreased within 1 hr of high dose MDMA (Fleckenstein et al. 1999; Metzger et al. 1998). MDMA can also acutely increase dopamine synthesis (Nash 1990). Mice are selectively vulnerable to MDMA-induced dopaminergic neurotoxicity (Logan et al. 1988; Miller and O'Callaghan 1994; Stone et al. 1987a). In some studies, long-term alterations
in dopaminergic functioning have been seen in other species, such as rats (Commins et al. 1987b).

The time course of damaging events in rats can be seen by administering SSRIs, such as fluoxetine and citalopram, after MDMA. Administering fluoxetine or citalopram before or simultaneous to MDMA has been shown to block the neurotoxicity of MDMA (Battaglia et al. 1988a; Malberg et al. 1996; Schmidt 1987; Schmidt and Taylor 1990; Shankaran et al. 1999a; Virden and Baker 1999), probably by blocking interactions of MDMA with SERT (Berger et al. 1992b). More interestingly, fluoxetine remains almost fully protective if given 3 or 4 hours after MDMA. By 4 hrs, most of the MDMA-induced release of 5HT and DA has already occurred (Gough et al. 1991; Hiramatsu and Cho 1990) and increases in extracellular free radicals (Colado et al. 1997b; Shankaran et al. 1999a) and lipid peroxidation (Colado et al. 1997b) can be measured. Nevertheless, the administration of fluoxetine at this point decreases subsequent extracellular oxidative stress (Shankaran et al. 1999a) and long-term 5HT depletions (Schmidt 1987; Shankaran et al. 1999a). Fluoxetine will still be partially protective if given 6 hrs after MDMA but has no protective effect at post 12 hrs (Schmidt 1987). This shows that neurotoxic MDMA regimens initiate a series of events that become increasingly damaging between 3 and 12 hrs after drug administration in rats.

Slow recovery of indices of serotonergic functioning can be seen following a neurotoxic dose of MDMA. Recovery is probably at least partially due to axonal regrowth since increases follow a regionally specific pattern. For example, there is a rostral to caudal pattern of recovery in the cortex and hippocampus (Lew et al. 1996; Molliver et al. 1990). It appears that recovery is greatest in brain regions that are nearer to 5HT nerve cell bodies in the raphe or major 5HT axon bundles (Fischer et al. 1995; Hatzidimitriou et al. 1999). Interestingly, serotonergic indices have been found to continue to increase beyond their normal levels during recovery in some nearer areas such as the amygdala and hypothalamus (Fischer et al. 1995; Lew et al. 1996; Ricaurte et al. 1992; Sabol et al. 1996). Thus, “recovery” does not necessarily mean that the animal returns to its predrug state.

Extent of recovery is different in different species. In rats, there is extensive recovery of indices of serotonergic functioning 1 year after drug exposure (Battaglia et al. 1988b; Lew et al. 1996; Sabol et al. 1996; Scanzello et al. 1993), although there is significant variation in recovery between individual animals (Fischer et al. 1995). In primates, some recovery of serotonergic function occurs but is less extensive than in the rat. Altered serotonergic axon density was still detectable 7 years after MDMA exposure in one study employing squirrel monkeys (Hatzidimitriou et al. 1999). Therefore, despite some recovery, MDMA-induced serotonergic changes are likely permanent in this primate species. This apparent species difference may be partially related to the more severe initial serotonergic damage usually seen in primates compared to rats, but likely also indicates a species difference in regrowth of serotonergic axons.
MDMA-Induced Apoptosis (Programmed Cell Death)

While MDMA has generally been found to selectively affect axons rather than cell bodies, two \textit{in vitro} studies have suggested that MDMA may trigger programmed cell death under certain conditions. In one study, exposure to MDMA for 48 hrs dose-dependently decreased survival of cultured human placental serotonergic cells (Simantov and Tauber 1997). This decreased cell viability was accompanied by DNA fragmentation and cell cycle arrest (in the G2M phase). 48 hr exposure to 0.4 mM MDMA decreased cell survival by $1.4 \pm 4\%$, while 1.2 mM MDMA decreased cell survival by $61 \pm 9\%$. This cytotoxicity appeared to be the result of a specific pharmacological interaction as cultured dopaminergic cells were unaffected and toxicity to serotonergic cells was dose-dependently blocked by imipramine. In another study, the effects of MDMA and structurally related amphetamines on cultured rat neocortical neurons were studied at concentrations of 125 to 1000 $\mu$M MDMA and exposure times of 1, 24, and 96 hours (Stumm et al. 1999). Cell survival was not significantly affected by 125 $\mu$M MDMA at any exposure time. However, cell survival was decreased by $34.2 \pm 11.4\%$ at 96 hours after an average exposure of 500 $\mu$M MDMA. Stumm et al. also noted DNA fragmentation and altered expression of the bcl-xL\textsubscript{S} gene, which supports the interpretation that programmed cell death had occurred. The degree of cytotoxicity noted for MDMA in this study was comparable to the toxicity produced by other structurally related amphetamines.

The relevance of these \textit{in vitro} studies to humans is difficult to assess because MDMA concentrations likely differ in the brain and blood. In a human fatality, MDMA concentrations were 4.8 times higher in brain than blood (Rohrig and Prouty 1992). However, postmortem changes in drug levels are possible. If it is assumed that postmortem redistribution did not occur and MDMA levels in the brain are about 5 times higher than in blood, then 150 mg MDMA might produce peak brain levels of 2.5 mg/L. This estimated peak level is significantly less than the lowest drug concentration used in either study (0.4 $\mu$M MDMA is 77.3 mg/L, while 125 $\mu$M is 24.2 mg/L). Given these concentration differences and the long exposure times used in these studies, it does not seem likely that human oral doses of MDMA would be sufficient to induce programmed cell death.

Non-serotonergic MDMA Neurotoxicity in the Somatosensory Cortex

Non-serotonergic cell damage has been detected after MDMA exposure to the rat somatosensory cortex using silver staining. This region is similarly affected by methamphetamine and amphetamine (Commins et al. 1987b; Ryan et al. 1990). Research with methamphetamine has shown that these cells are likely glutamatergic (Pu et al. 1996) and may comprise a corticostriatal pathway. MDMA-induced silver staining in this region was detected after 80 mg/kg MDMA exposure in Sprague-Dawley rats (Commins et al. 1987a).
Behavioral and Functional Correlates of MDMA Exposure in Animals

A number of studies have looked for evidence that MDMA neurotoxicity causes lasting behavioral or functional changes in nonhuman animals. These studies are summarized in Table 4.3 and are, perhaps, impressive for the limited nature of their behavioral findings. It is clear that neurotoxic MDMA exposure can both alter neurochemical functioning and the response of animals to subsequent drug exposures. However, so far five published studies suggest that drug-free MDMA-exposed animals also have behavioral alterations or functional impairments at seven or more days after last MDMA exposure.

Lasting thermoregulatory impairment has been demonstrated in MDMA-exposed animals by two research groups (Dafters and Lynch 1998; Mechan et al. 2001). In the earlier study, rats were placed in a warm environment (30° C) fourteen weeks after exposure to a neurotoxic MDMA or placebo regimen. MDMA-exposed rats had significantly larger increases in core temperature than control rats. In the second study, a similar effect was seen 5 to 6 wk after neurotoxic MDMA exposure (Mechan et al. 2001). Rats that had been previously exposed to MDMA had a quicker increase in core temperature when placed in a warm environment (30° C) and had a longer-lasting increase in temperature when removed from that environment. It has been known for many years that individuals who experience heat stroke have increased susceptibility to subsequent episodes for some time (Shapiro et al. 1979) and it appears possible that the same phenomenon is being detected here. Alternatively, this may be an effect of neurotoxic changes in the hypothalmus. The serotonergic neurotoxin 5,6-dihydroxytryptamine (5,6-DHT) produces a similar thermoregulatory impairment when injected into the rat anterior hypothalmus (Myers 1975).

Rats exposed to a neurotoxic MDMA regimen showed reductions in diurnal and nocturnal locomotor activity at 7 to 14 days after drug treatment (Wallace et al. 2001). Neostriatal 5HT levels were measured at 15 to 17 days after treatment and were found to be 31% of control levels. It is not clear if this reduction in activity is the result of neurotoxicity rather than some other non-neurotoxic effect of MDMA. Some regimens of repeated non-neurotoxic exposure to d-amphetamine can reduce nocturnal activity in rats (Robinson and Camp 1987). The authors speculate that the hyperactivity in MDMA-treated rats may relate to a possible dysregulation of the sleep-wake cycle, which is thought to be influenced by serotonergic neurons originating in the dorsal raphe nucleus. This hypothesis is consistent with the reported differences in sleep between MDMA users and nonusers (Allen et al. 1993; McCann et al. 2000).

Two studies have suggested that neurotoxic MDMA exposure may cause neurocognitive impairment in rats. The first study used adult animals and the second study used newborn rats. In the study with adult animals, drug-free alterations in performance were detected using a delayed memory task (Marston et al. 1999). MDMA-exposed rats displayed significantly reduced accuracy and increased response bias at the longer (20 or more sec) delays between presentation of information and testing. This difference appeared to be the result of less improvement in accuracy by the MDMA-exposed
### Table 4.3. Studies of Long-term Behavioral or Functional Changes after MDMA Exposure in Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Neurotoxic MDMA Regimen</th>
<th>Significant Effects of MDMA Exposure</th>
<th>Measures not Significantly Different</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhesus Monkeys</td>
<td>10 mg/kg IM, twice a day, for 4 days</td>
<td>Right shift in MDMA and d-fenfluramine dose-response curve for time estimation, learning task, and motivation tasks at post 1 mo.</td>
<td>Drug-free performance on all tasks at post 1 mo.</td>
<td>(Frederick et al. 1998)</td>
</tr>
<tr>
<td>Rhesus Monkeys</td>
<td>Escalating doses of 0.10, 0.3, 1.0, 1.75, 3.0, 5.6, 7.5, 10.0, 15.0, and 20 mg/kg, IM, twice daily for 14 consecutive days at each dose. (2 of 3 animals 'skipped' the 1.75, 7.5, and 15 mg/kg dose levels). Preceded by one period of dose response testing using doses up to 1.75 mg/kg IM and followed by three two month periods of dose-response testing using doses up to 5.7 mg/kg IM.</td>
<td>Right shift in MDMA dose-response curve for time estimation, short-term memory, color and position discrimination, and motivation tasks post 5, 12 or 19 mo from chronic regimen (post 12 and 19 mo measures were post 5 mo from a dose-response determination).</td>
<td>Drug-free performance on all tasks at all time points.</td>
<td>(Frederick et al. 1995)</td>
</tr>
<tr>
<td>Rhesus Monkeys</td>
<td>10 mg/kg IM, twice a day for 4 days</td>
<td>Altered latencies of brainstem auditory evoked EEG potentials (P3 faster at post 2, 9, and 13 wk; P4 faster at post 2, 4, 9, and 13 wk; P5 slower at post 2 wk).</td>
<td>Tests of memory, reinforcer efficacy, bimanual coordination, and reaction time at all time points after post 2 wk; latencies of auditory and visual evoked EEG potentials at all time points; latencies of brainstem auditory evoked EEG potentials (P3 at 4, 17, and 21 wk; P4 at 17 and 21 wk; P5 at 4, 9, 13, 17, and 21 wk).</td>
<td>(Taffe et al. 2001)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC, twice a day for 4 days</td>
<td>None, although researchers note that 2 of 8 MDMA-exposed rats failed to acquire lever pressing with 20 sec reinforcement delays during the 8 hr session at post 14 days.</td>
<td>Acquisition of and behavior on a lever-press responding task at post 14 days.</td>
<td>(Byrne et al. 2000)</td>
</tr>
</tbody>
</table>
Table 4.3 (continued). Studies of Long-term Behavioral or Functional Changes after MDMA Exposure in Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Neurotoxic MDMA Regimen</th>
<th>Significant Effects of MDMA Exposure</th>
<th>Measures not Significantly Different</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprague-Dawley Rats</td>
<td>10 mg/kg SC, twice a day for 4 days</td>
<td>Significant pretreatment x treatment x crossing times interaction, suggesting altered S(+) -MDMA -induced behavioral activation at post 21 days.</td>
<td>Drug-free locomotion at 21 days; RU24969-induced behavioral activation at 21 days.</td>
<td>(Callaway and Geyer 1992)</td>
</tr>
<tr>
<td>Wistar Rats</td>
<td>10 mg/kg SC, once per day for 4 days</td>
<td>Increased core temperature when placed in either 22 °C or 28 °C ambient temperature at post 4 or 14 wks.</td>
<td>None</td>
<td>(Dafters and Lynch 1998)</td>
</tr>
<tr>
<td>Long-Evans Rats</td>
<td>40 mg/kg SC, twice a day for 4 days</td>
<td>None</td>
<td>Sexual behaviors at post 10 days; Spontaneous motor activity.</td>
<td>(Dornan et al. 1991)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC, twice a day for 4 days</td>
<td>Decreased cortical 5HT release in response to electrical stimulation in DRN at post 10-12 days.</td>
<td>Electrical-stimulated 5HT release in MRN or hippocampus at post 2 wks; Number and firing pattern of classical 5HT neurons and burst-firing neurons in DRN.</td>
<td>(Gartside et al. 1996)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC, twice a day for 4 days</td>
<td>None</td>
<td>DOI-induced head twitch responses, locomotion, and rearing activity at post 1 mo.</td>
<td>(Granoff and Ashby 1998)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC, twice a day for 4 days</td>
<td>Increased conditioned place preference response to cocaine in MDMA group at 2 post wks.</td>
<td>None</td>
<td>(Horan et al. 2000)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>5 mg/kg SC, once a day for 4 days, or 20 mg/kg SC, twice a day for 4 days, followed by 5 mg/kg MDMA 2 days later</td>
<td>Increased motor stimulant effects of 5.0 mg/kg SC MDMA or 15.0 mg/kg IP cocaine in both MDMA-treated groups at post 11 days; increased MDMA-stimulated DA release in the nucleus accumbens at post 2 wks.</td>
<td>Basal DA in nucleus accumbens at post 2 wks.</td>
<td>(Kalivas et al. 1998)</td>
</tr>
</tbody>
</table>
### Table 4.3 (continued). Studies of Long-term Behavioral or Functional Changes after MDMA Exposure in Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Neurotoxic MDMA Regimen</th>
<th>Significant Effects of MDMA Exposure</th>
<th>Measures not Significantly Different</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprague-Dawley Rats</td>
<td>15 mg/kg IP</td>
<td>Loss of rate-dependence of response of nigrostriatal cells to either quinpirole or apomorphine at post 1 wk.</td>
<td>Basal activity of nigrostriatal DA neurons; Quinpirole-induced inhibition of nigrostriatal DA cell firing for all cells at post 1 wk.</td>
<td>(Kelland et al. 1989)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>6 mg/kg SC, twice a day daily for 4 days</td>
<td>Left shift in MDMA dose-response curve on DRL task in MDMA group at post 4 wks.</td>
<td>None</td>
<td>(Li et al. 1989)</td>
</tr>
<tr>
<td>Lister Hooded Rats</td>
<td>ascending regimen of 10, 15, and 20 mg/kg IP, each dose given twice daily for one day</td>
<td>Decreased performance in operant delayed match to nonsample task beginning at post 12 days.</td>
<td>Spontaneous behavior, body temperature, and skilled paw reach (&quot;staircase task&quot;) up to post 16 days.</td>
<td>(Marston et al. 1999)</td>
</tr>
<tr>
<td>Dark Agouti Rats</td>
<td>12.5 mg/kg IP</td>
<td>Faster increase in core temperature in warm (30°C) environment and longer-lasting hyperthermia when returned to normal environment at post 33 days.</td>
<td>Hypothermic response to the 5HT1A agonist 8-OH-DPAT</td>
<td>(Mechan et al. 2001)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC, twice a day for 4 days</td>
<td>Increased cocaine-induced dopamine release in nucleus accumbens in MDMA group at post 2 wks.</td>
<td>None</td>
<td>(Morgan et al. 1997)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC, twice a day for 4 days</td>
<td>Increased morphine-induced antinociception (assessed by tail flick test) at post 2 wks.</td>
<td>Drug free behavior in tail flick test at post 2 wks.</td>
<td>(Nencini et al. 1988)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC, twice a day for 4 days</td>
<td>Decreased inhibitory effects of DA and SKF38393 on glutamate-evoked firing in nucleus accumbens cells at post 9-15 days.</td>
<td>Inhibitory effects of GABA on glutamate-evoked firing in nucleus accumbens cells at post 9-15 days.</td>
<td>(Obradovic et al. 1998)</td>
</tr>
</tbody>
</table>
Table 4.3 (continued).  Studies of Long-term Behavioral or Functional Changes after MDMA Exposure in Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Neurotoxic MDMA Regimen</th>
<th>Significant Effects of MDMA Exposure</th>
<th>Measures not Significantly Different</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC</td>
<td>Increased 8-OH-DPAT-induced prolactin release at post 2 wks. Decreased 8-OH-DPAT-stimulated ACTH release at post 2 wks.</td>
<td>Basal ACTH and prolactin concentrations and ACTH and prolactin response to saline injection at post 2 wks.</td>
<td>(Poland 1990)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC</td>
<td>Increased d,l-Fenfluramine-stimulated prolactin release at post 2 wks and 4 mo. Decreased d,l-Fenfluramine-stimulated ACTH release at post 2 wks, 4 mo, and 8 mo.</td>
<td>d,l-Fenfluramine-stimulated ACTH at post 12 mo; d,l-Fenfluramine-stimulated prolactin at post 8 and 12 mo.</td>
<td>(Poland et al. 1997)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC, twice a day for 4 days</td>
<td>Increased d,l-Fenfluramine-stimulated prolactin release at post 4 and 8 mo. Decreased d,l-Fenfluramine-stimulated ACTH release at post 4, 8, and 12 mo.</td>
<td>Saline-stimulated ACTH and prolactin release at post 2 weeks; d,l-Fenfluramine-stimulated prolactin release at post 12 mo.</td>
<td>(Poland et al. 1997)</td>
</tr>
<tr>
<td>Long-Evans Rats</td>
<td>20 mg/kg SC, twice a day for 4 days with entire regimen repeated 1 wk later</td>
<td>None</td>
<td>Performance in a spatial memory task using a T-maze (at post 7-10 wks) and scopolamine-induced changes in performance on this task (at post 15-16 wks).</td>
<td>(Ricaurte et al. 1993)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>10 mg/kg IP, twice a day for 4 days</td>
<td>None (increased time to find hidden platform in first trial of spatial navigation task at post 2 days).</td>
<td>Spatial navigation and learning set task at post 7-9 days, skilled reaching task at post 17-19 days, foraging task at post 26-29 days, with or without atropine pretreatment.</td>
<td>(Robinson et al. 1993)</td>
</tr>
</tbody>
</table>
Table 4.3 (continued): Studies of Long-term Behavioral or Functional Changes after MDMA Exposure in Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Neurotoxic MDMA Regimen</th>
<th>Significant Effects of MDMA Exposure</th>
<th>Measures not Significantly Different</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC, twice a day for 4 days</td>
<td>Decreased discrimination of 1.0 mg/kg MDMA from saline at post 13-15 days.</td>
<td>Discrimination of 0.5 or 1.5 mg/kg; conditioned place preference from MDMA at post 13-15 days.</td>
<td>(Schechter 1991)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>10, 20, and 40 mg/kg SC, twice a day for 4 days</td>
<td>None</td>
<td>Food and water intake, schedule-controlled behavior, open field behavior, acquisition of one- and two-way avoidance, swimming ability, acquisition and extinction in 8-arm radial maze test, and morphine-induced antinociception at post 14-28 days.</td>
<td>Seiden, et al., 1993</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>10 mg/kg IP, every 2 h for 4 injections</td>
<td>Decreased d-fenfluramine-stimulated 5HT release in frontal cortex at post 2 wks.</td>
<td>None</td>
<td>(Series et al. 1994)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg SC, twice a day for 4 days</td>
<td>Increased cerebral glucose utilization in molecular layer of dentate gyrus and in CA2 and CA3 fields of Ammon's horn in hippocampus at post 14 days.</td>
<td>Cerebral glucose utilization in neocortex, raphe nuclei, and some hippocampal areas at post 14 days.</td>
<td>(Sharkey et al. 1991)</td>
</tr>
</tbody>
</table>
### Table 4.3 (continued): Studies of Long-term Behavioral or Functional Changes after MDMA Exposure in Animals

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>Neurotoxic MDMA Regimen</th>
<th>Significant Effects of MDMA Exposure</th>
<th>Measures not Significantly Different</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprague-Dawley Rats</td>
<td>5 or 10 mg/kg PO, daily for 4 days</td>
<td>None</td>
<td>Auditory startle, emergence from darkened chamber, complex maze navigation, response to hot plate, FI 90 operant behavioral task at post 2 to 4 weeks.</td>
<td>(Slikker et al. 1989)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>20 mg/kg, SC, twice a day for 4 days</td>
<td>Decreased S(+) - MDMA-appropriate responding after S(+) - MDMA and increased S(+) - MDMA-appropriate responding after saline at post 10 days.</td>
<td>None</td>
<td>(Virden and Baker 1999)</td>
</tr>
<tr>
<td>Sprague-Dawley Rats</td>
<td>10 mg/kg IP, every 2 hr for 4 injections</td>
<td>Decreased diurnal and nocturnal spontaneous locomotor activity at post 7 to 14 days.</td>
<td>Number of crossings into different quadrants of cage at all times.</td>
<td>(Wallace et al. 2001)</td>
</tr>
<tr>
<td>Young Sprague-Dawley Rat Pups</td>
<td>10 mg/kg SC, every 12 hrs for 4 or 7 injections</td>
<td>Decreased rate of ultrasonic vocalization measured up to post 11 days.</td>
<td>Behavioral responses to the 5HT₁₅ agonist 8-OH-DPAT, the 5HT₁₅ agonist TFMPP, and the 5HT₂ agonist DOI at post 8 days.</td>
<td>(Winslow and Insel 1990)</td>
</tr>
</tbody>
</table>

Time from MDMA treatment is expressed as time from last exposure.

Abbreviations: DA - dopamine; DRN - dorsal raphe nucleus; DRL - differential reinforcement of low rate (behavioral task); FI - fixed interval of reinforcement (behavioral task); IM - intramuscular injection.

animals across days of testing and became statistically significant in post hoc comparisons beginning 12 days after last MDMA exposure. In contrast, other studies were unable to demonstrate any long-term effect of MDMA neurotoxicity on spatial navigation memory tasks in rats (Ricaurte et al. 1993; Robinson et al. 1993). However, Robinson and colleagues did detect short-term residual effects of MDMA on this task when animals were tested 2 days after the last MDMA exposure.

A recent study of newborn rats found that repeated MDMA exposure dose-dependently impaired sequential learning and spatial learning and memory (Broening et al. 2001). MDMA was administered twice daily for ten days, with individual doses of 5 to 20 mg/kg. Because of interspecies differences, newborn rats are thought to be the developmental equivalent of a third-trimester human fetus. Thus, the newborn rats were exposed to MDMA during the equivalent of the third-trimester in humans. Some rats were administered MDMA during the equivalent of the early part of the third trimester, while others were exposed during the late part of this period. MDMA decreased body
animals. The apparent discrepancy between these two studies may be due to the different weight for both groups. In behavioral tests beginning at least 1 mo after MDMA exposure, rats exposed in the late (but not early) third trimester had significantly impaired learning and memory. These impairments were not correlated to the serotonergic neurotoxicity seen in both groups, which was measured as a 20% or less depletion of hippocampal serotonin.

### Behavioral Effects of Other Serotonergic Neurotoxins

Given the apparently subtle behavioral effects of MDMA neurotoxicity, it may be useful to briefly survey the behavioral effects of other serotonergic neurotoxins such as 5,6 and 5,7-DHT (hereafter “DHT neurotoxins”). As discussed earlier, neurotoxic MDMA exposure produces fewer consistent changes in markers of neural cell injury than DHT neurotoxins. This has been interpreted by some as evidence that MDMA is not truly neurotoxic. If MDMA also differed from DHT neurotoxins in behavioral effects, the difference could be seen as further evidence that MDMA is not neurotoxic. However, once the regional selectivity of these neurotoxins is taken into account, there are few clear differences in the behavioral and axonal effects of MDMA and other serotonergic neurotoxins.

For the purposes of this discussion, it is not necessary to distinguish between 5,6-DHT and 5,7-DHT. 5,7-DHT has greater chemical stability and typically causes fewer fatalities than 5,6-DHT. In both cases, researchers generally pretreat animals with the norepinephrine reuptake inhibitor desipramine to prevent damage to noradrenergic axons. Because of their polarity, DHT neurotoxins do not cross the blood-brain barrier and must be injected into a specific brain region or infused into the cerebral ventricles (allowing the toxin to spread throughout the brain). Thus, regionally selective or relatively global serotonergic neurotoxicity can be produced. MDMA is similar to DHT neurotoxins in that both damage serotonergic axons that subsequently regrew from surviving cell bodies and axons (Bjorklund and Stenevi 1979). MDMA differs from DHT neurotoxins in that MDMA is generally thought to only damage those serotonergic axons originating in the dorsal raphe nucleus. However, microinjection of DHT neurotoxins into the dorsal raphe nucleus should produce localized serotonergic changes similar to those seen in MDMA-induced neurotoxicity. Although the technique is less selective and may damage non-serotonergic cells and surrounding tissue, it is also possible to electrolytically lesion the dorsal raphe nucleus.

The effects of selective lesioning of the dorsal raphe serotonergic system are fairly subtle. An increase in motor activation was seen when DHT-lesioned rats were placed in a novel environment at 7 to 12 days after lesioning (Morrow and Roth 1996). This effect was transient and was not detectable after 12 days. Locomotor activity was correlated with SHT levels in the median prefrontal cortex, which were an average of 35% of control levels. A study using electrolytical lesioning of the dorsal raphe nucleus reported decreased wheel running activity from 1 to 4, but not 5 to 8, weeks after lesioning in rats with forebrain SERT activity reduced to 54% of controls (Heym and Gladfelter 1982). Food and water intake and body weight were unaltered in the electrolytically-lesioned animals. The apparent discrepancy between these two studies may be due to the different
lesioning techniques or the environment in which behavior was measured. It may be that dorsal raphe lesioning transiently increases activity in novel environments while decreasing activity in familiar ones. Similarly transient changes were reported in a study that employed a behavioral test of impulsivity in the involving choice between an immediate, smaller reward and a delayed, larger one (Bizot et al. 1999). Beginning 1 week after dorsal raphe nucleus lesioning with 5,7-DHT, lesioned rats were more likely to choose the smaller, immediate reward when the larger reward was delayed by 15 seconds. This difference was only detected 7 to 8 days after lesioning and not subsequently. 24 days after lesioning, tryptophan hydroxylase activity was found to be 36% of controls in the cerebral cortex and hippocampus, confirming that extensive neurotoxicity had occurred. In another study, dorsal raphe nucleus lesioning with 5,6-DHT did not influence passive avoidance behavior in rats at 10 days post-lesioning, despite a reduction of dorsal hippocampal SERT activity to 20% of controls (Kovacs et al. 1979). However, lesioned rats were insensitive to microinjection of arginine-vasopressin into the dorsal raphe nucleus, a treatment that normally improves consolidation of learning. In summary, lesioning of the dorsal raphe serotonergic system is associated with transient behavioral changes that could be interpreted as increased interest in novel environments and more impulsive behavior.

Because lesioning of the dorsal raphe serotonergic system with established neurotoxins is associated with subtle and often transient effects, it does not appear plausible to draw strong conclusions from the difficulty researchers have had associating MDMA neurotoxicity with behavioral alterations. Similarly, strong conclusions cannot be drawn from studies directly comparing the behavioral effects of MDMA and DHT neurotoxicity if DHT lesions were not limited to the dorsal raphe nucleus. Although three studies (Lorens et al. 1989; Ricaurte et al. 1993; Seiden et al. 1993) detected behavioral effects of 5,7-DHT but not MDMA, 5,7-DHT was given intracerebroventicularly in all cases and likely produced a different pattern of serotonergic damage than MDMA.

**How Can Neurotoxic Damage be Without Detectable Behavioral Consequences?**

Two concepts help to explain why neurodegeneration or neurotoxic damage is not always associated with predictable behavioral effects. First, there is a threshold of damage that must be exceeded in some brain systems before symptoms develop. This has been primarily investigated with dopaminergic cell loss and Parkinson’s disease (Brownell et al. 1999; Calne et al. 1985; Di Monte et al. 2000). There are less data on the serotonergic system. A rat study using the serotonergic neurotoxin, 5,7-DHT (Kirby et al. 1995) found that basal extracellular 5HT levels in the ventral striatum were not altered in rats with striatal 5HT levels reduced to 3.1% of controls. In contrast, Hall et al. (1999) concluded that a loss of greater than 60% of serotonergic neurons was necessary to decrease extracellular 5HT levels in the striatum. Alterations in behavior were seen with slightly smaller depletions (51% or more), possibly due to regional variations in neurotoxicity. Hall et al. suggest that the previous study failed to find decreases in extracellular 5HT levels because the recently implanted microcanulae may have damaged cells, increasing extracellular 5HT. One might speculate that even smaller depletions may not affect many serotonergic-related behaviors, although the maximal serotonergic
response to drugs or other stimuli is likely to be reduced (reduced electrical-stimulated 
5HT release in MDMA-exposed rats was documented by (Gartside et al. 1996). Another 
concept - called cognitive reserve - has been developed to explain why greater education, 
intelligence, or brain size is associated with less severe impairment in conditions such as 
Alzheimer’s disease, AIDS, and normal aging (Alexander et al. 1997; Coffey et al. 1999; 
Graves et al. 1996; Stern et al. 1996). This cognitive reserve may be seen as a surplus of 
processing capacity that protects the individual against loss of functioning when 
processing capacity is decreased.
Neurotoxicity Research in Humans
Matthew Baggott, B.A., and Lisa Jerome, Ph.D.

Introduction and Overview

This chapter reviews the studies that explore the possibility of neurotoxicity in ecstasy users. The primary purpose of this review is to aid in assessing risks of clinical MDMA studies. This chapter attempts to interpret findings in a manner that produces a conservative risk assessment. Studies of illicit ecstasy users are useful in risk assessment because they identify possible areas of toxicity and identify the possible severity of toxic changes. Studies of ecstasy users are limited because it is not always possible to distinguish the effects of MDMA exposure from other factors and many questions have not been adequately studied. Studies in ecstasy users are important because research in animals (reviewed in a separate chapter) shows that MDMA can cause neurotoxicity, damaging serotonergic axons and permanently changing their distribution in the brain. It is likely that some MDMA exposures cause similar or identical changes in humans.

Most research on ecstasy users can be categorized into two areas of study: neurofunctional measures and neurocognitive measures. In this document, “neurofunctional” is loosely used to indicate measures of how the brain is working and measures of the concentration or density of neurochemicals. “Neurocognitive measures” refers to performance on standardized tests of mental abilities. Research on ecstasy users supports associations between MDMA exposure and alterations in both neurofunctional and neurocognitive measures. Measures that do not cleanly fit either of these categories include those examining mood and personality in ecstasy users. These measures are also reviewed, even though they are difficult to interpret and have questionable relevance for neurotoxicity risk assessment.

Reported neurofunctional differences between ecstasy users and nonusers include concentration of a serotonin metabolite in cerebrospinal fluid (CSF 5HIAA levels), serotonin transporter (SERT) density, 5HT2A receptor density, neuroendocrine response to serotonergic drugs, EEG measures, altered sleep architecture, cerebral myo-inositol concentration, cerebral glucose utilization, and cerebral blood flow/volume. There is insufficient evidence to assess the permanence or reversibility of most reported neurofunctional differences.

Statistically significant correlations have been reported between ecstasy exposure and specific neurofunctional measures, such as CSF 5HIAA levels, SERT density, global brain volume, myo-inositol increases, 5HT2A receptor density, and EEG alterations. The most conservative interpretation of these correlations is to regard them as evidence that ecstasy exposure caused the neurofunctional differences. A less conservative interpretation would be that differences in these neurofunctional measures predate ecstasy exposure and indicate a tendency to use ecstasy. The authors find this interpretation to be implausible.
In some cases, there are questions as to whether these changes can be considered evidence of serotonergic neurotoxicity rather than responses to the nontoxic pharmacological effects of MDMA. To distinguish between neurotoxicity and responses to pharmacological effects of MDMA, it is helpful to consider (1) animal data on the effects of MDMA and other serotonergic neurotoxins and (2) human data on the effects of drugs that are not serotonergic neurotoxins, particularly stimulants. When these additional data are considered, some neurofunctional differences can conservatively be regarded as evidence of serotonergic neurotoxicity in users, because they are documented in animals after neurotoxic regimens of MDMA and other serotonergic neurotoxins. These differences include decreases in serotonin transporter and CSF 5HIAA.

Nonetheless, most neurofunctional differences are not clear evidence of selective serotonergic neurotoxicity. Some, such as increased alpha and beta EEG and altered sleep architecture, occur in users of stimulant drugs that do not cause serotonergic neurotoxicity. Others, such as cerebral blood flow/volume and cerebral glucose utilization, are altered in the opposite direction in ecstasy users compared to neurotoxin-exposed animals. Still others, such as increased $5HT_{2A}$ receptor density, have not been seen in animals exposed to serotonergic neurotoxins. These reported differences are of unknown significance.

Neurocognitive performance studies suggest that, under some conditions or patterns of use, ecstasy exposure can decrease performance in some measures of neurocognitive functioning into the lower range of what is considered clinically normal. There is no conclusive evidence that a specific domain of cognitive functioning is impaired in ecstasy users, although some have suggested that a category of mental abilities called “executive function” that includes the ability to plan ahead may be specifically altered. Measures of verbal memory have most consistently detected differences between ecstasy users and nonusers, but many other measures have also sometimes detected differences.

We do not know the relationship between these neurocognitive changes and serotonergic neurotoxicity. Decreased neurocognitive performance can occur in users of other drugs of abuse, such as cocaine or marijuana. Only 2 of at least 11 studies have found evidence of long-term impairment in the neurocognitive performance of animals exposed to neurotoxic MDMA regimens. This suggests that serotonergic neurotoxicity might occur in the absence of neurocognitive performance changes and that neurocognitive performance changes in ecstasy users may or may not be caused by serotonergic neurotoxicity.

There are not yet sufficient data to conclude whether these neurocognitive differences would lessen after the discontinuation of frequent ecstasy exposure. One study and one analysis described in this document found evidence of recovery, while another study and a second analysis in this document found no evidence of recovery. The issue of recovery is worrisome because even small changes in illicit users could be important if they were permanent.
While statistically significant, the reported differences between matched groups of ecstasy users and nonusers are subtle and can for the most part only be detected with sensitive neurofunctional and neurocognitive measures. The limited data from volunteers in clinical MDMA studies have not shown evidence of toxicity. This suggests that cautious clinical MDMA research can be conducted with low risks. Nonetheless, the possibility of currently undetected chronic toxicity cannot be excluded and ethics requires discussing this matter with volunteers. It is important to be aware that published studies have compared, at most, groups of 30 individuals and excluded those with histories of serious psychiatric or neurological problems. This has at least two implications. First, there are only anecdotal data on whether individuals with a history of psychiatric or neurological illness are affected differently by MDMA exposure than other ecstasy users. Second, the limited sample sizes in these studies means that only common adverse effects of MDMA will have been detected. There may be rare adverse events that are not yet identified.

It is possible that impairment will manifest as users age. Some hypothesize that serotonergic neurotoxicity could lead to depression and anxiety disorders as individuals’ serotonergic systems undergo age-related decreases in functioning. Although age-related decreases in serotonergic functioning appear relatively modest compared to those seen in the dopaminergic system, age-related changes in the brain are not sufficiently understood to make predictions about the possible long-term consequences of serotonergic neurotoxicity with any confidence.

Furthermore, there is currently no direct evidence on this issue. There are no published studies with rodents or other animals with short lifespans suggesting MDMA exposure causes significant toxicity that only becomes apparent in the aged animal. There are also no published studies or other evidence of problems developing in humans. MDMA has been widely used for over 20 years and similar drugs with similar capacity for long-term serotonergic changes (e.g., 3,4-methylenedioxymethamphetamine, MDA) have been used since the 1960s without evidence of dramatic age-related toxicity. Methamphetamine, which produces both long-term serotonergic and dopaminergic changes, has been used clinically for over 60 years without reported incidents of neurocognitive deficits appearing with age. This lack of evidence of problems developing with age is reassuring, but not conclusive. Until appropriate studies are conducted, lack of evidence of problems cannot be taken as evidence of lack of problems.

Overall, it is very likely that repeated ecstasy exposure causes neurofunctional changes in some illicit users. It is also very likely that some of these changes are due to serotonergic neurotoxicity. Nevertheless, the reported differences between matched groups of ecstasy users and nonusers are clinically subtle and can, so far, only be detected with sensitive neurofunctional and neurocognitive measures. Studies of illicit ecstasy users give no indication that one or two exposures to MDMA in a clinical setting would produce significant or lasting toxicity. Preliminary data from clinical MDMA studies support this conclusion. However, the risks and benefits of proposed MDMA studies must be assessed on an individual basis.
Limitations of The Research Literature

**Differences may be Pre-existing.** In retrospective studies, correlation cannot be taken as a demonstration of causality. While ecstasy exposure may be associated with user-nonuser differences in a given study measure, ecstasy exposure may simply be a marker for some other variable that causes the observed differences between ecstasy users and nonusers. This other variable may be a habitual behavior (e.g., repeated sleep and nutrition deprivation from attending raves) or a pre-existing trait (e.g., genetic serotonergic differences influencing personality). People who prefer drugs may simply be different from those who do not. For example, Uhlenhuth et al. (1981) found that volunteers (with no history of drug abuse) who preferred amphetamine to placebo had significantly higher baseline scores on POMS subscales for anxiety, depression, fatigue, and confusion than other volunteers. Such an association between preexisting dysphoric mood and preference for euphoric drugs could easily be mistaken for stimulant-induced dysphoria in a retrospective study of stimulant abusers.

One report (Schifano 2000) recently described currently unpublished survey data from high school students in Italy that found students attending less academic secondary schools were 2.89 times more likely to have used MDMA than those attending more academic schools. In another survey of 737 Italian MDMA users, cited in the same publication, there was reportedly evidence of inverse relationships between the tendency to take higher MDMA doses and both lower schooling level and family income (Schifano 2000). These findings provide evidence that there are differences between MDMA users and nonusers that predate illicit drug use.

The possibility of such pre-existing differences is particularly significant when studying serotonergic differences between drug users and nonusers. It is known that there are genetic influences on the serotonergic system. Increasing evidence suggests that these differences may influence response to drugs of abuse. For example, genetic variation of the promoter for the serotonin transporter (SERT) gene has been associated with level of SERT activity. *In vitro* studies show carriers of a short allele of the SERT promoter may have significant reductions in SERT activity (Lesch et al. 1996). Recently, Heinz et al. (2000) suggested that homozygous carriers of the long allelic variant of the serotonin transporter gene promoter region may have increased susceptibility to the neurotoxic effects of ethanol, which were measured as decreased serotonin reuptake transporter (SERT) availability in the raphe. In addition, decreased serotonergic functioning is thought to be related to impulsivity and sensation-seeking (Zuckerman 1996). Individuals with greater tendency to use illicit drugs may therefore have a higher prevalence of serotonergic abnormalities. Furthermore, it is not implausible to hypothesize that individuals with lower serotonergic tone might be specifically vulnerable to self-administration of drugs that are serotonin releasers, such as MDMA (Laviola et al. 1999). Thus, when correlations between ecstasy use and altered serotonergic functioning or psychopathology are detected in retrospective studies, it is impossible to determine the direction of causality.
Table 5.1: Summary of Common Study Limitations

<table>
<thead>
<tr>
<th>Reference</th>
<th>Volunteer Sampling</th>
<th>Group Matching</th>
<th>Other Issues</th>
<th>Non-independent samples</th>
<th>Lack of Adequate Established Norms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al, 1993</td>
<td>X</td>
<td>X</td>
<td>U, B</td>
<td>2 w +</td>
<td>1</td>
</tr>
<tr>
<td>Bolla et al, 1998</td>
<td>X</td>
<td>X</td>
<td>U, B</td>
<td>4 (2-36) w</td>
<td>1</td>
</tr>
<tr>
<td>Brody et al, 1998</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Chang et al, 2000</td>
<td>X</td>
<td>X</td>
<td>U</td>
<td>6.6 ± 7.7 (0.5-26) m</td>
<td>3 X</td>
</tr>
<tr>
<td>Chang et al, 1999</td>
<td>X</td>
<td>X</td>
<td>?</td>
<td>4.0 (0.5-26) m *</td>
<td>3</td>
</tr>
<tr>
<td>Croft et al, 2001</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>2 d +</td>
<td></td>
</tr>
<tr>
<td>Daffers et al, 1999</td>
<td>X</td>
<td>X</td>
<td>NA</td>
<td>S</td>
<td>X</td>
</tr>
<tr>
<td>Gamma et al, 2000</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>1 wk +</td>
<td>9 X</td>
</tr>
<tr>
<td>Gamma et al, 2001</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>1 wk +</td>
<td>9 X</td>
</tr>
<tr>
<td>Gerra et al, 1998</td>
<td>X</td>
<td>X</td>
<td>U</td>
<td>3 w</td>
<td>4</td>
</tr>
<tr>
<td>Gerra et al, 2000</td>
<td>X</td>
<td>X</td>
<td>U</td>
<td>3 w-12 m</td>
<td>4</td>
</tr>
<tr>
<td>Gouzoulis-Mayfrank et al, 2000</td>
<td>X</td>
<td>X</td>
<td>U</td>
<td>41 ± 71.1 (7-356) d</td>
<td>5</td>
</tr>
<tr>
<td>Krystal et al, 1992</td>
<td>X</td>
<td>X</td>
<td>NA</td>
<td>S</td>
<td>66 ± 50 (20-180) d</td>
</tr>
<tr>
<td>McCann et al, 1994</td>
<td>X</td>
<td>X</td>
<td>U, B</td>
<td>17.9 ± 24.7 (2-104) w</td>
<td>1</td>
</tr>
<tr>
<td>McCann et al, 1998</td>
<td>X</td>
<td>X</td>
<td>U</td>
<td>19 (3-147) w</td>
<td>X</td>
</tr>
<tr>
<td>McCann et al, 1999a</td>
<td>X</td>
<td>X</td>
<td>U, B</td>
<td>14 ± 29 (3-139) w</td>
<td>6</td>
</tr>
<tr>
<td>McCann et al, 1999b</td>
<td>X</td>
<td>X</td>
<td>U, B</td>
<td>13.91 ± 6.54 (3-147) w</td>
<td>6</td>
</tr>
<tr>
<td>Morgan et al, 1998 - Study 1</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>20.4 ± 33.6 d **</td>
<td></td>
</tr>
<tr>
<td>Morgan et al, 1998 - Study 2</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>65.1 ± 85.7 d</td>
<td>7</td>
</tr>
<tr>
<td>Morgan et al, 1999</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>65.1 ± 85.7 d</td>
<td>7</td>
</tr>
<tr>
<td>Obrocki et al, 1999</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>U</td>
</tr>
<tr>
<td>Parrott &amp; Lasky, 1998</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>7 d +</td>
<td></td>
</tr>
<tr>
<td>Parrott et al, 1998</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Parrott et al, 2000</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>1 d +</td>
<td></td>
</tr>
<tr>
<td>Peroutka et al, 1987</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>6 w +</td>
<td></td>
</tr>
<tr>
<td>Price et al, 1989</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>S</td>
<td>66 ± 50 (20-180) d</td>
</tr>
</tbody>
</table>

Abbreviations: B = blood drug screen; d = day; H = hair drug test; m = month; NA = not applicable; S = self report; U = urine drug screen; w = week.

Numbers in column on Non-Independent Samples indicates studies that contain some of the same individuals.

Some study limitations discussed in text are not indicated here due to space constraints.

* gives median, rather than mean, time since last use.

** 7 of 16 used 3-7 d before testing.
Recruitment and Matching of Volunteer Groups is Poorly Described. The procedures with which user and nonuser groups were recruited and matched are often poorly described. When attempting to detect subtle effects of drug exposure, it is crucial that comparison groups be as similar as possible. For example, if one comparison group has more education, it would not be surprising if they also perform better on neurocognitive tests. Unless education is comparable between groups or the difference is taken into consideration during statistical analysis, then a performance difference may be erroneously attributed to drug use when it is actually related to education. In this report, groups are described as matched with respect to a given variable if researchers indicated that there was no statistically significant difference between groups for that variable. Unless otherwise noted, this should not be taken to imply that matching was part of the inclusion/exclusion criteria or recruitment process.

Self-reports of Drug Use are Inaccurate and Many Ecstasy Users are Polydrug Users. A third significant limitation to this literature is the reliance on user self-reports of past ecstasy (and other drug) exposure. Both the accuracy of user recollections and the contents of illicit drug preparations are questionable. The inaccuracy of attempts to measure past ecstasy use is likely to make it more difficult to detect significant relationships between ecstasy exposure and user-nonuser differences. For example, given that one ‘brand’ of illicit ecstasy pills contained between 19 and 140 mg in one published
abstinence period is required to exclude this possibility with MDMA. While withdrawal-report (Sherlock et al. 1999), two individuals reporting ecstasy use of a single tablet of a single type once or twice per month for the last year may have actually consumed between 228 and 3360 mg MDMA total. This will obviously make attempts to correlate repeated drug use and other indices difficult. Furthermore, this estimate does not take into consideration the fact that some ecstasy pills contain other potentially neurotoxic compounds, such as ketamine (Shewan and Dalgarno 1996). As a result of these adulterants, even ecstasy users who do not report other drug use may actually be polydrug users.

Very few regular ecstasy users report restricting their substance use to ecstasy alone, and a large number of ecstasy users have also used other drugs. Several researchers have attempted to control for the effects of polydrug use by either employing drug matched controls (Bolla et al. 1998; Semple et al. 1999) or employed drug-naïve and drug-using controls, with cannabis users often serving as the drug-using controls (Croft et al. 2001; Gouzoulis-Mayfrank et al. 2000; Morgan 1998; 1999; Rodgers 2000). However, ecstasy users report a greater number of exposures to substances such as psychostimulants and hallucinogens and report having used a wider variety of substances than cannabis users or polydrug users who have not used ecstasy. Hence differences between ecstasy users and drug-matched controls may be due in part to differences in exposure to other drugs.

Polydrug use is often associated with more severe consequences than use of individual drugs of abuse (Selby and Azrin 1998). This may partially reflect the type of person who uses multiple drugs, but it also probably reflects the fact that simultaneous use of multiple drugs can lead to increased toxicity beyond that predicted from the individual drugs. Numerous studies in rats have documented the ability of other pharmacological agents to increase MDMA-induced neurotoxicity. For example, hallucinogens appear to increase MDMA-induced serotonergic neurotoxicity (Gudelsky et al. 1994). Thus, even if researchers attempt to control for other drug use in their analyses, it is possible that the apparent toxicity of ecstasy may be exaggerated in polydrug users due to drug interactions.

**Short-term Effects are not distinguished from Long-term Effects.** A related and probably more serious concern is the difficulty of separating short-term from long-term ecstasy effects. Unless hair samples or repeated urine samples are collected, it is impossible to confirm abstinence from MDMA for more than a few days. In many published studies, no attempts to confirm user reports of recent drug use appear to have been made. In other investigations, participants report their last use of ecstasy or MDMA to be fewer than seven days before the study day. User surveys have documented dysphoric mood for several days after ecstasy use in some users (Croft et al. 2001; Curran and Travill 1997; Parrott and Lasky 1998). Dysphoric mood has also been reported in clinical studies where MDMA has been administered to participants in a controlled setting (Liechti and Vollenweider 2000b; Vollenweider et al. 1998a). These short-term residual effects therefore presents a possible explanation for some of the reported changes in ecstasy users in studies where volunteers may have ingested ecstasy only a few days before testing (e.g., Gamma et al. 2000b; Parrott et al. 1998). It is not clear how long an abstinence period is required to exclude this possibility with MDMA. While withdrawal-
induced dysphoria is seldom significant in studies administering psychostimulants to healthy volunteers, recovery from psychostimulant use can reportedly take as long as 1 month in chronic stimulant abusers. In a recent study, dependent cocaine users improved in mood and self-reported cognitive skills over 28 days of abstinence (Coffey et al. 2000).

**Subjects may be Aware of Research Hypotheses.** The media has reported on research findings concerning the neurotoxic effects of MDMA in non-human animals and deficits in neurocognitive function in ecstasy users. It seems likely that ecstasy users have encountered this information, with awareness increasing over the last ten years. The impact of such widespread awareness of research hypotheses concerning the effects of MDMA is unknown. It is possible that individuals who perceive themselves as affected by regular ecstasy use may be more likely to participate in research studies than individuals who do not perceive any effects arising from regular ecstasy use. Some participants may strive to demonstrate their competence on neurocognitive tasks in order to refute hypotheses concerning the detrimental effects of ecstasy on cognitive function. However, they may also strive to be “good subjects” by attempting to confirm the researcher’s hypothesis by performing less well or by searching for and exaggerating any psychiatric symptoms they have experienced.

**Same Volunteers are used in Multiple Publications.** Another limitation of the literature comparing ecstasy users and nonusers is the low independence of publications. Multiple papers appear to use largely the same groups of volunteers. For example, Krystal et al. (1992) use the same group of ecstasy users as Price et al. (1989) which appears to be a subset of volunteers from Ricaurte et al. (1990). Similarly, ecstasy users in Bolla et al. (1998) appear to be mostly, but not completely, a subset of those in McCann et al. (1994). While it may be reasonable to separately publish different measures from the same volunteers, it is important to clearly state that this is being done. When the same volunteers are used in multiple studies, consistent findings of serotonergic differences may say more about the convergent validity of each publication’s serotonergic measures than about the effects of MDMA exposure.

**Serotonergic and Neurofunctional Measures do Not Indicate Toxicity Per Se.** There is a lack of well-validated measures of serotonergic toxicity. Serotonergic measures indicate altered serotonergic functioning, but may not indicate toxicity. Thus, measures are not clearly selective for toxic changes. One proposed method of deciding whether differences in biological markers indicate toxicity involves statistically defining an abnormal level based on the distribution characteristics in the study population. This interpretive method has been used in nonhuman MDMA toxicity studies to interpret neurochemical data (Gaylor and Slikker 1990) and is similar to the approach frequently used in clinical neurocognitive assessment. In neurocognitive assessment, it is common practice to consider test scores falling at least 1.3 standard deviations (SD) below the normative mean as “borderline” while those at least 2.0 SD below the mean are considered “impaired” (Lezak 1995). It should be noted that this approach relies on an adequately characterized study population. In some papers, measures are used which are sufficiently new (e.g., PET measures of estimated cortical SERT density) that values for the ecstasy-free comparison group in the paper(s) present the only available data on
“normal” values for the measure. As a result, it is not clear whether the full range of healthy, normal values is being represented. This is particularly unfortunate with SERT measures since increasing evidence suggests that there are genotypic and phenotypic variations in SERT functioning that are possibly associated with different vulnerabilities to substance abuse (Heinz and Jones 2000).

Table 5.2: Comparison of PET and Autoradiography Measures of SERT Density

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Cortex</td>
<td>37.9</td>
<td>14.9</td>
<td>23</td>
</tr>
<tr>
<td>Parietal Cortex</td>
<td>22.45</td>
<td>14.8</td>
<td>7.65</td>
</tr>
<tr>
<td>Occipital Cortex</td>
<td>26.73</td>
<td>26.9</td>
<td>-0.17</td>
</tr>
<tr>
<td>Temporal Cortex</td>
<td>136.64</td>
<td>21.2</td>
<td>115.44</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>223.46</td>
<td>171.2</td>
<td>52.26</td>
</tr>
<tr>
<td>Midbrain</td>
<td>200.59</td>
<td>255.1</td>
<td>-54.51</td>
</tr>
<tr>
<td>Thalamus</td>
<td>145.69</td>
<td>67.6</td>
<td>78.09</td>
</tr>
</tbody>
</table>

Mean Absolute Difference: 47.30
Stand. Dev.: 40.93

Data are from Scheffel et al. (1998) and compare two methods of assessing SERT changes in a baboon administered 5 mg/kg s.c. MDMA twice daily for 4 days 14 weeks. A single MDMA-treated animal was compared to a single control animal.

Non-invasive Serotonergic Measures Have Unclear Sensitivity. In addition to the interpretive problems of trying to measure toxicity with neurochemical or neurofunctional markers that are not selective for toxic changes, putative in vivo measures of the serotonergic system appear to have unclear or only moderate sensitivity. Nonhuman animal studies attempting to establish the use of potential clinical in vivo serotonergic measures consistently find that these measures underestimate central serotonergic changes. For example, Table 5.2 shows data from an animal study (Scheffel et al. 1998) comparing in vivo estimates of regional serotonin reuptake transporter (SERT) density (made using PET and [11C]McN5652) to post-mortem measures of SERT density (which employed [3H]Paroxetine binding). In most brain regions, actual SERT density is underestimated by the PET measure. The researchers suggest that differences in the temporal cortex and thalamus may be due to differences in the boundaries of the measured regions with the two methods. Even if these two regions are excluded from consideration, it can be seen that the PET measure of SERT density tends to overestimate changes in comparison to autoradiography. Similarly, primate studies of cerebral spinal fluid (CSF) concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid (5HIAA) show that MDMA-induced changes in CSF 5HIAA are about 20% less than either brain serotonin or brain 5HIAA changes (Ricaurte et al. 1988b).

Interpreting Studies for Risk Assessment

The above limitations complicate interpretation of retrospective studies. For the purpose of risk assessment, user-nonuser differences that correlate with ecstasy exposure or are consistent with the nonhuman animal toxicity literature should be accepted as possible effects of MDMA exposure. This approach differs from a purely scientific one in that the
standards of proof are lowered and correlation is taken to imply causality. This should produce a conservative risk analysis.

It should be noted that some of the apparent changes seen in ecstasy users are in the opposite direction of those reported in nonhuman animals. Such discrepancies between nonhuman neurotoxicity studies and studies of human ecstasy users may be due to (1) differences in MDMA administration patterns or time from last exposure, (2) actual species differences in response to MDMA, or (3) differences between ecstasy users and nonusers which predate ecstasy use. There is unfortunately little information about the time course of neurofunctional changes after MDMA exposure in nonhuman animals. Thus, reported increases at one time point cannot be taken to exclude decreases at another time point (or vice versa). In nonhuman MDMA studies, serotonin depletions in some brain regions are followed by increases as axons regrow. Similarly, human cerebral blood flow (CBF) data suggest a biphasic response to some MDMA exposures with decreases for several weeks followed by possible increases (Chang et al. 2000). One approach is to consider animal studies as demonstrating whether, in principle, MDMA exposure can alter a given index, ignoring discrepancies in the direction of changes.

It is more difficult to interpret studies that measure aspects of functioning in ecstasy users that have not been studied in MDMA-exposed animals. When these studies find differences between ecstasy users and nonusers, it is unclear whether these differences are due to serotonergic neurotoxicity or the repeated pharmacological effects of ecstasy. In evaluating these possibilities it is helpful to consider whether the possible changes have been seen in animals exposed to other serotonergic neurotoxins, such as dihydroxytryptamine (DHT). This can provide evidence that serotonergic neurotoxicity can alter this aspect of functioning. However, MDMA is thought to selectively damage axons originating in the dorsal raphe nucleus, while DHT will damage serotonergic (and noradrenergic, if no blocking agent is used) axons wherever it is infused. Unless DHT is infused into the dorsal raphe nucleus, it can be expected to produce a different pattern of serotonergic damage than MDMA, which may limit comparisons.

It is also helpful to consider whether the possible changes in ecstasy users have been documented in users of stimulant drugs that are not selective serotonergic neurotoxins, such as cocaine and amphetamine. If these other drugs can cause such changes, then it is possible that they can occur in ecstasy users in the absence of serotonergic neurotoxicity. This does not mean that the putative changes are not evidence of toxicity. It simply means that they are not evidence of selective serotonergic neurotoxicity. It is well established that cocaine, amphetamine, and other stimulant drugs can cause clinically significant toxicity, including impaired neurocognitive performance and ischemic damage to the brain.

A final important consideration concerns to magnitude of the apparent changes. In neurocognitive assessment, it is common practice to interpret test scores following at least 1.3 SD units below the normative mean as “borderline” and those 2.0 SD units below the mean as “impaired” (Lezak 1995). This approach is most useful for comparing two populations, such as ecstasy users and the general population. Such an approach can
establish whether individuals are still within the “normal” range on a given measure. However, remaining in the normal range of functioning can be a rather lax test, if changes are permanent or long lasting. Therefore, evidence of recovery must also be considered when assessing risks.

In summary, there are many limitations in existing studies of ecstasy users. Given the partially unknown long-term risks of MDMA exposure, it is important to be conservative in risk assessment. This can be achieved by assuming that there were no preexisting differences between ecstasy users and nonusers. One must then tentatively evaluate whether these differences are evidence of serotonergic neurotoxicity, some other type of toxicity, or neurofunctional changes of unknown significance. Nonhuman MDMA studies are obviously an important source of evidence for these assessments, although the lack of time course information makes it difficult to reconcile differences in the apparent direction of changes between human and nonhuman studies. The most conservative course appears to be to ignore these directional differences. In addition to nonhuman MDMA studies, it is helpful to consider nonhuman studies employing other serotonergic neurotoxins and studies of users of non-neurotoxic stimulant drugs. Finally, one must consider both the magnitude of apparent changes and any evidence of recovery.

Evidence of Serotonergic Differences between Ecstasy Users and Nonusers

Cerebral Spinal Fluid Levels of 5HIAA. The earliest attempts to detect possible serotonergic changes in ecstasy users involved measuring cerebral spinal fluid (CSF) concentrations of the serotonin metabolite 5-hydroxyindole acetic acid (5HIAA) (Peroutka et al. 1987). As summarized in Table 5.3, CSF 5HIAA appears to be modestly reduced in very experienced ecstasy users (McCann et al. 1999b; McCann et al. 1994; Ricaurte et al. 1990).

Table 5.3: Cerebral Spinal Fluid Levels of 5HIAA in Ecstasy Users and Nonusers

<table>
<thead>
<tr>
<th>Study</th>
<th>Controls</th>
<th>Ecstasy Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroutka et al., 1989</td>
<td>22.5 ± 9.8</td>
<td>19.6 ± 0.7 n.s.</td>
</tr>
<tr>
<td></td>
<td>N = 17</td>
<td>N = 5</td>
</tr>
<tr>
<td>z-score=</td>
<td>0 ± 1</td>
<td>-0.296 ± 0.07 n.s.</td>
</tr>
<tr>
<td>Ricaurte et al., 1990</td>
<td>19.1 ± 4.3</td>
<td>14.2 ± 4.8*</td>
</tr>
<tr>
<td></td>
<td>N = 24</td>
<td>N = 33</td>
</tr>
<tr>
<td>z-score=</td>
<td>0 ± 1</td>
<td>-1.14 ± 1.1*</td>
</tr>
<tr>
<td>McCann et al., 1994</td>
<td>15.2 ± 7.9</td>
<td>10.3 ± 3.1*</td>
</tr>
<tr>
<td></td>
<td>N = 28</td>
<td>N = 30</td>
</tr>
<tr>
<td>z-score=</td>
<td>0 ± 1</td>
<td>-0.62 ± 0.39*</td>
</tr>
<tr>
<td>McCann et al., 1999b</td>
<td>14.77 ± 7.1</td>
<td>10.97 ± 3.8*</td>
</tr>
<tr>
<td></td>
<td>N = 23</td>
<td>N = 22</td>
</tr>
<tr>
<td>z-score=</td>
<td>0 ± 1</td>
<td>-0.535 ± 0.54*</td>
</tr>
</tbody>
</table>

Raw values are means ± SD expressed in ng/ml of CSF.
* indicates values are significant less than those of controls, P <= 0.05.
McCann et al. (1994) were unable to detect a significant correlation between CSF 5HIAA levels and ecstasy exposure. In contrast, Bolla et al. (1998) describe a significant correlation between CSF 5HIAA and estimated milligrams of ecstasy per month in what appears to be largely a subset of the volunteers from McCann et al. (1994). No other significant correlations between exposure and this index have been reported. However, comparison of mean CSF 5HIAA values and ecstasy exposure across studies (Figure 5.1) suggest such a correlation might exist if all individual data collected by McCann and Ricaurte were pooled. Thus, while no significant decrease was noted by Peroutka et al. (1987) in volunteers who had 18.2 ± 11.5 (1-33) exposures to ecstasy, significant decreases were noted by McCann and Ricaurte in studies using volunteers with 52 ± 45 (11-219) exposures (Ricaurte et al. 1990), 215 ± 33 (30-725) exposures (McCann et al. 1999b), and 94.4 ± 90.6 (25-300) exposures (McCann et al. 1994). In contrast to this suggested relationship between exposure and decreased CSF 5HIAA, no apparent pattern exists when evidence of recovery is sought by comparing average time from last exposure to CSF 5HIAA levels. This may be due to the narrow range of times from last exposure in published studies.

MDMA-related reductions in CSF 5HIAA are consistent with nonhuman primate data that have documented long-lasting changes. Ricaurte et al. (1988b) reported that CSF 5HIAA in squirrel monkeys was 40% of controls (or approximately 2.8 SD units), brain 5HIAA 21% of controls, and brain serotonin was approximately 15% of controls at 2 weeks after administration of 5 mg/kg s.c. MDMA twice daily for 4 days. A second study (Insel et al. 1989) reported that CSF 5HIAA decreases were detectable up to 14 weeks after MDMA exposure in rhesus monkeys administered 10 mg/kg i.m. MDMA twice daily for 4 days. Figure 5 of the paper by Insel et al. graphically indicates that CSF 5HIAA levels were reduced to approximately 60% of controls (approximately 1 SD units) at 14 weeks post-exposure.
Figure 5.1: Relationship between ecstasy exposure and CSF 5HIAA in 4 studies

Logarithmic curve fitting:
\[ y = -3.7545 \ln(x) + 29.509 \]
\[ R^2 = 0.8447 \]

Serotonin Reuptake Transporter Density. Two studies using positron emission tomography (PET) have reported reduced serotonin transporter binding in ecstasy users (McCann et al. 1998; Semple et al. 1999). These reports have proven controversial and interpretations have been disputed (Heinz and Jones 2000; Kuikka and Ahonen 1999; Reed et al. 1999). The novelty of PET measures of cortical serotonergic functioning makes their interpretation difficult.

In contrast to these studies of ecstasy users, preliminary unpublished results from Dr. Franz Vollenweider and colleagues did not detect changes in SERT density (using the same PET ligand as McCann et al.) at four weeks after six MDMA-naïve volunteers were administered either 1.5 or 1.7 mg/kg po (Vollenweider et al. 2001; personal communication). Thus, it would appear that single doses up to 1.7 mg/kg MDMA do not produce detectable long-term effects on the serotonin transporter when administered once in a clinical setting.
However, comparisons of illicit ecstasy users and nonusers have detected significant differences in estimated SERT density. One study (Semple et al. 1999) reported significant SERT decreases in the left occipital, left and right calcarine, and right posterior cingulate cortices when results were analyzed by ANCOVA using cerebellar activity as a covariate. These decreases were moderate in magnitude and ranged from \(-0.629 \pm 0.8\) standard deviation (SD) units in the left occipital cortex to \(-0.971 \pm 0.83\) SD units in the left calcarine cortex. Significant decreases in other brain regions were detected using statistical parametric mapping. McCann et al. (1998) graphically depict but do not numerically report their results. Figure 4 in their paper, a graph of estimated SERT binding (i.e., “in distribution volume”), indicates that data from only one ecstasy user is obviously lower than those of control volunteers and data from other ecstasy users remain within the range of nonuser volunteers.

Both research groups reported correlations between ecstasy exposure and SERT binding. Specifically, Semple et al. (1999) reported significant correlations between time from last ecstasy exposure and apparent SERT binding, suggesting an unexpectedly fast recovery of SERT levels over a several week period after ecstasy exposure. McCann et al. (1998) did not detect evidence of recovery but did report a correlation between lifetime number of ecstasy exposures and apparent SERT binding. However, this correlation has been criticized for its inclusion of control volunteers (Kuikka and Ahonen 1999).

Using PET to estimate SERT density requires complex modeling (Buck et al. 2000), and methodological criticisms have been made of the PET studies of ecstasy users (Heinz and Jones 2000; Kuikka and Ahonen 1999). Most significantly, it has been argued that there is little evidence that the binding of \([^{125}\text{I}]\text{beta-CIT}\) or \([^{11}\text{C}]\text{MCN-5652}\) in the cerebral cortex reflect specific binding to serotonin transporters (Heinz and Jones 2000). This suggests that the findings of altered cortical binding by these radioligands may be partially or completely due to differences in blood flow, blood-brain barrier permeability, or other factors. In fact, Chang et al. (2000) have reported decreases in regional cerebral blood flow 10-21 days after MDMA administration in a prospective controlled clinical trial. Decreased cerebral blood flow in ecstasy users could potentially produce a lowering in apparent SERT density. Because decreases in regional cerebral blood flow were not detectable in two subjects who were measured at 43 or 80 days after drug administration, this phenomenon may be an important confounding variable in PET studies only when MDMA exposure has occurred in the last few weeks. Thus, a normalizing of cerebral blood flow may explain Semple et al.’s (1999) dramatic correlation (see Figure 3 in Semple’s paper) between apparent SERT density and time since last ecstasy use (which was an average of \(18 \pm 8\) days). It does not appear that reduced rCBF can explain the findings of McCann et al. (1998) since time from last ecstasy exposure was reportedly an average of 19 (range: 3-147) weeks in that study.

An additional issue is that neither PET study controlled for genetic influences on SERT density. Polymorphisms in the SERT gene and encoder regions have been reported (Heils et al. 1996; Lesch et al. 1996) and may be associated with anxiety-related traits (Lesch et al. 1996) and vulnerability to drug abuse (Heinz and Jones 2000). These genetic variations influence the expression and activity of the SERT. For example, a
postmortem study of suicide victims and controls reported that the density (Bmax) of [3H]-paroxetine-labeled SERT in the prefrontal cortex of individuals who were homozygous or heterozygous for the long allele variant of the SERT gene was only about 46% of individuals who were homozygous for the short allele (Du et al. 1999). Although studies on this issue have found conflicting results, it would appear helpful in future retrospective studies of ecstasy users to confirm that genotype distributions are in Hardy-Weinburg equilibrium within each study group.

In summary, one small, still unpublished, prospective study did not find changes in estimated SERT density after up to 1.7 mg/kg MDMA. On the other hand, SERT binding appears modestly lower in ecstasy users than nonusers. One study suggests that there is rapid recovery of SERT density while another finds no such evidence. There is some doubt that SERT binding is being accurately measured. As discussed earlier and depicted in Table 5.2, a nonhuman animal study also suggests that PET measures may be somewhat insensitive to SERT changes.

**Neuroendocrine Measures of Serotonergic Functioning.** Alterations in neuroendocrine response to 5HT$_{1A}$ agonist 8-OH-DPAT have been reported in rats at 2 weeks after a non-neurotoxic dose (2.0 mg/kg) of MDMA (Poland 1990), suggesting that such neuroendocrine changes are not necessarily evidence of neurotoxicity. Altered neuroendocrine response to serotonergic drugs has also been shown in a variety of psychiatric disorders and may be related to personality. For example, humans with high scores on a measure of “sensation seeking” have been shown to have blunted neuroendocrine response to the partial 5HT$_{1A}$ agonist ipsapirone (Netter et al. 1996). Thus, altered neuroendocrine response in ecstasy users cannot be assumed to have been caused by MDMA exposure nor can it be considered a measure of toxicity. Despite these caveats, there is evidence that psychostimulant abuse can lead to alterations in the neuroendocrine response to serotonergic drugs. For example, the prolactin response to fenfluramine in a group of cocaine-dependent individuals was significantly increased between the first and third weeks after discontinuing cocaine use (Buydens-Branchey et al. 1999), suggesting a drug-induced decrease followed by recovery.

A number of studies have measured the neuroendocrine response to serotonergic compounds as a method of probing the serotonergic systems of ecstasy users. Former ecstasy users (with confirmed 12 months of abstinence from ecstasy) in substance abuse treatment programs have been found to differ from healthy nondrug users in the neuroendocrine response to the serotonin releaser, d-fenfluramine (Gerra et al. 2000). Despite obvious limitations in comparing individuals in treatment to healthy controls, these results are consistent with two other studies reporting decreased neuroendocrine response to serotonergic drugs in ecstasy users (McCann et al. 1999a; Verkes et al. 2001). In an earlier study, Price et al. (1989) reported a nonsignificant trend towards decreased response to L-tryptophan in ecstasy users whom had been preselected for low CSF 5HIAA compared to control volunteers (R. Doblin, personal communication). A subsequent report also failed to detect effects of ecstasy exposure on the neuroendocrine response to L-tryptophan (McCann et al. 1994). The findings of these studies differ somewhat from the nonhuman animal literature. The prolactin response to dl-
fenfluramine in rats is reportedly enhanced at 4 months and normal at 12 months after a neurotoxic MDMA regimen (Poland et al. 1997).

**Serotonin-Related EEG Differences.** Tuchtenhagen et al. (2000) reported that ecstasy users had increased stimulus dependence for event related potential EEG N1/P2 amplitudes, a measure that may indicate low serotonergic activity. The selectivity of this measure for serotonergic changes was cast in doubt by one study that was unable to find a significant effect of acute 5HT depletion (achieved with acute dietary tryptophan depletion) on the stimulus dependence of auditory evoked potentials (Dierks et al. 1999). Thus, the difference between ecstasy users and controls may not reflect a specific serotonergic difference, although it undeniably represents a neurofunctional difference. Results of two other studies investigating EEG differences between users and nonusers are discussed below.

**5HT<sub>2A</sub> Receptor Density Differences.** A recent study by Reneman et al. (2000a; Reneman et al. 2000b) suggested that ecstasy users have altered 5HT<sub>2A</sub> receptor density in the cortex. While the first published report from this study suggested increased 5HT<sub>2A</sub> receptors in the occipital cortex of five ecstasy users, the second published report from the same group suggested that cortical 5HT<sub>2A</sub> receptors may be initially decreased then increased in ecstasy users. Although not reported in either paper, increased 5HT<sub>2A</sub> density correlated with the extent of previous ecstasy exposure in the five ecstasy users whose data appeared in both papers (Reneman, personal communication to R. Doblin).

In contrast, animal studies have found evidence of only transient changes in 5HT<sub>2A</sub> receptor density after serotonergic neurotoxicity. A rodent study found that neurotoxic MDMA exposure was associated with a transient decrease in 5HT<sub>2A</sub> receptor density, which normalized by 21 weeks (Scheffel et al. 1992). In another study (Granoff and Ashby 1998), researchers were unable to detect any change in a behavioral measurement of central 5HT<sub>2A</sub> functioning (DOI-induced head twitch and locomotion) in rats one month after a neurotoxic regimen of MDMA. Finally, serotonergic neurotoxicity achieved using dihydroxytryptamine (DHT) has generally not been found to cause alterations in 5HT<sub>2A</sub> receptors (Compan et al. 1998; Fischette et al. 1987). These studies suggest that changes in 5HT<sub>2A</sub> receptor density may not be the result of neurotoxicity, but may be a response to the pharmacological effects of MDMA.

**Other (Possibly Nonserotonergic) Neurofunctional Differences between Ecstasy Users and Nonusers**

If much of the evidence of serotonergic differences between frequent illicit ecstasy users and nonusers can be disputed, it is only because the measurements may not be specific to serotonergic toxicity and may reflect some more general neurofunctional differences (which may or may not be caused by MDMA exposure). There is strong evidence of such neurofunctional differences between ecstasy users and nonusers. These reported neurofunctional differences are summarized in Table 5.4.
Cerebral Blood Flow and Volume Differences. In the retrospective study discussed above, Reneman et al. (2000a, 2000b) recently reported preliminary data that two ecstasy users had increased regional cerebral blood volume (rCBV) in some areas compared to three ecstasy users with more recent exposure and six nonuser volunteers. In contrast, two larger studies have failed to find significant regional cerebral blood flow (rCBF) differences between users and nonusers (Chang et al. 2000; Gamma et al. 2001). Thus, there is mixed evidence for lasting alterations in rCBF/V.

More compelling evidence of rCBF changes after MDMA use comes from a prospective clinical study measuring rCBF before and after volunteers were administered MDMA. As mentioned above, Chang et al. (2000) reported that 8 volunteers had decreased cerebral blood flow in several brain regions 10-21 days after participating in a study employing two oral doses of 1.0 to 2.5 mg/kg MDMA given two weeks apart. Apparent increases in rCBF were found in an additional 2 volunteers who were measured 43 and 80 days, respectively, after MDMA, suggesting that the decreases in rCBF are not lasting or that a biphasic response with decreases followed by increases may have occurred.

Given this evidence of short-term rCBF decreases, the conflicting results in the retrospective studies may be due to the different ecstasy exposure patterns for the volunteers, with short-term decreases in rCBF influencing the results. The use patterns and time from last exposure to ecstasy are not described for the five ecstasy users in the Reneman study. However, the larger groups of 10 recent and 5 less recent users (called “ex-users” in the paper) from which these volunteers were selected had reportedly been last exposed to ecstasy an average of 1.75 ± 1.25 and 4.5 ± 3.75 months previously, respectively. Thus, some of the volunteers had reported abstinence times in which decreases are expected (i.e., 2 weeks). The abstinence times in the Reneman et al. study are less than those of the larger study by Chang et al. (1999) which examined 21 nonusers and 21 ecstasy users with times from last ecstasy exposure of 6.6 ± 7.7 (0.5-26) months and failed to detect any differences. In total, the overall evidence appears to suggest that these rCBF/V changes are not persistent, although further research is needed.

Possible late increases in CBF are consistent with the animal literature. McBean et al. (1990) examined young rodents for changes in CBF 6 to 9 weeks after exposure to a neurotoxic MDA regimen and found significant increases in CBF and the ratio of CBF-to-cerebral glucose utilization in some regions. In a subsequent report, the same investigators described enhanced cerebrovascular responsiveness to hypercapnia (excessive carbon dioxide) in the frontal cortices of similarly treated animals (Kelly et al. 1994). Given the reportedly separate regulation of cerebral blood flow from peripheral cardiovascular functioning, it seems unlikely that this phenomenon is related to the altered cardiovascular regulation reported in ecstasy users by Brody et al. (1998). Decreased cerebral blood flow has been previously noted in cocaine abusers (Volkow et al. 1988) with some limited evidence of abstinence-related recovery (Herning et al. 1999; Holman et al. 1993; Kosten et al. 1998).
Table 5.4: Reported Neurofunctional Differences Between Ecstasy Users and Nonusers

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Putative Serotonergic Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased CSF 5HIAA</td>
<td>Yes</td>
<td>Decreased up to 2 weeks after MDMA in squirrel monkeys (Ricaurte et al., 1988) and 14 weeks after MDMA in rhesus monkeys (Insel et al., 1989).</td>
<td>No</td>
<td>No</td>
<td>Decreased in McCann et al., 1999, 1994; Ricaurte et al., 1990; Unchanged in Peroutka et al., 1989</td>
</tr>
<tr>
<td>Decreased then Increased 5HT(_{2A}) receptor density</td>
<td>Yes</td>
<td>Decreased at 24 hr, normal at 21 d after MDMA in rats (Scheffel et al., 1992).</td>
<td>Yes</td>
<td>Not reported</td>
<td>Increased in Reneman et al., 2000a; Decreased then increased in Reneman et al., 2000b</td>
</tr>
<tr>
<td>Decreased neuroendocrine response to serotonergic drugs, in 4 of 6 studies</td>
<td>Yes</td>
<td>Increased at 2 months, normal at 12 months in rats (Poland et al. 1997)</td>
<td>Yes</td>
<td>No</td>
<td>Decreased in Gerra et al., 2000, 1998; McCann et al., 1999a; Unchanged in Price et al., 1989; McCann et al., 1994.</td>
</tr>
<tr>
<td>Decreased SERT density, estimated with PET, in 2 of 2 studies</td>
<td>Disputed - ligand kinetics may be altered by other changes (Kuikka &amp; Ahonen 1998).</td>
<td>PET measures apparently decreased in one baboon up to 14 weeks after MDMA (Scheffel et al., 1998).</td>
<td>Yes, though McCann included controls.</td>
<td>Mixed (Yes in Semple; No in McCann)</td>
<td>Semple et al., 1999; McCann et al., 1998.</td>
</tr>
<tr>
<td>Increased stimulus dependence for ERP EEG N1/P2 amplitudes</td>
<td>Disputed – 5HT depletion did not change measure in one study (Dierks et al., 1999).</td>
<td>Unknown</td>
<td>No</td>
<td>Not reported</td>
<td>Tuchtenhagen et al., 2000</td>
</tr>
<tr>
<td><strong>Nonspecific Neurofunctional Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased brain myo-inositol measured as 1H MRS in 1 of 1 study</td>
<td>-</td>
<td>Unknown</td>
<td>Yes</td>
<td>Not reported</td>
<td>Chang et al., 1999</td>
</tr>
<tr>
<td>Altered sleep patterns in 2 of 2 studies</td>
<td>-</td>
<td>Unknown</td>
<td>No</td>
<td>Not reported</td>
<td>Allen et al., 1993; McCann et al., 2000.</td>
</tr>
<tr>
<td>Altered cerebral blood flow or volume in 2 of 4 studies</td>
<td>-</td>
<td>Increased blood flow 6-9 wks after MDA in rats (McBean et al., 1990)</td>
<td>Yes</td>
<td>Yes</td>
<td>Altered in Reneman et al., 2000a,b and in Chang et al., 2000 (prospective study); Unchanged in Chang et al., 2000 (user-nmuser study) and Gamma et al., in press.</td>
</tr>
<tr>
<td>Decreased cerebral glucose utilization in 1 of 1 study</td>
<td>-</td>
<td>Increased in some hippocampal areas 2 wks (Sharkey et al., 1991) after MDA and 6-9 wks after MDA (McBean et al., 1990) in rats</td>
<td>No</td>
<td>No</td>
<td>Obrocki et al., 1999</td>
</tr>
<tr>
<td>Increased alpha and beta EEG power in 2 of 2 studies</td>
<td>-</td>
<td>Unknown</td>
<td>Yes</td>
<td>Not reported</td>
<td>Dafters et al., 1999; Gamma et al., 2000</td>
</tr>
</tbody>
</table>
**Electroencephalogram Differences.** In addition to the report by Tuchtenhagen (2000) discussed above, two other studies have looked for evidence of EEG alterations in ecstasy users (Dafters et al. 1999; Gamma et al. 2000b). Both studies reported increased alpha and beta EEG power in ecstasy users. Although no control group was included in the report by Dafters et al., the authors detected a significant association between ecstasy use in the previous year and EEG measures. Whether these apparent changes reflect neurotoxicity (as suggested by Dafters et al.) or nontoxic functional differences (a possibility raised by Gamma et al.) is unclear. Average time from last ecstasy exposure was not reported in these studies. Dafters et al. state that no volunteers reported use within 7 days. Thus, it is also not clear to what extent short-term changes are being detected. Beta increases have been reported 4 to 15 days from last exposure in cocaine dependent individuals and correlated with 30 day cocaine exposure in one study (Herning et al. 1997), suggesting a possible role for short-term effects in these changes. However, the fact that Dafters et al. found that EEG measures correlated with ecstasy use in the previous year (which was 14.04 (1-60) tablets) suggests that long-term changes may have contributed to the findings. Gamma et al. reported increased depressiveness and anxiety (measured using self-report EWL ratings) in the ecstasy users, which may be related to the EEG changes. Both alpha and beta increases have been reported in depressed individuals (Pollock and Schneider 1990), while increased alpha power is generally associated with decreased brain activation.

**Sleep Differences.** Allen et al. (1993) reported that 23 ecstasy users with 79.4 (25-300) previous exposures had decreased total sleep time, NREM sleep time, and stage 2 sleep time in comparison to nonusers. For example, ecstasy users slept approximately 20 minutes less than nonusers. Twelve of the 23 ecstasy users but only 5 of the 22 nonusers had traveled from two or three time zones to participate in the study. However, the authors reported that the differences were still significant when these possible jetlagged volunteers were removed. In a recent review of evidence for MDMA-induced neurotoxicity in humans, McCann et al. (2000) referred to a currently unpublished study of ecstasy users that found increased sleep efficiency and sleep time with specific increases in stage 3 and stage 4 sleep. These increases in stage 3 and stage 4 sleep are somewhat consistent with nonsignificant trends toward increases in the Allen et al. study. However, there seems to be no consistent pattern of changes in sleep efficiency or sleep time in ecstasy users.

Changes in sleep architecture are not necessarily caused by serotonergic neurotoxicity. Evidence for this claim comes from rat locomotor studies and a study of chronic amphetamine users. One study found that rats had decreased diurnal and nocturnal locomotor activity at 7 to 14 days after a neurotoxic MDMA regimen (Wallace et al. 2001). One possible explanation for this is that serotonergic neurotoxicity led to the dysregulation of the sleep-wake cycle. However, the rats appeared to have a generalized decrease in locomotor activity that is more consistent with drug withdrawal than sleep-wake alterations. Decreased locomotor activity has been reported in rats that have been sensitized to non-neurotoxic doses of \( d \)-amphetamine (Robinson and Camp 1987). DHT lesions in a number of brain areas produce hyperactivity (Williams and Azmitia 1981),

Page 119 of 367
while selective dorsal raphe lesions do not alter activity (Geyer et al. 1976). In a study of 6 female volunteers in withdrawal from chronic amphetamine use, researchers found changes in sleep architecture lasting 3 to 8 weeks (Oswald and Thacore 1963). Because amphetamine does not produce serotonergic neurotoxicity, this suggests that long-lasting changes in sleep architecture may be produced in chronic ecstasy users by mechanisms other than serotonergic neurotoxicity.

**Magnetic Resonance Spectroscopy Differences.** Proton Magnetic Resonance Spectroscopy (MRS) was used by Chang et al. (1999) to compare cerebral metabolite concentrations in ecstasy users and nonusers. N-acetyl-aspartate concentrations, an indicator of cell damage or death, which is sensitive to the effects of methamphetamine abuse (Ernst et al. 2000), were unchanged. However, myo-inositol (MI) concentrations were raised in the parietal white matter of ecstasy users. This appears to be related to ecstasy exposure since the increase correlated with the logarithm of lifetime ecstasy use. MI is found in high concentration in astrocytes where it appears to act as an osmolyte (a regulator of cell volume). Increased MI therefore suggests possible astrocyte proliferation in ecstasy users. This may be the result of neurotoxic insult (chemical markers of glial activation are used as measures of neurotoxicity). This possibility cannot currently be excluded. However, in an earlier report, Chang et al. (1997) found a similar degree of MI elevation in abstinent cocaine users, suggesting that elevated MI may be a nonspecific effect of psychostimulant (including MDMA) use and not necessarily linked to serotonergic damage. Chang et al. point out that in vitro research has demonstrated that MDMA and 5HT can increase glial glycogen phosphorylase activity (Poblete and Azmitia 1995), indicating the possibility of non-neurotoxic effects of MDMA on glial processes. Because 5HT$_{2A}$ receptors are expressed on astrocytes and increased by astrocyte activation (Wu et al. 1999), it is intriguing to speculate that the preliminary report of increased 5HT$_{2A}$ expression in ecstasy users (Reneman et al. 2000a) may also be related to glial activity.

**Cerebral Glucose Utilization Differences.** Changes in local cerebral glucose utilization have also been reported in ecstasy users with most recent ecstasy exposures ranging from 2 to 16 months ago (Obrocki et al. 1999). Using FDG-PET, significant decreases were noted in the left hippocampus with trends towards decreases in some other brain regions. Studies using rats have reported increases rather than decreases in glucose utilization. Increased glucose utilization in the hippocampus and several other brain regions was detected in rats 6-9 weeks after neurotoxic MDA exposure (McBean et al. 1990). Similarly, increased glucose utilization was found in some hippocampal areas in rats treated 14 days earlier with neurotoxic MDMA regimens (Sharkey et al. 1991). Examined by brain region, these changes did not seem to correlate with SERT changes, and thus may be a response to the serotonergic changes in other areas. It has been reported that local cerebral glucose utilization was not altered in adult rats at 3 weeks after neurotoxic 5,7-DHT exposure, despite an 80% decrease in 5HT levels (Cudennec et al. 1988). This suggests that serotonin neurotoxicity per se may not cause local cerebral glucose utilization alterations.
Mood Differences. Ecstasy use has been associated with increased self-reported dysphoria in comparisons between ecstasy users and nonusers and surveys of users. This dysphoric mood appears to peak several days after ecstasy use (Curran and Travill 1997; Liechti and Vollenweider 2000b; Parrott and Lasky 1998; Vollenweider et al. 1998a), but is likely more lasting in chronic users. Because dysphoria is a known residual effect of psychostimulant drugs, it is likely that ecstasy use plays a causal role in this phenomenon. Table 5.5 summarizes studies of mood in ecstasy users and comparison groups.

Interestingly, mood alterations are not always seen in chronic ecstasy users, despite serotonergic or neurofunctional differences in some cases (Krystal et al. 1992; McCann et al. 1994; Verkes et al. 2001).

The most extensive characterization of mood and psychological differences between illicit ecstasy users and nonusers was carried out by Parrott et al. (2000). Using several self-report instruments (the SCL-90R, Eysenck’s IVE, and an Uplifts/Hassles questionnaire), the authors found significant increases in dysphoric mood and reported psychological problems in a group of polydrug users with an average of 371 (30-1000) ecstasy exposures compared to a group of ecstasy-naïve volunteers. In contrast, less experienced ecstasy (and polydrug) users with an average of 6.8 (1-20) ecstasy exposures differed from nonusers in only two SCL-90R subscales (psychoticism and paranoid ideation), although their scores tended to be nonsignificantly higher than nonusers in other measures as well. The primary limitation of this study is that time from last drug exposure was not recorded (volunteers had reportedly not used any drugs on the day of assessment). This is a particularly important point because the standard instructions on the SCL-90R ask volunteers to report how they have felt in the last week, a time period during which the volunteers may have used drugs. Thus, it is not clear to what extent residual effects of a number of different drugs were detected rather than chronic ecstasy effects.

Current research cannot adequately address whether ecstasy use is associated with increased risk of mood or anxiety disorders, such as major depression. Case reports (discussed in a subsequent chapter) have described severe depressive episodes and anxiety disorders that seemed to be associated with ecstasy use. However, it is impossible to distinguish between ecstasy triggering symptoms in vulnerable individuals and ecstasy creating problems de novo. A review of case reports of psychiatric complications after ecstasy use concluded that there was insufficient evidence to conclude that ecstasy use was a main responsible factor for the reported psychiatric symptoms (Bango et al. 1998). Similarly, Curran noted that the majority of reports concerning ecstasy-related psychiatric complications involve polydrug users who are self-referred to psychiatric or drug abuse services (Curran 2000). These individuals may not be representative of the broader population of ecstasy users. However, given the apparent role of serotonergic dysfunction in affective disorders, further research comparing abstinent ecstasy users and properly matched controls is warranted.
### Table 5.5: Mood Alterations in Ecstasy Users

<table>
<thead>
<tr>
<th>Ecstasy Use (Mean ± SD)</th>
<th>Different from comparison group in…</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (per mo)</td>
<td>Duration (mo)</td>
<td>Time Since Last Use (days)</td>
</tr>
<tr>
<td>..</td>
<td>6.8</td>
<td>..</td>
</tr>
<tr>
<td>..</td>
<td>1 to 9</td>
<td>..</td>
</tr>
<tr>
<td>..</td>
<td>&gt;10</td>
<td>..</td>
</tr>
<tr>
<td>..</td>
<td>271</td>
<td>..</td>
</tr>
<tr>
<td>..</td>
<td>222 ± 358.4</td>
<td>..</td>
</tr>
<tr>
<td>..</td>
<td>235</td>
<td>51.6 ± 31.2</td>
</tr>
<tr>
<td>..</td>
<td>270 ± 397.2</td>
<td>..</td>
</tr>
<tr>
<td>0.5</td>
<td>73 ± 68</td>
<td>52.8 ± 28.8</td>
</tr>
<tr>
<td>1.9 ± 1.7</td>
<td>..</td>
<td>61 ± 27.6</td>
</tr>
<tr>
<td>2.94 ± 0.93</td>
<td>35.6 ± 17.5</td>
<td>25.44 ± 16.32</td>
</tr>
<tr>
<td>4.16 ± 4.79</td>
<td>94.4 ± 90.6</td>
<td>59.7 ± 35.52</td>
</tr>
<tr>
<td>4.36 ± 1.15</td>
<td>49.6 ± 33.2</td>
<td>49.4 ± 15.2</td>
</tr>
<tr>
<td>4.7 ± 2.7</td>
<td>62.7 ± 34.2</td>
<td>14 ± 8</td>
</tr>
<tr>
<td>4.7 ± 2.7</td>
<td>69.3 ± 38</td>
<td>15 ± 9</td>
</tr>
<tr>
<td>5 ± 1</td>
<td>196 ± 24</td>
<td>60 ± 36</td>
</tr>
<tr>
<td>8.43 ± 3.33</td>
<td>..</td>
<td>49.2 ± 16.44</td>
</tr>
</tbody>
</table>

Table was adapted from Morgan (2000).

Abbreviations: BDHI = Buss-Durkee Hostility Index; GHQ = General Health Questionnaire; HAMD = Hamilton Depression; MMPI-D = Minnesota Multiphasic Personality Inventory depression subscale; NIMH Panic = National Institute of Mental Health Self-Report Panic Scale; NIMH Symptom = National Institute of Mental Health Self-Report Symptom Scale; SCL90 = Symptom Check List 90; STAXI = State Traits Anxiety Scale; VAS Mood = Visual Analog Mood Scale.
Impulsivity and Other Personality Differences. Studies yield some mixed evidence that ecstasy use may be associated with increased impulsivity. It is not yet clear to what extent this represents a preexisting trait in individuals vulnerable to frequent ecstasy ingestion, a value espoused by the “rave culture” with which ecstasy is associated, or an effect of ecstasy exposure. It should be noted that, within limits, impulsivity is not itself an indicator of psychopathology (although research has examined links between impulsivity and the tendency to use drugs). Self-report measures of impulsivity include items that are likely to be viewed as positive traits by some.

Many of the personality differences between ecstasy users and control volunteers who do not use illicit drugs likely reflect preexisting differences. Increased novelty-seeking (Gerra et al. 1998), venturesomeness and impulsivity (Morgan 1998) can be expected in users of illicit drugs compared to nonusers. This interpretation has been advanced by several authors including Gerra et al. (2000) who suggested that the enhanced Novelty Seeking (measured with the self-report Tridimensional Personality Questionnaire) in ecstasy users undergoing substance abuse treatment reflected a preexisting psychobiological trait. Similarly, the increased Buss-Durkee Hostility Index (BDHI) Direct Aggression scores of ecstasy users in substance abuse treatment (Gerra et al. 2000) and the decreased BDHI Indirect Hostility in untreated ecstasy users (McCann et al. 1994) may be partially explained by social circumstances and subcultural values, respectively.

Comparisons of (1) ecstasy users with different total ecstasy exposures or (2) polydrug users with and without ecstasy experience can provide a potentially stronger basis for concluding that ecstasy use is specifically associated with certain personality traits. There is only limited support for this possible conclusion. Morgan (1998) reported that a post-hoc comparison of more (30+ tablets ingested) and less experienced (20 – 30 tablets ingested) ecstasy users revealed heightened Impulsivity (measured with Eysenck’s self-report IVE questionnaire) in the more experienced group. Parrott, Sisk, and Turner (2000) reported a nonsignificant trend towards greater IVE Impulsivity in polydrug-using ecstasy users with an average of 371 (30-1000) exposures compared to a group of users with an average of 6.8 (1-20) exposures. Tuchtenhagen et al. (2000) found that ecstasy users with an average of 93.4 ± 119.9 (20-500) exposures have significantly higher scores for Nonplanning Impulsivity (measured with the self-report Barratt Impulsiveness Scale) compared to controls matched for other drug use. The researchers also noted a trend towards increased Experience Seeking (measured with the self-report Sensation Seeking Scale) that reached statistical significance only when ecstasy users were compared to nondrug users. These findings differ from those of McCann et al. (1994) who compared ecstasy users with an average of 94.4 ± 90.6 (25-300) exposures compared to nonusers (but did not control for other drug use). McCann et al. reported decreased Impulsivity (measured as increases in the Control subscale of the Multidimensional Personality Questionnaire) but failed to find significant differences in self-reported Impulsivity with a second questionnaire (the self-report Eysenck Personality Questionnaire). Thus, there is mixed evidence that ecstasy use is associated with increases in self-reported impulsivity.
There are less data and consistency in findings on behavioral impulsivity, which is thought to be different from self-reported impulsivity (Evenden 1999). Gouzoulis-Mayfrank et al. (2000), using the same volunteers as in the Tuchtenhagen et al. (2000) report, did not find evidence of behavioral impulsivity in ecstasy users undergoing a cognitive test battery. In contrast, Morgan (1998) reported that ecstasy users made increased errors in a Matching Familiar Figures task, a difference he interpreted as evidence of increased impulsivity. Morgan suggested that his behavioral findings were an indication of decreased capacity to cope with high levels of cognitive demands. The evidence for such impairments is discussed below.

**Neurocognitive Differences between ecstasy users and nonusers**

As summarized in **Table 5.6**, repeated ecstasy exposure is associated with decreased performance on measures of neurocognitive function. Tests of verbal memory have been frequently used to detect this decrease (Gouzoulis-Mayfrank et al. 2000; Morgan 1999; Parrott 1998; Parrott and Lasky 1998; Reneman et al. 2000a). The results of these tests are summarized in **Table 5.7** and **5.8**. However, user-nonuser differences have been detected with a broad range of neurocognitive tasks (Gouzoulis-Mayfrank et al. 2000; McCann et al. 1999b; Rodgers 2000), including tests of executive function, visual memory, selective attention, and logic. Some have suggested that specific alterations in executive function and working memory may explain the observed differences (Dafters et al. 1999; Gouzoulis-Mayfrank et al. 2000; Wareing et al. 2000), but evidence for this is not conclusive. Results from tests of executive functioning are summarized in **Table 5.9**. The possibility that ecstasy users are impaired in a specific area of neurocognitive functioning is discussed below.

### Table 5.6: Summary of Significant Neurocognitive Findings

<table>
<thead>
<tr>
<th>Function</th>
<th>Significant group differences found in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Function</td>
<td>22.8% (13/57) of measures in 11 studies</td>
</tr>
<tr>
<td>Memory:</td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>42.9% (30/70) of measures in 13 studies</td>
</tr>
<tr>
<td>Visual</td>
<td>55.8% (24/43) of measures in 13 studies</td>
</tr>
<tr>
<td>Attention</td>
<td>16% (4/25) of measures in 7 studies</td>
</tr>
<tr>
<td>Information Processing</td>
<td>23.7% (9/38) of measures in 7 studies</td>
</tr>
<tr>
<td>Logic / Problem Solving</td>
<td>22.2% (2/9) of measures in 3 studies</td>
</tr>
<tr>
<td>Psychomotor Speed</td>
<td>50% (3/6) of measures in 1 study</td>
</tr>
<tr>
<td>Intelligence</td>
<td>14.3% (1/7) of measures in 3 studies</td>
</tr>
<tr>
<td>Time Estimation</td>
<td>50% (3/6) of measures in 2 studies</td>
</tr>
<tr>
<td></td>
<td>0% (0/3) of measures in 1 study</td>
</tr>
</tbody>
</table>

Tests were categorized as measuring one of the above neurocognitive functions. However, no test relies entirely on one area of functioning and other categorization schemes are possible.
Correlations across studies. In order to explore possible relationships between ecstasy exposure and neurocognitive performance, we correlated average performance in different studies with average time since last ecstasy use (in days), duration of ecstasy use (in months), frequency of ecstasy use (in times per month), average dose per use (in tablets) and number of exposures (in occasions or tablets). Each ecstasy exposure parameter was separately correlated with performance. Executive function and verbal memory were selected for analysis from the various areas of neurocognitive performance because these areas had been most frequently assessed. Neurocognitive performance of current ecstasy users was normalized in comparison to performance of the volunteer group in each study having the least drug use. Only one measure per volunteer group was used in each analysis. When a published paper appeared to have more than one test assessing executive function or verbal memory, the test finding the largest difference between ecstasy users and nonusers was included in the analysis. Correlations were individually performed. No corrections were made for multiple correlations.

These analyses are limited by small sample sizes, the inaccuracy of retrospective reporting of drug use, the varying contents of ecstasy pills, and because ecstasy exposure parameters are not independent. Furthermore, findings of significant group differences are more likely to be published and therefore be available for analysis. Volunteers using ecstasy more frequently also had a greater number of lifetime exposures to ecstasy and took higher average doses (in tablets) per use. Given the small sample sizes in these analyses, it is not clear whether decreased performance is more closely associated with frequent use, greater number of exposures, or higher dose. In theory, multiple regression could be used to address this issue. However, ecstasy exposure parameters are inconsistently reported in individual studies and very few studies present enough parameters to be used in such a multiple regression.

Selected results of executive function correlations are displayed in Figures 5.2 and 5.3. Executive function was significantly and negatively correlated with number of ecstasy exposures (occasions or tablets) \( (r = -0.633, p = 0.049, n = 10) \) and approached significance with time since last use \( (r = 0.652, p = 0.057, n = 9) \). The relationships between executive function and ecstasy exposure parameters are consistent with ecstasy use decreasing performance and recovery in performance occurring with abstinence. Verbal memory performance was not correlated with any measure of ecstasy exposure.

In addition, we conducted individual correlations between neurocognitive performance and volunteer gender distribution, age, and education. Neurocognitive performance was unrelated to the age, or education of either ecstasy users or nonusers. Performance on tests of executive function was positively correlated with proportion of female ecstasy users \( (r = 0.625, p < 0.05, n = 11) \). However, it was found that number of total lifetime exposures \( (r = -0.72, p < 0.05, n = 11) \) and average dose per use \( (r = -0.837, p < 0.05, n = 7) \) were negatively correlated with proportion of female ecstasy users. There was a trend for duration of use to be negatively correlated with proportion of women participating in a study as well \( (r = -0.613, p = 0.06, n = 10) \). This suggests that the relationship between gender and performance on these measures arose because women in these studies
Table 5.7: Immediate Verbal Memory in Ecstasy Users Compared to Nonusers.

<table>
<thead>
<tr>
<th>Test</th>
<th>Users/Non-Users</th>
<th>Memory (Z-scores)</th>
<th>Days From Last Use</th>
<th>Number Of Uses</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>WMS Story Recall</td>
<td>15/15</td>
<td>-2.58</td>
<td>0.92</td>
<td>60</td>
<td>..</td>
</tr>
<tr>
<td>RBMT Story Recall</td>
<td>25/19</td>
<td>-0.75</td>
<td>0.78</td>
<td>65.1</td>
<td>85.7</td>
</tr>
<tr>
<td>WMS Story Recall</td>
<td>24/24</td>
<td>-0.59</td>
<td>0.97</td>
<td>30</td>
<td>..</td>
</tr>
<tr>
<td>WMS Verbal Memory Index</td>
<td>15/15</td>
<td>-1.82</td>
<td>1.00</td>
<td>60</td>
<td>..</td>
</tr>
<tr>
<td>WMS Verbal Paired Assoc.</td>
<td>15/15</td>
<td>-0.44</td>
<td>1.12</td>
<td>60</td>
<td>..</td>
</tr>
<tr>
<td>WMS Verbal Paired Assoc.</td>
<td>24/24</td>
<td>-0.38</td>
<td>1.71</td>
<td>30</td>
<td>..</td>
</tr>
<tr>
<td>Coughlan List B</td>
<td>11/31</td>
<td>-0.44</td>
<td>0.96</td>
<td>&gt; 2</td>
<td>..</td>
</tr>
<tr>
<td>VLMT</td>
<td>28/28</td>
<td>-0.88</td>
<td>0.85</td>
<td>41</td>
<td>71.1</td>
</tr>
<tr>
<td>Word Recall</td>
<td>15/15</td>
<td>-0.95</td>
<td>0.71</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Word Recall</td>
<td>10/10</td>
<td>-1.06</td>
<td>0.81</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Digit Span – Forward and</td>
<td>15/15</td>
<td>-0.24</td>
<td>0.95</td>
<td>60</td>
<td>..</td>
</tr>
<tr>
<td>Backwards combined</td>
<td>11/31</td>
<td>-0.72</td>
<td>0.89</td>
<td>&gt; 2</td>
<td>..</td>
</tr>
<tr>
<td>Digit Span - Forward</td>
<td>24/24</td>
<td>-0.18</td>
<td>0.82</td>
<td>30</td>
<td>..</td>
</tr>
<tr>
<td>Digit Span - Forward</td>
<td>28/28</td>
<td>-0.27</td>
<td>1.43</td>
<td>41</td>
<td>71.1</td>
</tr>
<tr>
<td>Digit Span - Forward</td>
<td>10/10</td>
<td>-0.24</td>
<td>0.95</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

Abbreviations: RAVLT – Rey Auditory Verbal Learning Test. RBMT – Rivermead Behavioural Memory Test. WMS – Weschler Memory Scale, Revised. WRB – Walter Reed Army Institute of Research Performance Assessment Battery.

have taken less ecstasy than men have, and for shorter periods of time. Overall, these analyses suggest that the apparently decreased neurocognitive performance of ecstasy users is not explained by differences in the gender distribution, age, or education of volunteer groups.

**Does ecstasy use cause this poor neurocognitive performance?** The current data suggest the answer is “yes”. A recent study found that 15 polydrug-using ecstasy users decreased in neurocognitive performance over the course of 12 months (Zakzanis and Young 2001). During these 12 months, volunteers used the drug in average of 2.4 times per month. Volunteers did not use ecstasy within two weeks of testing. Performance tended to decrease in all of the neurocognitive tasks used in the study, but the difference was only significant in tests of immediate and delayed verbal memory. Although this study lacked a nonuser comparison group, it suggests that something associated with the lifestyle of these volunteers causes decreased neurocognitive performance.
### Table 5.8: Delayed Verbal Memory in Ecstasy Users Compared to Nonusers.

<table>
<thead>
<tr>
<th>Test</th>
<th>Users/Non-Users</th>
<th>Memory (Z-scores)</th>
<th>Days From Last Use</th>
<th>Number Of Uses</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>WMS Story Recall</td>
<td>15/15</td>
<td>-2.12</td>
<td>1.32</td>
<td>60</td>
<td>..</td>
</tr>
<tr>
<td>RBMT Story Recall</td>
<td>25/19</td>
<td>-0.82</td>
<td>0.91</td>
<td>65.1</td>
<td>85.7</td>
</tr>
<tr>
<td>WMS Story Recall</td>
<td>24/24</td>
<td>-0.67</td>
<td>0.97</td>
<td>30</td>
<td>..</td>
</tr>
<tr>
<td>WMS Verbal Paired Assoc.</td>
<td>15/15</td>
<td>-0.89</td>
<td>1.03</td>
<td>60</td>
<td>..</td>
</tr>
<tr>
<td>WMS Verbal Paired Assoc.</td>
<td>24/24</td>
<td>-0.33</td>
<td>1.67</td>
<td>30</td>
<td>..</td>
</tr>
<tr>
<td>Coughlan List6 Word Recall</td>
<td>11/31</td>
<td>-0.63</td>
<td>1.69</td>
<td>&gt; 2</td>
<td>..</td>
</tr>
<tr>
<td>RAVLT</td>
<td>24/24</td>
<td>-0.43</td>
<td>0.83</td>
<td>30</td>
<td>..</td>
</tr>
<tr>
<td>VLMT</td>
<td>28/28</td>
<td>-0.41</td>
<td>1.70</td>
<td>41</td>
<td>71.1</td>
</tr>
<tr>
<td>RAVLT</td>
<td>5/9</td>
<td>-2.31</td>
<td>1.89</td>
<td>138</td>
<td>..</td>
</tr>
<tr>
<td>Word Recall</td>
<td>10/10</td>
<td>-1.13</td>
<td>0.88</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>WRB Code Recall Day 1</td>
<td>22/23</td>
<td>-0.63</td>
<td>0.56</td>
<td>97.37</td>
<td>44.38</td>
</tr>
<tr>
<td>WRB Code Recall Day 2</td>
<td>22/23</td>
<td>-0.49</td>
<td>1.03</td>
<td>97.37</td>
<td>44.38</td>
</tr>
<tr>
<td>WRB Code Recall Day 3</td>
<td>22/23</td>
<td>-0.22</td>
<td>1.22</td>
<td>97.37</td>
<td>44.38</td>
</tr>
</tbody>
</table>

**Abbreviations:** RAVLT – Rey Auditory Verbal Learning Test. RBMT – Rivermead Behavioural Memory Test. WMS – Weschler Memory Scale, Revised. WRB – Walter Reed Army Institute of Research Performance Assessment Battery.

In addition, many studies have found that users with more ecstasy exposure perform worse than those with less exposure (Bolla et al. 1998; Dafters et al. 1999; Gouzoulis-Mayfrank et al. 2000; McCann et al. 1999; Verkes et al. 2001). A certain skepticism concerning these correlations is warranted in some cases, such as when associations are sought between three different measurements of ecstasy exposure and performance on seven tasks and only one significant relationship is found without apparent correction for the twenty-one multiple comparisons (McCann et al. 1999). More robust relationships between several measures of ecstasy exposure and neurocognitive performance are reported by Gouzoulis-Mayfrank et al. (2000). Also, Bolla et al. (1998) reported that greater previous exposure to ecstasy was associated with decreased immediate verbal memory and delayed visual memory, although decreases were apparently only statistically significant in users with “high” monthly ecstasy exposure (more than 4.4 pills per month). As described above, the trend-level correlation between decreased executive function and frequency of ecstasy use suggests repeated ecstasy exposure is associated with decreased neurocognitive performance. In contrast, the gender distribution, age, and education of volunteers appears unrelated to neurocognitive performance.
<table>
<thead>
<tr>
<th>Test</th>
<th>Users/Non-Users</th>
<th>N</th>
<th>Executive Function (Z-scores)</th>
<th>Days From Last Use</th>
<th>Number Of Uses</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consonants 1 s.-Redund.</td>
<td>10/10</td>
<td>10</td>
<td>10.24 - 25.53</td>
<td>376.74 ± 87.4</td>
<td>323.25 ± 130.05</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 1 s.-Redund.</td>
<td>10/10</td>
<td>10</td>
<td>3.63 - 3.00</td>
<td>414.92 ± 54.9</td>
<td>8.2 ± 5.75</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 1 s.-Letters</td>
<td>10/10</td>
<td>10</td>
<td>-4.51 -1.40</td>
<td>376.74 ± 87.4</td>
<td>323.25 ± 130.05</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 1 s.-Letters</td>
<td>10/10</td>
<td>10</td>
<td>-3.78 - 3.06</td>
<td>414.92 ± 54.9</td>
<td>8.2 ± 5.75</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 1 s.-Vowels</td>
<td>10/10</td>
<td>10</td>
<td>-2.19 4.72</td>
<td>376.74 ± 87.4</td>
<td>323.25 ± 130.05</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 1 s.-Vowels</td>
<td>10/10</td>
<td>10</td>
<td>-2.13 1.53</td>
<td>414.92 ± 54.9</td>
<td>8.2 ± 5.75</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 2 s.-Redund.</td>
<td>10/10</td>
<td>10</td>
<td>-1.69 4.95</td>
<td>376.74 ± 87.4</td>
<td>323.25 ± 130.05</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 2 s.-Redund.</td>
<td>10/10</td>
<td>10</td>
<td>-0.61 1.58</td>
<td>414.92 ± 54.9</td>
<td>8.2 ± 5.75</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 2 s.-Letters</td>
<td>10/10</td>
<td>10</td>
<td>-12.91 3.63</td>
<td>376.74 ± 87.4</td>
<td>323.25 ± 130.05</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 2 s.-Letters</td>
<td>10/10</td>
<td>10</td>
<td>-6.45 8.94</td>
<td>414.92 ± 54.9</td>
<td>8.2 ± 5.75</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 2 s.-Vowels</td>
<td>10/10</td>
<td>10</td>
<td>2.78 -6.32</td>
<td>376.74 ± 87.4</td>
<td>323.25 ± 130.05</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 2 s.-Vowels</td>
<td>10/10</td>
<td>10</td>
<td>5.32 -3.48</td>
<td>414.92 ± 54.9</td>
<td>8.2 ± 5.75</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 4 s.-Redund.</td>
<td>10/10</td>
<td>10</td>
<td>0.85 1.83</td>
<td>414.92 ± 54.9</td>
<td>8.2 ± 5.75</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 4 s.-Redund.</td>
<td>10/10</td>
<td>10</td>
<td>1.45 5.64</td>
<td>376.74 ± 87.4</td>
<td>323.25 ± 130.05</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 4 s.-Vowels</td>
<td>10/10</td>
<td>10</td>
<td>-1.42 2.95</td>
<td>376.74 ± 87.4</td>
<td>323.25 ± 130.05</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Consonants 4 s.-Vowels</td>
<td>10/10</td>
<td>10</td>
<td>-2.99 1.90</td>
<td>414.92 ± 54.9</td>
<td>8.2 ± 5.75</td>
<td>Wareing et al., 2000</td>
</tr>
<tr>
<td>Digit Span Backwards</td>
<td>11/31</td>
<td>11</td>
<td>-0.59 1.18</td>
<td>41.8 ± 49.3</td>
<td>2</td>
<td>Croft et al., 2000</td>
</tr>
<tr>
<td>Digit Span Backwards</td>
<td>28/28</td>
<td>28</td>
<td>-0.79 0.88</td>
<td>93.4 ± 119.9</td>
<td>41 ± 71.1</td>
<td>Gouzoulis-Mayfrank et al., 2000</td>
</tr>
<tr>
<td>Digit Span Backwards</td>
<td>10/10</td>
<td>10</td>
<td>-0.90 1.14</td>
<td>672 ± 647</td>
<td>18 ± 8</td>
<td>Semple et al., 1999</td>
</tr>
<tr>
<td>Match to Sample 1</td>
<td>22/23</td>
<td>22</td>
<td>0.31 1.09</td>
<td>215 ± 33</td>
<td>97.37 ± 44.38</td>
<td>McCann et al., 1999</td>
</tr>
<tr>
<td>Match to Sample 2</td>
<td>22/23</td>
<td>22</td>
<td>0.37 1.20</td>
<td>215 ± 33</td>
<td>97.37 ± 44.38</td>
<td>McCann et al., 1999</td>
</tr>
<tr>
<td>Match to Sample 3</td>
<td>22/23</td>
<td>22</td>
<td>-0.15 0.50</td>
<td>215 ± 33</td>
<td>97.37 ± 44.38</td>
<td>McCann et al., 1999</td>
</tr>
<tr>
<td>Spatial Span-Blocks</td>
<td>21/20</td>
<td>21</td>
<td>-0.85 0.00</td>
<td>73 ± 68</td>
<td>15.7 ± 9.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td>Spatial Span-Blocks</td>
<td>21/20</td>
<td>21</td>
<td>-0.69 0.92</td>
<td>230 ± 170</td>
<td>9 ± 7.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td>Spatial Span-Computer</td>
<td>15/15</td>
<td>15</td>
<td>-0.34 1.23</td>
<td>20 -</td>
<td>60 -</td>
<td>Rodgers, 2000</td>
</tr>
<tr>
<td>Spatial Span-Computer</td>
<td>16/16</td>
<td>16</td>
<td>0.13 0.76</td>
<td>35.6 ± 17.5</td>
<td>20.4 ± 33.6</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>Spatial Span-Computer</td>
<td>28/28</td>
<td>28</td>
<td>-0.21 0.37</td>
<td>93.4 ± 119.9</td>
<td>41 ± 71.1</td>
<td>Gouzoulis-Mayfrank et al., 2000</td>
</tr>
</tbody>
</table>

Table 5.9: Executive Functioning in Ecstasy Users Compared to Nonusers.
### Table 5.9 continued: Executive Functioning in Ecstasy Users Compared to Nonusers.

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial Span Errors-</td>
<td>16/16</td>
<td>-0.23</td>
<td>0.83</td>
<td>35.6</td>
<td>17.5</td>
<td>20.4</td>
<td>33.6</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>Computer</td>
<td></td>
<td></td>
<td></td>
<td>73</td>
<td>68</td>
<td>15.7</td>
<td>9.5</td>
<td>Semple et al., 1999</td>
</tr>
<tr>
<td>Spatial Span Errors-</td>
<td>10/10</td>
<td>-0.98</td>
<td>2.47</td>
<td>672</td>
<td>647</td>
<td>18</td>
<td>8</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td>Computer</td>
<td></td>
<td></td>
<td></td>
<td>672</td>
<td>647</td>
<td>18</td>
<td>8</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>Spatial Span plus one-</td>
<td>21/20</td>
<td>-0.82</td>
<td>0.00</td>
<td>73</td>
<td>68</td>
<td>15.7</td>
<td>9.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td>Blocks</td>
<td></td>
<td></td>
<td></td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td>Spatial Span plus one-</td>
<td>21/20</td>
<td>-0.64</td>
<td>0.91</td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td>Blocks</td>
<td></td>
<td></td>
<td></td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>Spatial Span Secs.-</td>
<td>10/10</td>
<td>-1.81</td>
<td>4.46</td>
<td>672</td>
<td>647</td>
<td>18</td>
<td>8</td>
<td>Semple et al., 1999</td>
</tr>
<tr>
<td>Computer</td>
<td></td>
<td></td>
<td></td>
<td>672</td>
<td>647</td>
<td>18</td>
<td>8</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>Spatial Span Usage Errors-</td>
<td>16/16</td>
<td>-0.50</td>
<td>2.15</td>
<td>35.6</td>
<td>17.5</td>
<td>20.4</td>
<td>33.6</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>Computer</td>
<td></td>
<td></td>
<td></td>
<td>35.6</td>
<td>17.5</td>
<td>20.4</td>
<td>33.6</td>
<td>Semple et al., 1999</td>
</tr>
<tr>
<td>Sternberg Figure Serial</td>
<td>21/20</td>
<td>-1.18</td>
<td>0.68</td>
<td>73</td>
<td>68</td>
<td>15.7</td>
<td>9.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td>Sternberg Figure Serial</td>
<td>21/20</td>
<td>-1.04</td>
<td>1.29</td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>Sternberg Figure Simult.</td>
<td>21/20</td>
<td>-1.28</td>
<td>-0.24</td>
<td>73</td>
<td>68</td>
<td>15.7</td>
<td>9.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td>Sternberg Figure Simult.</td>
<td>21/20</td>
<td>-0.93</td>
<td>1.17</td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>Sternberg Word Serial</td>
<td>21/20</td>
<td>-2.17</td>
<td>0.33</td>
<td>73</td>
<td>68</td>
<td>15.7</td>
<td>9.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td>Sternberg Word Serial</td>
<td>21/20</td>
<td>-0.75</td>
<td>1.50</td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>Sternberg Word Simult.</td>
<td>21/20</td>
<td>-0.90</td>
<td>0.59</td>
<td>73</td>
<td>68</td>
<td>15.7</td>
<td>9.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>230</td>
<td>170</td>
<td>9</td>
<td>7.5</td>
<td>Verkes et al., 2001</td>
</tr>
<tr>
<td>Stroop-Errors</td>
<td>10/10</td>
<td>-1.00</td>
<td>2.57</td>
<td>672</td>
<td>647</td>
<td>18</td>
<td>8</td>
<td>Semple et al., 1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>672</td>
<td>647</td>
<td>18</td>
<td>8</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>Stroop-Sec</td>
<td>10/10</td>
<td>-0.46</td>
<td>1.36</td>
<td>672</td>
<td>647</td>
<td>18</td>
<td>8</td>
<td>Semple et al., 1999</td>
</tr>
<tr>
<td>TOL Excess Moves</td>
<td>16/16</td>
<td>-0.39</td>
<td>1.38</td>
<td>35.6</td>
<td>17.5</td>
<td>20.4</td>
<td>33.6</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>49.6</td>
<td>33.2</td>
<td>65.1</td>
<td>65.3</td>
<td>Morgan, 1998, Study 2</td>
</tr>
<tr>
<td>TOL Excess Moves-1</td>
<td>25/19</td>
<td>0.37</td>
<td>0.92</td>
<td>49.6</td>
<td>33.2</td>
<td>65.1</td>
<td>65.3</td>
<td>Morgan, 1998, Study 2</td>
</tr>
<tr>
<td>TOL Excess Moves-2</td>
<td>25/19</td>
<td>0.19</td>
<td>-1.11</td>
<td>49.6</td>
<td>33.2</td>
<td>65.1</td>
<td>85.7</td>
<td>Morgan, 1998, Study 2</td>
</tr>
<tr>
<td>TOL Initial Think</td>
<td>16/16</td>
<td>-0.08</td>
<td>0.69</td>
<td>35.6</td>
<td>17.5</td>
<td>20.4</td>
<td>33.6</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>TOL Initial Think-1</td>
<td>25/19</td>
<td>-0.69</td>
<td>0.87</td>
<td>49.6</td>
<td>33.2</td>
<td>65.1</td>
<td>85.7</td>
<td>Morgan, 1998, Study 2</td>
</tr>
<tr>
<td>TOL Initial Think-2</td>
<td>25/19</td>
<td>-0.67</td>
<td>0.85</td>
<td>49.6</td>
<td>33.2</td>
<td>65.1</td>
<td>85.7</td>
<td>Morgan, 1998, Study 2</td>
</tr>
<tr>
<td>TOL Proportion Perfect</td>
<td>16/16</td>
<td>-0.15</td>
<td>1.27</td>
<td>35.6</td>
<td>17.5</td>
<td>20.4</td>
<td>33.6</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>TOL Proportion Perfect-1</td>
<td>25/19</td>
<td>-0.55</td>
<td>0.95</td>
<td>49.6</td>
<td>33.2</td>
<td>65.1</td>
<td>85.7</td>
<td>Morgan, 1998, Study 2</td>
</tr>
<tr>
<td>TOL Proportion Perfect-2</td>
<td>25/19</td>
<td>-0.17</td>
<td>0.95</td>
<td>49.6</td>
<td>33.2</td>
<td>65.1</td>
<td>85.7</td>
<td>Morgan, 1998, Study 2</td>
</tr>
<tr>
<td>TOL Subsequ. Think</td>
<td>16/16</td>
<td>0.61</td>
<td>1.66</td>
<td>35.6</td>
<td>17.5</td>
<td>20.4</td>
<td>33.6</td>
<td>Morgan, 1998 Study 1</td>
</tr>
<tr>
<td>TOL Subsequ. Think-1</td>
<td>25/19</td>
<td>0.31</td>
<td>1.05</td>
<td>49.6</td>
<td>33.2</td>
<td>65.1</td>
<td>85.7</td>
<td>Morgan, 1998, Study 2</td>
</tr>
<tr>
<td>TOL Subsequ. Think-2</td>
<td>25/19</td>
<td>-0.11</td>
<td>0.91</td>
<td>49.6</td>
<td>33.2</td>
<td>65.1</td>
<td>85.7</td>
<td>Morgan, 1998, Study 2</td>
</tr>
</tbody>
</table>

Abbreviations: TOL – Tower of London. WMS – Weschler Memory Scale, Revised.
Could the rave lifestyle cause the neurocognitive differences? Probably not. The neurocognitive performance of ecstasy users may be somewhat influenced by aspects of their lifestyle, such as repeated sleep and nutrient deprivation associated with attending late-night dance events. Nonetheless, the few scientific studies on these other possible factors (Cho et al. 2000; Dinges and Kribbs 1991; Kretsch et al. 1997) would not lead us to expect an effect comparable to what we see in studies of ecstasy users. Some studies have tried to control for the influence of lifestyle. Gouzoulis-Mayfrank et al. recruited volunteers (including the drug-free group) at dance events. This would tend to minimize differences in lifestyle, although it is still possible that volunteer groups had differences in the frequency with which they attended dance events. In the first published study that attempted to control for lifestyle (Verkes et al. 2001), researchers found that “moderate” ecstasy users (with 73 ± 68 reported exposures to ecstasy) had lower performance than nonusers attending a similar number of raves in the previous 12 months.

Could other drugs cause these neurocognitive differences? Other drugs may contribute to these differences, but they probably cannot fully account for them. Polydrug use is common in ecstasy users. In published studies, cannabis use has often been greater in ecstasy-using volunteers than in ecstasy-naïve volunteers. This is significant because chronic cannabis use can cause long-lasting residual decreases in neurocognitive performance (Pope and Yurgelun-Todd 1996). Three studies have compared users of both ecstasy and cannabis to users of cannabis alone. Selected results from these studies are shown in Table 5.10. Two of these studies have suggested that ecstasy is associated with lowered neurocognitive performance beyond that expected for cannabis (Gouzoulis-Mayfrank et al. 2000; Rodgers 2000). Rodgers et al. (2000) found that cannabis users and cannabis-using ecstasy users performed worse than volunteers who did not use drugs in two tests of delayed recall (Visual Paired Associates and

### Table 5.9 continued: Executive Functioning in Ecstasy Users Compared to Nonusers.

<table>
<thead>
<tr>
<th>Test</th>
<th>Users/Non-Users</th>
<th>Executive Function (Z-scores)</th>
<th>Days From Last Use</th>
<th>Number Of Uses</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Trails B - Time</td>
<td>10/10</td>
<td>-0.40</td>
<td>1.13</td>
<td>672</td>
<td>647</td>
</tr>
<tr>
<td>WMS Mental Control</td>
<td>15/15</td>
<td>-0.10</td>
<td>0.63</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Word Fluency - Phonologic</td>
<td>11/31</td>
<td>-0.39</td>
<td>0.81</td>
<td>41.9</td>
<td>49.3</td>
</tr>
<tr>
<td>Word Fluency - Phonologic</td>
<td>28/28</td>
<td>-0.43</td>
<td>0.57</td>
<td>93.4</td>
<td>119.9</td>
</tr>
<tr>
<td>Word Fluency - Phonologic</td>
<td>10/10</td>
<td>0.48</td>
<td>1.63</td>
<td>672</td>
<td>647</td>
</tr>
<tr>
<td>Word Fluency - Semantic</td>
<td>11/31</td>
<td>-1.67</td>
<td>1.24</td>
<td>41.9</td>
<td>49.3</td>
</tr>
<tr>
<td>Word Fluency - Semantic</td>
<td>28/28</td>
<td>-0.51</td>
<td>1.18</td>
<td>93.4</td>
<td>119.9</td>
</tr>
<tr>
<td>Word Fluency - Alternating</td>
<td>28/28</td>
<td>-0.35</td>
<td>0.71</td>
<td>93.4</td>
<td>119.9</td>
</tr>
</tbody>
</table>

Abbreviations: TOL – Tower of London. WMS – Weschler Memory Scale, Revised.
Figure 5.2: Relationship between Number of Exposures and Executive Function

\[ y = -0.0034x - 0.3715 \]
\[ R^2 = 0.3883 \]
\[ p = 0.049 \]

Figure 5.3: Relationship between Abstinence from Ecstasy and Executive Function

\[ y = 0.0257x - 1.9523 \]
\[ R^2 = 0.4323 \]
\[ p = 0.057 \text{ (ns)} \]
Table 5.10. Evidence for Contribution of Cannabis Use to Neurocognitive Performance in Ecstasy Users.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sample Sizes for E&amp;C / C / Nonusers</th>
<th>Users of Ecstasy and Cannabis (E&amp;C) Z-scores</th>
<th>Users of Cannabis (C) Z-Scores</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed Memory Coughlan Words</td>
<td>11/18/31</td>
<td>-0.63 1.69</td>
<td>-0.87 1.88</td>
<td>Croft et al, 2000</td>
</tr>
<tr>
<td>Delayed Memory VLMT</td>
<td>28/28/28</td>
<td>-0.41 1.70</td>
<td>0.21 1.04</td>
<td>Gouzoulis-Mayfrank et al, 2000</td>
</tr>
<tr>
<td>Immediate Memory Coughlan Words</td>
<td>11/18/31</td>
<td>-0.44 0.96</td>
<td>-0.74 0.81</td>
<td>Croft et al, 2000</td>
</tr>
<tr>
<td>Immediate Memory VLMT</td>
<td>28/28/28</td>
<td>-0.88 0.85</td>
<td>-0.49 0.89</td>
<td>Gouzoulis-Mayfrank et al, 2000</td>
</tr>
<tr>
<td>Digit Span</td>
<td>15/15/15</td>
<td>-0.24 0.95</td>
<td>0.48 1.37</td>
<td>Rodgers, 2000</td>
</tr>
<tr>
<td>Digit Span Backwards</td>
<td>11/18/31</td>
<td>-0.59 1.18</td>
<td>-0.64 0.82</td>
<td>Croft et al., 2000</td>
</tr>
<tr>
<td>Digit Span Backwards</td>
<td>28/28/28</td>
<td>-0.79 0.88</td>
<td>-0.42 0.70</td>
<td>Gouzoulis-Mayfrank et al., 2000</td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>28/28/28</td>
<td>-0.27 1.43</td>
<td>0.03 1.17</td>
<td>Gouzoulis-Mayfrank et al, 2000</td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>11/18/31</td>
<td>-0.72 0.89</td>
<td>-0.50 0.83</td>
<td>Croft et al, 2000</td>
</tr>
<tr>
<td>Spatial Span Computer</td>
<td>28/28/28</td>
<td>-0.21 0.37</td>
<td>0.13 0.87</td>
<td>Gouzoulis-Mayfrank et al., 2000</td>
</tr>
<tr>
<td>Spatial Span Computer</td>
<td>15/15/15</td>
<td>-0.34 1.23</td>
<td>0.15 0.87</td>
<td>Rodgers, 2000</td>
</tr>
<tr>
<td>Word Fluency Phonologic</td>
<td>28/28/28</td>
<td>-0.43 0.57</td>
<td>-0.24 0.55</td>
<td>Gouzoulis-Mayfrank et al, 2000</td>
</tr>
<tr>
<td>Word Fluency Phonologic</td>
<td>11/18/31</td>
<td>-0.39 0.81</td>
<td>-0.08 0.96</td>
<td>Croft et al., 2000</td>
</tr>
<tr>
<td>Word Fluency Semantic</td>
<td>28/28/28</td>
<td>-0.51 1.18</td>
<td>-0.08 0.84</td>
<td>Gouzoulis-Mayfrank et al, 2000</td>
</tr>
<tr>
<td>Word Fluency Semantic</td>
<td>11/18/31</td>
<td>-1.67 1.24</td>
<td>-0.52 1.43</td>
<td>Croft et al., 2000</td>
</tr>
</tbody>
</table>

Abbreviations: VLMT = Verbal Learning Memory Test. Measures were selected for inclusion if they assessed executive function or verbal memory and if similar measures had been used in other studies. In each case, neurocognitive scores have been normalized to those of nonusers.
Logical Memory). In a third study, another group (Croft et al. 2001) was unable to detect performance differences between cannabis users and users of both cannabis and ecstasy using a battery of neurocognitive tests. Furthermore, covariate analysis suggested that performance decreases were more closely related to cannabis than ecstasy use. In another study that attempted to control for the influence of other drugs, Morgan failed to detect differences between polydrug-using ecstasy users and polydrug users on tests of executive function (Morgan 1998) but detected lower verbal memory performance in the same group of ecstasy users compared to polydrug users (Morgan 1999). However, matching of drug use between comparison groups was imperfect in this study. Furthermore, Morgan found that immediate memory performance correlated as highly with cannabis use ($r = -0.48$, $p = 0.016$) as it did with ecstasy use ($r = -0.47$, $p = 0.019$). It is clear that future studies should control for use of cannabis and that the apparent magnitude of the ecstasy-associated neurocognitive performance decrease is likely exaggerated by cannabis use in studies. But other drug use probably does not fully explain the neurocognitive differences.

**Are these changes due to serotonergic neurotoxicity?** This is not yet known. The lower neurocognitive performance of ecstasy users may be due to either serotonergic neurotoxicity or some different ecstasy-related neurochemical alteration. Evidence that serotonin is involved is indirect. It has been demonstrated that acute serotonergic depletion (by dietary manipulation) can impair declarative verbal memory in healthy volunteers (Riedel et al. 1999). Three studies of ecstasy users have reported correlations between alterations in serotonergic measures and decreased neurocognitive performance (Bolla et al. 1998; Reneman et al. 2000a; Verkes et al. 2001), while one study failed to find a relationship between alterations in serotonergic measures and decreased performance on measures of cognitive function (McCann et al. 1999b). Bolla et al. reported that decreased CSF 5HIAA levels correlated with decreased visual memory performance in ecstasy users. Verkes et al. found that $d$-fenfluramine-induced cortisol release in ecstasy users significantly correlated with their memory span on the Corsi Block Tapping test. Reneman et al. reported that estimated cortical 5HT$_{2A}$ receptor density correlated with impaired declarative memory in 5 ecstasy users. McCann et al found that ecstasy users had lower cerebrospinal 5HIAA than non-users and that ecstasy users exhibited deficits on tests of sustained attention, recall and logical reasoning. However, the researchers did not find a relationship between concentration of cerebrospinal 5HIAA and neurocognitive test performance. Taken together, these findings suggest a relationship between lower neurocognitive performance and ecstasy-induced serotonin depletions or neurotoxicity but with some qualifications. On the other hand, if MDMA-induced loss of serotonin or damage to serotonergic axons were sufficient to impair memory to the degree suggested by human studies, one would expect this effect to have been readily detected in prospective nonhuman animal studies. As discussed in the previous chapter, two studies (Broening et al. 2001; Marston et al. 1999) out of at least eleven (Frederick et al. 1998; Frederick et al. 1995; LeSage et al. 1993; McCreary et al. 1999; Ricaurte et al. 1993; Robinson et al. 1993; Seiden et al. 1993; Slikker et al. 1989; Spanos and Yamamoto 1989) have found evidence of lasting behavioral or memory impairment in MDMA-exposed animals.
Alternatively, some other effect of repeated ecstasy use may decrease neurocognitive performance. It is well established that chronic psychostimulant use lowers neurocognitive performance. For example, repeated cocaine use is associated with impaired neurocognitive functioning (Beatty et al. 1995; Bolla et al. 1999; O’Malley et al. 1992), although cocaine use per se does not necessarily produce neurocognitive deficits (Bolla et al. 1999). Cocaine is not a selective neurotoxin but, like MDMA, can cause both serotonergic (Jacobsen et al. 2000; Little et al. 1998) and cerebrovascular (Bartzokis et al. 1999; Herning et al. 1999) alterations. Selected measures from several studies assessing memory in cocaine users are summarized in Table 5.11. As can be seen, frequent cocaine use is associated with neurocognitive performance decreases similar in magnitude to those seen in some ecstasy users. In addition, normalizing scores tends to obscure the fact that ecstasy users in published studies generally performed substantially better than cocaine users and their matched nonusers when raw scores are compared.

Table 5.11. Memory Performance in Chronic Cocaine Users

<table>
<thead>
<tr>
<th>Cocaine Using Population</th>
<th>Cocaine Use History</th>
<th>Drug Free Period</th>
<th>Memory Test</th>
<th>Z-score ± SD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 chronic users</td>
<td>15.8 ± 10.3 g in preceding m; 6.3 ± 4.1 y total</td>
<td>181.7 ± 158.9 h</td>
<td>WMS Story Recall Immediate</td>
<td>-0.49 ± 0.71</td>
<td>(Gillen et al. 1998)</td>
</tr>
<tr>
<td>23 in treatment users</td>
<td>at least 2 x/w for last y; 3.0 ± 3.6 g/w for 7.1 ± 4.7 y</td>
<td>21-40 d</td>
<td>WMS Story Recall Immediate</td>
<td>-1.07 ± 0.77</td>
<td>(Beatty et al. 1995)</td>
</tr>
<tr>
<td>30 chronic users</td>
<td>at least 4 x/mg for 1 y; 2.3 ± 2.2 g/w, 4.5 ± 1.3 d/w for 6.7 ± 4.7 y</td>
<td>28 d</td>
<td>WMS Story Recall Immediate</td>
<td>-0.03 ± 0.86</td>
<td>(Bolla et al. 1999)</td>
</tr>
<tr>
<td>60 incarcerated users</td>
<td>8.63 ± 4.36 g/w for 12.52 ± 4.36 y</td>
<td>35.85 ± 15.85 m</td>
<td>WMS Story Recall Immediate</td>
<td>0.13 ± 1.1</td>
<td>(Selby and Azrin 1998)</td>
</tr>
<tr>
<td>19 chronic users</td>
<td>15.8 ± 10.3 g in preceding m; 6.3 ± 4.1 y total</td>
<td>181.7 ± 158.9 h</td>
<td>WMS Story Recall Delayed</td>
<td>-0.52 ± 0.65</td>
<td>(Gillen et al. 1998)</td>
</tr>
<tr>
<td>23 in treatment users</td>
<td>at least 2 x/w for last y; 3.0 ± 3.6 g/w for 7.1 ± 4.7 y</td>
<td>21-40 d</td>
<td>WMS Story Recall Delayed</td>
<td>-1.25 ± 0.84</td>
<td>(Beatty et al. 1995)</td>
</tr>
<tr>
<td>20 in treatment users</td>
<td>454 ± 65 g in 49.8 ± 38.0 m</td>
<td>23.6 ± 15 d</td>
<td>Story Recall - Delayed</td>
<td>1.21 ± 1.52</td>
<td>(O'Malley et al. 1992)</td>
</tr>
<tr>
<td>30 chronic users</td>
<td>at least 4 x/mg for 1 y; 2.3 ± 2.2 g/w, 4.5±1.3 d/w for 6.7±4.7 y</td>
<td>28 d</td>
<td>WMS Story Recall - Delayed</td>
<td>-0.06 ± 0.81</td>
<td>(Bolla et al. 1999)</td>
</tr>
<tr>
<td>60 incarcerated users</td>
<td>8.63 ± 4.36 g/w for 12.5 ± 4.36 y</td>
<td>35.85 ± 15.85 m</td>
<td>WMS Story Recall - Delayed</td>
<td>0.13 ± 0.99</td>
<td>(Selby and Azrin 1998)</td>
</tr>
</tbody>
</table>

Abbreviations: d = day; m = month; w = week; WMS – Weschler Memory Scale, Revised; y = year.

A number of studies have found that patients with depression have decreased performance in tests of executive function and verbal memory (Dupont et al. 1990; Fossati et al. 1999; Martin et al. 1991; Rush et al. 1983). It is possible that dysphoric mood, which borders on clinical depression in some repeated ecstasy users, lowers neurocognitive performance. Although these mood changes may contribute to lowered neurocognitive performance, they seem unlikely to fully explain performance reductions. In some studies, evidence of neurocognitive changes has been found in ecstasy users without apparent mood changes (McCann et al. 1999a; McCann et al. 1999b; McCann et
Does performance recover with abstinence from ecstasy? Only a few studies have looked for evidence of recovery. Morgan (1999) reported that a subset of three ecstasy users who had not taken ecstasy in over 6 months had significantly better immediate and delayed verbal memory than users with more recent use. In contrast, Wareing et al. (2000) were unable to find evidence of a significant abstinence-related improvement in working memory and executive function when 10 current ecstasy users were compared to 10 volunteers who reportedly had not used ecstasy in 6 months. It is therefore not clear from individual studies if there is recovery from this lower neurocognitive performance. Comparison of performance across studies yields mixed results. The trend-level correlation between improvement in executive function and time from last ecstasy use described above suggests that at least some recovery may occur with abstinence. On the other hand, we found no evidence of improvement in verbal memory with abstinence. In fact, studies in which volunteers had greater average time from last ecstasy use tended to perform worse on verbal memory tests (this was not significant due to the small sample size).

Is ecstasy use associated with alteration of a specific neurocognitive function? Parrott et al. (1998) suggest that changes in neurocognitive performance could be due to either a change in cognitive strategy or impaired abilities. Because there is no evidence of improved ability in ecstasy users, it currently seems unlikely that a change in cognitive strategy has occurred. Parrott (2000) presents two theories that might explain decreased neurocognitive performance in ecstasy users. First, Parrott hypothesizes that changes in the functioning of specific brain regions might explain specific neurocognitive alterations. For example, loss of serotonin in the frontal cortex might lead to impulsivity, while hippocampal changes might decrease memory performance. Parrott points out that this hypothesis fails to account for the many areas of functioning that appear unaltered in ecstasy users, despite theoretically widespread serotonergic changes. However, as discussed above, there seems to be no a priori reason to assume that performance changes are due to serotonergic changes. Second, Parrott hypothesizes that inhibition of cortical functioning may explain the specific pattern of changes in ecstasy users. Because the prefrontal cortex is important for executive function, this second possibility is consistent with other reports in which researchers hypothesized specific changes in working memory and/or executive function (Dafters et al. 1999; Gouzoulis-Mayfrank et al. 2000; Wareing et al. 2000).

Executive function is typically associated with complex cognition, such as novel problem solving and the ability to modify behavior in response to environmental changes. Executive function relies heavily on working memory, the ability to hold and manipulate information in short time memory. Impairments in executive function or working memory would be expected to alter functioning in a range of neurocognitive tasks. Ecstasy-induced changes in working memory are consistent with the nonhuman animal literature. The first published evidence of drug-free, long-term alteration in behavior after MDMA exposure was detected in performance of a delayed non-match to place memory task (Marston et al. 1999).
Of the tasks categorized as measuring executive function, statistically significant differences between ecstasy users and non-users were detected in 13 of 57 measures (22.8%) in 11 different studies. The trend-level correlations between executive function and both number of ecstasy exposures and time since last ecstasy use suggest that ecstasy has a modest effect on some aspects of executive function. Nonetheless, it is not yet possible to pick out a particular area of executive function that is affected. The percent of statistically significant tests in this area is lower than for tests of verbal memory (55.8%, 24/43 in 13 studies). Thus, one might argue that some aspect of executive function involving working memory may be particularly affected. Evidence for changes in verbal recall and recognition is stronger than evidence for changes in visual memory (significant group differences seen in 16% (4/25) of measures in 7 studies). Overall, there does not yet seem to be sufficient evidence to implicate one particular area of functioning.

Possible Significance of Neurocognitive Differences and MDMA Neurotoxicity

How severe are these neurocognitive decreases? They do not indicate impairment in day-to-day activities. The differences occur in neurocognitive tests in which young, healthy people perform well. Thus, these differences are generally small in magnitude despite their statistical significance. In fact, neither the investigators nor the MDMA-using volunteers themselves appear to be aware of any cognitive impairment in volunteers in most studies (McCann et al. 1999b; Rodgers 2000).

However, there is a method of interpreting neurocognitive performance that would classify the ecstasy-using volunteers in some publications as having clinically significant impairments in performance. In neurocognitive assessment, it is common practice to interpret test scores following at least 1.3 SD units below the normative mean as “borderline” and those 2.0 SD units below the mean as “impaired” (Lezak 1995). If one were to use similar standards for studies comparing ecstasy users to non-users, then several studies could be considered to have detected “impairment”. This interpretation is limited by the fact that it assumes that neurocognitive performance by the nonusers represents the full range of normal scores, which is often not true.

The earliest study (Krystal et al. 1992) suggesting clinically significant impairment compared the performance of 9 ecstasy users who had been pre-selected for low CSF 5HIAA (R. Doblin, personal communication) to published norms for the revised Weschler Memory Scale. Krystal et al. reported that five of nine volunteers had scores on the initial or delayed paragraph tests of the Weschler Memory Scale that were at least 1 SD unit less than normative values. Studies using published normative scores rather than groups of nonusers for comparison are susceptible to biases since the comparison cannot control for any unusual testing conditions. For example, the results reported by Krystal et al. were possibly influenced by the intravenous l-tryptophan infusion given approximately 3 hr earlier to many of the volunteers. In addition, some of the volunteers had reportedly traveled from other states the day of testing or the previous day. Furthermore, there was a high prevalence of personal and/or family history of psychopathology in the volunteers. Subsequent reports have used matched comparison
groups with less psychopathology and found more modest differences between users and nonusers. For example, Bolla et al. (1998) did not detect significant differences between ecstasy users with 60 (25-300) exposures and nonusers using the same memory test employed by Krystal’s group.

Wareing et al. (2000) detected large differences between ecstasy users and nonusers in a task involving working memory. When volunteers were asked to generate consonants in a random order at a rate of one per second, the ten ecstasy users performed dramatically worse than the ten nonusers (3.78 ± 3.06 SD units decrease in the number of consonants produced, P < 0.01). This difference is much larger than that seen in other studies using tasks involving working memory (e.g., -0.79 ± 0.88 SD units in the backwards Digit Span task in the Gouzoulis-Mayfrank study). It appears possible that short-term residual effects contributed to this impairment. Ecstasy users in the Wareing study had last used ecstasy only 8.20 ± 5.75 days ago. Volunteers had also used more frequently than in most other studies (8.43 ± 3.33 times per month). It is also possible that tasks with external time constraints (i.e., are not self-paced) are best at distinguishing between users and nonusers.

Rodgers (2000) compared 15 users of ecstasy and cannabis to 15 cannabis users and 15 drug-free individuals. Neurocognitive testing was performed on a day when volunteers reported that they had not used any drugs, but time since last drug use was not recorded. Both drug-using groups had lower scores on immediate and delayed recall for the details of a story than drug-free volunteers. However, only the ecstasy users performed worse than drug-free volunteers on delayed verbal and visual paired associates. Although normalized performance differences were modest in delayed visual paired associates, the small distribution of scores for drug-free volunteers created a large difference when scores in delayed visual paired associates are normalized. Scores for ecstasy users were -2.73 ± 2.92 standard deviation units, while cannabis users scored an average of -0.50 ± 1.65 standard deviation units. Furthermore, when all tests of immediate visual memory were combined to form an index score for visual memory, Rodgers did not detect any differences in immediate visual memory between ecstasy users and the other two groups. The difference in visual paired associates was larger than seen in other studies using similar or identical tests. For example, Bolla et al. (1998) found that performance of ecstasy users with an average of 60 previous exposures, most recently an average of 30 days previously, had performance on delayed visual paired associates that was not significantly different (-0.33 ± 1.67 standard deviation units) from that of drug-free volunteers. In fact, statistically significant decreases in visual memory performance were only detected in 16% (4/25) of measures in the 7 different studies in which visual memory was assessed. Because the difference seen by Rodgers is significantly larger than seen in other studies using the same tests, it appears possible that volunteers had used ecstasy very recently and short-term withdrawal effects of ecstasy were being detected. Alternatively, it is possible that there was some particular condition associated with ecstasy exposure in the volunteers in Rodgers’s study that led to unusually large toxicity.
Finally, Reneman et al. (2000b) reported dramatic differences in delayed verbal memory between 5 ecstasy users who had used an average of 218 (50-500) tablets and 9 nonuser volunteers. Time from last ecstasy use was an average of 138 (60-360) days. Frequency of use was not reported. In this study, delayed verbal recall was $-2.31 \pm 1.89$ SD units in comparison to nonusers. Interestingly, the first author stated in a personal communication that no differences were seen between these ecstasy users and nonusers in other measures from the Rey Auditory Verbal Learning Test, the Rivermead Behavioural Memory Test, the revised Weschler Memory Scale (Dr. Liesbeth Reneman, personal communication to R. Doblin). Given the many other studies that have measured delayed verbal memory and found more modest differences, it seems likely that the magnitude of the differences in this study is largely due to the small sample size of this preliminary report. This would be consistent with the lack of significant effects in the same volunteers using closely related measures of memory.

Overall these few measures finding large differences between ecstasy users and nonusers appear to be exceptions. The differences between ecstasy users and nonusers are clinically very small and could be considered insignificant if we were certain that recovery occurred.

**Will ecstasy neurotoxicity become more obvious as users age?** This is difficult to predict. From a neurochemical perspective, age-related decrease in SERT density appears modest — estimated at 4.3% per decade in one recent study (van Dyck et al. 2000) — while 5HT receptors undergo more complex age-related changes (reviewed in Meltzer et al. 1998). One would hope that these changes will not cause ecstasy users to exceed a hypothetical threshold for developing symptoms of neurotoxicity. However, we simply do not understand 5HT or serotonin-related disorders sufficiently to make predictions with any confidence. For example, late onset affective disorders are probably influenced by many nonserotonergic factors, such as social isolation and cerebrovascular disease.

**What types of problems could ecstasy neurotoxicity cause?** No one knows. Some have speculated that ecstasy neurotoxicity may lead to dysregulation of a range of areas, with psychopathology developing based on whichever systems are most vulnerable to functional impairment in a given individual. There is currently no direct evidence that addresses this speculation. This speculation is based on theories of what role the serotonergic system plays in the brain. The serotonergic system has been thought of as a modulatory system, interacting with both behavioral inhibition and facilitation systems (Depue and Spoont 1986; Spoont 1992). Increasing 5HT is frequently seen as inhibiting behavioral activation, while decreasing 5HT is seen as facilitating responsiveness to external stimuli.

Another approach to predicting problems that could result from serotonergic neurotoxicity is to examine the various psychiatric disorders that are treated with SSRIs and other serotonergic drugs. Disorders that are treated with serotonergic drugs include depression, obsessive-compulsive disorder, and anxiety disorders (such as panic disorder, generalized anxiety disorder, and social phobia). Taken together, these disorders affect
more than 10% of the general population. Because serotonergic drugs are useful in these disorders and serotonergic abnormalities can be seen in many patients with these disorders, some have speculated that serotonergic neurotoxicity may increase risk of affective disorder. This makes sense based on our limited understanding of serotonin, but has not been demonstrated. Furthermore, given the modulatory role of 5HT, one cannot assume that all disorders treatable with serotonergic drugs are caused by serotonergic malfunction.

It is worth noting that neurotoxic phenethylamines have been self-administered by humans for over 60 years. In this time, no evidence has been published suggesting that methamphetamine or amphetamine increase risk of Parkinson’s disease, despite damaging dopaminergic axons. In contrast, the link between Parkinson’s disease and MPTP, a meperidine analogue and dopaminergic neurotoxin, was rapidly discovered (Davis et al. 1979; Langston et al. 1983). Similarly, concerns about the selective serotonergic neurotoxicity induced by ecstasy and other drugs are not fueled by a toxic syndrome identified in users. Instead, they are motivated by the intuition that the potentially dramatic decreases in indices of serotonergic functioning must have some adverse behavioral consequences.

Risks of Neurotoxicity in Clinical MDMA Studies

In assessing risks of MDMA neurotoxicity, it is necessary to separately consider the risks of serotonergic changes and those of neurocognitive performance changes. This is because these changes may have different mechanisms and may occur after different ecstasy exposures. These two areas of risk are discussed below. It is concluded that the risks of neurotoxicity in volunteers exposed to 125 mg MDMA in a clinical setting are minimal. While risks of neurocognitive performance changes after one or two doses of up to 2.5 mg/kg MDMA (175 mg in a 70 kg person) appear to remain very small, risks of serotonergic neurotoxicity after doses above 125 mg MDMA are difficult to assess. Furthermore it is important to acknowledge that the risks of MDMA neurotoxicity are controversial and other knowledgeable scientists believe that risks are more than minimal (Gijsman et al. 1999; McCann and Ricaurte 2001).

Possible serotonergic neurotoxicity. There is extensive evidence that illicit ecstasy users often develop changes in neurofunctioning. Correlations have been reported between ecstasy exposure and measures such as CSF 5HIAA levels, SERT density, myo-inositol increases, 5HT2A binding, and EEG alterations. In some cases, there are questions as to whether these changes can be considered evidence of serotonergic neurotoxicity rather than responses to the pharmacological effects of MDMA. However, as discussed in the section on interpreting studies, long-lasting decreases in SERT density and CSF 5HIAA levels of ecstasy users can be considered as evidence of neurotoxicity. These studies therefore indicate that commonly consumed doses of illicit ecstasy can produce serotonergic neurotoxicity. Animal studies suggest that there is a threshold exposure required for serotonergic neurotoxicity (O'Shea et al. 1998). Doses below this threshold do not produce long-term serotonergic changes in animals. Therefore, the most salient question is what dose of MDMA produces neurotoxicity in humans. As discussed
in the chapter on animal neurotoxicity studies, there are not sufficient data to estimate the neurotoxic MDMA dose in humans with any confidence. However, theoretical and empirical evidence indicate 125 mg MDMA is probably not neurotoxic.

Interspecies pharmacokinetic comparisons suggest that neurotoxic doses in rats produce MDMA blood concentrations that are significantly higher than those produced by 125 mg MDMA in a human. Vollenweider et al. (2001) compare published pharmacokinetic data for humans and rats and conclude that human exposure to MDMA after 125 mg, po, (1.78 mg/kg for a 70 kg human) is significantly less than the lowest known consistently neurotoxic MDMA dose in Sprague-Dawley rats, 20 mg/kg, sc, (Battaglia et al. 1988b; Commins et al. 1987b). At these doses, human MDMA plasma AUC are approximately 30% of the rat AUC. Similarly, human Cmax are approximately 10% of rat Cmax.

While this comparison is reassuring, it is limited because the threshold for neurotoxicity is not well established in rats. The threshold for neurotoxicity in this rat strain appears to be above 10 mg/kg (Battaglia et al. 1988b) and below 20 mg/kg (Commins et al. 1987b). Therefore human MDMA exposure (measured as AUC) after 125 mg is likely between 30% and 60% of the exposure required for neurotoxicity in rats. It is not known whether rats and humans have different vulnerability to the same MDMA exposure. Furthermore, human pharmacokinetic data suggest that small increases in dose above 125 mg may lead to large increases in exposure to MDMA. Thus, while 125 mg MDMA is not expected to produce neurotoxicity based on these comparisons, the neurotoxic dose in humans may be only modestly higher. Interspecies scaling is further discussed in the chapter on animal neurotoxicity.

The calculated safety of 125 mg MDMA is supported by preliminary empirical evidence. Vollenweider et al. (2001; personal communication) measured SERT density using PET before and after clinical MDMA exposure. They were unable to detect any lasting effect of 1.5 or 1.7 mg/kg MDMA in six MDMA-naive healthy volunteers. Given the small sample size and unclear sensitivity of this measure, it is possible that a modest change in SERT density could have gone undetected. It is a fact of science that small changes may go undetected in individual studies. Therefore, risks of neurotoxicity must be discussed with all volunteers in MDMA studies, even though animal studies and data from ecstasy users give no indication that such small changes would have any detectable consequence.

Studies of illicit users provide some insight into the number of ecstasy exposures required to produce detectable serotonergic alterations. However, this type of analysis is limited because it must assume that all illicit ecstasy exposures are neurotoxic, which is probably not true. As discussed below, measures of serotonergic alterations may have a complex relationship with actual damage.

Reported correlations in many studies suggest a linear relationship between ecstasy exposure and measured alterations. For example, estimated SERT density in ecstasy users in one study (McCann et al. 1998) was linearly correlated with number of ecstasy exposures (r = -0.50, p = 0.005). If this linear relationship in users with 70 or more exposures could be generalized to individuals with fewer exposures, then the effects of one or two exposures in a clinical setting should be too small to measure. The average
decrease in estimated SERT density in these volunteers was approximately 1 SD unit and only one ecstasy user was clearly outside the range of nonuser values. In the conference comments compiled by Turner and Parrott, Gamma extrapolates from the correlation in the McCann PET study (Turner and Parrott 2000). Given the modest effects of more than 70 ecstasy exposures, Gamma calculates that the effects of a single ecstasy exposure should cause a decrease of only 0.1%, which is within normal SERT density variance. However, the apparent linear correlation seen in these papers may be an artifact of the limited exposure ranges of the studied users. Even if there is a linear exposure-toxicity relationship over a given exposure range, it cannot be assumed that this relationship remains linear over the entire range of possible exposures.

The interpolated curve in Figure 5.1 provides some limited evidence that CSF 5HIAA decreases may be logarithmically related to number of illicit ecstasy exposures. A logarithmic dose-response function would imply that illicit users could experience large alterations in neurofunctioning early in their ecstasy use history. The absolute magnitude of further changes from subsequent exposures would become progressively smaller and could appear linear over limited exposure ranges. This possibility appears consistent with the reported resistance of some serotonergic axons to ecstasy-induced neurotoxicity in the nonhuman animal studies (O’Hearn et al. 1988). Of course, this would not mean that there is an upper limit to possible ecstasy-induced toxicity since the behavioral or cognitive consequences of ecstasy exposure may have complex relationships with these neurofunctional measures.

If the interpolated curve in Figure 5.1 is accurate, 2 ecstasy exposures would be predicted to decrease CSF 5HIAA by 2.6 ng/ml. Because the standard deviation for CSF 5HIAA is around 7 ng/ml, such a decrease would be unlikely to reduce this metabolite to a level that could be considered abnormal. This calculation is a simplification given that serotonergic neurotoxicity is dose-dependent and unlikely to occur after lower doses.

There are intrinsic limitations to our ability to quantify serotonergic neurotoxicity. We can measure indices of serotonergic functioning. Changes in these indices of serotonergic functioning reflect, to some unknown degree, the permanent redistribution of axons. The long-term consequences of this axonal redistribution are unknown. Theoretical arguments not withstanding, there is no evidence that the consequences of this axonal redistribution are severe. Drugs with capacity to produce similar changes have been used for over 60 years without evidence of clinical impairment due to serotonergic neurotoxicity. However, without large population studies, some changes may not have been detected.

Possible changes in neurocognitive performance. Increasing evidence suggests that repeated ecstasy exposure can sometimes cause neurocognitive changes. These changes are clinically small and could be considered insignificant if it was clear that they were short-term and reversible. Because evidence of reversibility is inconsistent and data are few, risks of neurocognitive changes should be taken seriously when designing and assessing possible clinical studies. Exposure to MDMA in previous clinical studies has not been found to cause lasting neurocognitive changes. However, chronic exposure to
seemingly similar doses in illicit contexts appears to sometimes cause such changes. It is not known if these changes are due to occasional high doses, the frequency of drug exposure, or conditions of illicit use. Therefore, clinical exposure to MDMA should be kept at the minimum necessary to achieve study goals.

Not every ecstasy exposure causes lasting neurocognitive changes. No lasting changes in neurocognitive performance have been reported in clinical MDMA studies. Dr. Charles Grob et al. administered doses of up to 2.5 mg/kg MDMA in a clinical setting, testing neurocognitive performance before and approximately two weeks after drug exposure. As illustrated in Table 2.5, no significant changes occurred in the 14 volunteers assessed. Dr. Franz Vollenweider et al. also report that neurocognitive performance in their volunteers was unchanged by one or two exposures of up to 1.7 mg/kg MDMA in a clinical setting (Vollenweider et al. 2001). Testing by Grob et al. appears to have been adequately powered to detect even small changes. Vollenweider et al. have not yet published or made available details of their analyses. When published, data from Vollenweider et al. will be particularly interesting because many of their volunteers were previously MDMA-naive. These reports suggest that there are minimal risks of neurocognitive changes after one or two exposures to MDMA in a clinical setting.

In contrast to the findings of these clinical studies, studies of illicit ecstasy users have sometimes found evidence of decreased performance in neurocognitive tasks. These studies of illicit ecstasy users are important to consider when designing clinical trials because they provide evidence of what types of ecstasy exposure could lead to toxicity. Taken together, studies of illicit ecstasy users support the conclusion that MDMA exposure per se does not necessarily cause lasting neurocognitive performance changes. But, there is evidence that, under certain unknown-but-common conditions, as few as 20 exposures to illicit ecstasy may lead to decreased neurocognitive performance (e.g., Rodgers 2000). The conclusion that not all ecstasy exposures cause lasting neurocognitive changes is consistent with nonhuman MDMA neurotoxicity research. Despite extensive serotonergic damage, animals in these studies have generally not shown evidence of lasting behavioral changes or neurocognitive impairments. As discussed in the previous chapter, two studies (Broening et al. 2001; Marston et al. 1999) out of at least eleven (Frederick et al. 1998; Frederick et al. 1995; LeSage et al. 1993; McCreary et al. 1999; Ricaurte et al. 1993; Robinson et al. 1993; Seiden et al. 1993; Slikker et al. 1989; Spanos and Yamamoto 1989) have found evidence of lasting behavioral or memory impairment in MDMA-exposed animals.

The most relevant studies of illicit ecstasy users are prospective studies and those retrospective studies that adequately controlled for use of other drugs. Gouzoulis-Mayfrank et al. (2000) found that users of ecstasy and cannabis performed worse than a comparison group matched for the use of cannabis in a variety of tasks. In this study, ecstasy users had taken $1.4 \pm 0.9$ pills $2.4 \pm 1.6$ times per month for $27 \pm 18$ months. Thus, these individuals had used $93.4 \pm 119.9$ tablets, or $3.36$ pills per month. Rodgers (2000) found that 15 cannabis-using ecstasy users who had used ecstasy an average of 20 times over 5 years performed worse than 15 cannabis users in tests of delayed verbal and visual memory. In an important prospective study, Zakzanis et al. (2001) found that 15
polydrug-using ecstasy users decreased in performance of a memory task (and tended to
decrease in other tasks) over 12 months. During that time, the volunteers used an average
of 1.75 pills an average of 2.4 times per month. Volunteers were free from ecstasy use
for at least two weeks before each testing session. Thus, as few as 29 exposures to 50
ecstasy pills may decrease neurocognitive performance. Considered in another way,
volunteers in this study ingested 4.2 pills per month. In contrast, Croft et al. (2001) were
unable to detect an effect of ecstasy exposure in users of ecstasy and cannabis who had
taken $41.5 \pm 49.3$ ecstasy pills when they were compared to matched cannabis users. In
all these cases, it is unclear whether the decrease in performance is a cumulative residual
effect or a frank neurotoxic effect.

The contrasting findings of these studies suggest that only some conditions or patterns of
ecstasy exposure lead to neurocognitive changes. It is not known what conditions or
patterns of ecstasy exposure these are. Toxic ecstasy exposures may be ones that are
above a certain dose, are frequent, lead to hyperthermia, occur with certain other drugs,
or have some combination of these conditions. Each of these possible factors will now be
considered.

The doses consumed by ecstasy users are difficult to estimate. Volunteer reports of
previous ecstasy use may be inaccurate; the potency of ecstasy pills varies; and few
studies have quantitatively analyzed ecstasy pills. These uncertainties should be kept in
mind during the following discussion. In the report by Saunders and Doblin (1993), the
average potency of MDMA-containing pills was 87.4 mg MDMA, which is slightly
higher than the average of 76 mg MDMA per pill in the study by Sherlock et al. (1999).
If pills containing inactive amounts of MDMA (less than 20 mg) are excluded, the mean
potency across these two studies is $90.8 \pm 35.0$ mg MDMA. This suggests that the
average dose may have been $127 \pm 95.2$ mg MDMA in the study by Gouzoulis-Mayfrank
et al. and $159 \pm 61.3$ mg MDMA in that of Zakzanis et al. (the standard deviation is wider
and more accurate in the Gouzoulis-Mayfrank study because they provided standard
deviations for measures of ecstasy exposure). These estimated doses are also very similar
to doses used in clinical MDMA studies (and apparently not associated with
neurocognitive changes). This suggests that either neurocognitive changes in illicit users
are due to the occasional high dose or that some factor aside from dose is a risk factor for
neurocognitive changes.

Frequent ecstasy exposure may be a risk factor for lasting neurocognitive changes. In
both the Gouzoulis-Mayfrank and Zakzanis studies, volunteers used ecstasy 2.4 times per
month (Gouzoulis-Mayfrank provided a standard deviation of 1.6 times per month). In
most clinical MDMA studies, volunteers appear to have received MDMA at intervals of
14 days or more.

It is possible to hypothesize reasons that there could be increased toxicity with frequent
ecstasy exposure. It must be emphasized that these hypothetical reasons are speculative.
Doses of MDMA that are not neurotoxic have been shown to cause cerebral oxidative
stress in animal studies (Schmidt and Taylor 1988). Thus, recent MDMA exposure could
theoretically deplete endogenous defenses against oxidative stress, leaving the individual
vulnerable to subsequent toxicity from MDMA. Among other considerations, MDMA can oxidatively inactivate tryptophan hydroxylase, possibly lowering serotonin levels (Schmidt and Taylor 1988; Stone et al. 1989a; Stone et al. 1989b). Serotonergic depletion (by dietary manipulation) can impair declarative verbal memory in healthy volunteers (Riedel et al. 1999). Finally, Chang et al. (2000) found that two exposure to MDMA in a clinical setting decreased cerebral blood flow at 10 to 21 days after the second exposure. Although these decreases do not appear to be permanent (Chang et al. 2000; Gamma et al. 2001), one might speculate that further MDMA exposure during this period of decreased cerebral blood flow might carry increased risks of toxicity.

In addition to patterns of ecstasy exposure, conditions commonly present during illicit ecstasy exposure may be risk factors for neurocognitive changes. In rodents, hyperthermia potentiates MDMA neurotoxicity (Broening et al. 1995; Colado and Green 1995; Colado et al. 1993; Malberg and Seiden 1998). Hyperthermia associated with exercise or warm or humid conditions may potentiate toxicity in illicit users as well. Concurrent use of hallucinogens also potentiates neurotoxicity in rodents (Gudelsky et al. 1994) and is common in illicit ecstasy users. If serotonergic neurotoxicity in rodents can be related to neurocognitive changes in humans, these factors would increase risk of neurocognitive changes.

Based on the available literature, it seems likely that any long-term neurocognitive changes that occur as the result of clinical MDMA exposure will be subtle. In the only published prospective study of illicit ecstasy users, delayed memory of ideas from a story was decreased by 0.63 ± 2 SD units after approximately 29 ecstasy exposures over 12 mo (Zakzanis and Young 2001). Any neurocognitive changes, if they occur after one or two clinical MDMA exposures, seem likely to be much less than this amount. Assuming that each ecstasy exposure in the Zakzanis study contributed equally to these changes, a single MDMA exposure could be predicted to decrease performance in a similar task by about 0.02 SD units. It should again be noted that it is possible that some previously undetected toxicity will manifest itself as users age, since long-term follow-up studies have not been published.

**Monitoring for Chronic Neurotoxicity in Clinical MDMA Studies**

While current data suggest that MDMA can be safely administered in a clinical setting to healthy volunteers without lasting toxicity, neurotoxicity is still possible in some clinical studies. Measurable serotonergic neurotoxicity cannot be currently ruled out in studies that employ doses above 125 mg MDMA. Measurable neurocognitive changes remain possible in studies employing individual doses above 2.5 mg/kg MDMA. Subtle changes, too small to detect in small clinical trials, also cannot be excluded after any dose. In addition, current data only address the safety of studies that include healthy individuals receiving one or two doses. Given these data limitations, researchers may wish to monitor for neurotoxicity in some studies. Monitoring for neurotoxicity may be informative in studies of the possible therapeutic effects of MDMA in patients. Monitoring for neurotoxicity is unlikely to be useful in clinical studies employing
ecstasy users as volunteers. This is because previous and ongoing ecstasy use is likely to obscure the possible chronic effects of clinical MDMA exposure (if any occurred).

There are a number of putative measures of neurotoxicity, including neurocognitive, serotonergic, and neurofunctional measures. Although lumbar puncture (to measure CSF 5-HIAA) could be considered, it may not be informative in ongoing ecstasy users and may be unduely burdensome for patient populations. Other putively serotonergic measures are difficult to interpret. Therefore, neurocognitive performance measures may be the best method for detecting toxicity. Decreases in performance would represent an unambiguous measure of toxicity, in contrast to serotonergic and neurofunctional measures. Furthermore, studies of illicit ecstasy users suggest that neurocognitive performance measures are sensitive to the effects of relatively few toxic ecstasy exposures.

Because no specific deficits have been demonstrated, a standard neurocognitive test battery seems useful. Declarative verbal memory is an area of functioning for which there is the most extensive evidence of ecstasy-related changes and may be measured with the Ray Auditory Verbal Learning Test or similar tests. There is also evidence that executive function and working memory may be affected in ecstasy users and that deficits will be most apparent when there is high cognitive demand (such as when a high rate of responses is required). The Wisconsin Card Sorting Task is one of the most widely used measures of executive functioning and decreased performance on it reportedly correlated with ecstasy exposure in one study (Dafters et al. 1999).
Medical Emergencies and Adverse Events in Ecstasy Users
Matthew Baggott, B.A., Reid Stuart, M.A., Lisa Jerome, Ph.D.

Introduction and Overview

This chapter summarizes the literature on medical emergencies and adverse events related to MDMA/ecstasy. Published analyses suggest that most ecstasy pills contain MDMA. However, many other drugs have been detected in these pills, and some pills sold as ecstasy do not contain any MDMA. This chapter does not discuss cases involving drugs sold as ecstasy that were determined to contain no MDMA. Because serious adverse events are rare after illicit ecstasy exposure, they are even less likely in clinical settings. Nonetheless, this chapter may be useful for assessing and minimizing the risks of acute toxicity in clinical studies.

In 1999, there were 2,848 emergency department (ED) cases involving ecstasy in the United States. 78% of these cases also involved other drugs, most commonly alcohol. Most ecstasy-related ED cases occurred in young adults (age 18 to 25), as would be expected given the demographics of ecstasy use in the United States. Given the distribution of ecstasy use among young adults, it can be estimated that 2.9 to 3.6 in 10,000 ecstasy exposures in young adults resulted in an ED visit. A survey of 329 Australian ecstasy users suggests that this estimate is realistic. In this Australian survey, the equivalent of at least 11 ED visits in 10,000 ecstasy exposures occurred. Deaths relating to ecstasy use are poorly documented in the US. Gore (1999) estimated that 0.21 ecstasy-related deaths per 10,000 illicit users occurred annually in England from 1995-96 and 0.87 ecstasy-related deaths per 10,000 illicit users occurred annually in Scotland from 1995-97. Of course, the probability of an ED visit or death after ecstasy use is not evenly distributed among users. Possible risk factors for ecstasy-related medical emergencies or fatalities are discussed at a later point.

Serious adverse effects occurring after ecstasy use are documented in case reports in the medical literature. Before discussing these reports, it is worth considering that they may not indicate the true frequency of various adverse events. First, published case reports are probably often more severe than cases that go unpublished. Second, they probably under-represent adverse effects of ecstasy that do not require emergency treatment. Three reports – two from poison control centers and one from an emergency department (ED) – suggest that most ecstasy-related ED visits result from symptoms that are modest in severity. Signs and symptoms of ecstasy intoxication documented in these reports are similar to those of amphetamines.

We have obtained over 205 published case reports of adverse events in ecstasy users. Some of these reports describe severe forms of common side effects of ecstasy (difficulty urinating, dental problems), motor vehicle accidents, and other injuries due to intoxication. When these reports are excluded, 199 case reports remain. The most common categories of diagnosis are hyperthermia-related syndromes (24.6% of cases), psychiatric complications (22.1% of cases), hepatotoxicity (16.1% of cases), and
hyponatremia (9.5% of cases). Other reported problems include cardiovascular and cerebrovascular, neurological, hematological, respiratory (pneumomediastinum and subcutaneous emphysema), ophthalmic, dermatological, teratological, and dental problems.

Ecstasy-related hyperthermia is described in adverse case reports. While most cases of ecstasy-related hyperthermia were known to have occurred in dance settings, some cases involved individuals who were apparently not involved in “risky” behavior (aside from ecstasy ingestion).

There are reports of hepatotoxicity (liver damage) in ecstasy users. Three *in vitro* studies have confirmed that pure MDMA can damage liver cells and one of these studies found that hyperthermia increases vulnerability to this damage. Although the MDMA concentrations used in these studies are high, they could be attained in individuals taking high doses or having impaired MDMA metabolism (due to pharmacological interactions with other drugs or previous liver damage).

Cases of ecstasy-related hyponatremia (low salt levels) have been reported. The pharmacological effects of MDMA appear to place the user at increased risk of hyponatremia. Consumption of large volumes of water that would normally be safe may lead to symptoms of “water intoxication” after ecstasy ingestion.

The possible dose-dependence of ecstasy toxicity is discussed. It is argued that dose is probably a risk factor for toxicity, but that other risk factors (some of them unknown) are important and may mask the significance of dose. Probable risk factors include exercise, dehydration, over-hydration, and hot or humid settings. More frequent use or greater total lifetime dose may be risk factors for psychological problems. While rare, serious ecstasy toxicity cannot be predicted beforehand, and in many specific cases cannot be explained afterwards. Serious adverse reactions or even death can occur after modest amounts of ecstasy in the absence of known risk factors.

Finally, it is noted that a minority of users can be classified as dependent on ecstasy, using standard criteria.

**Emergency Department (ED) Visits After Ecstasy Use**

In the United States, the Drug Abuse Warning Network (DAWN) monitors ED cases involving drugs. DAWN produces weighted estimates of drug-related ED cases based on a representative sample of non-Federal, short stay hospitals with 24-hr EDs in the contiguous 48 states. The numbers of ED cases involving ecstasy from 1994 through 1999 are shown in Figure 6.1. As can be seen, (statistically significant) increases in cases involving ecstasy have occurred since 1997. Despite these increases, the number of ED cases involving ecstasy in 1999 was significantly lower than those involving either methamphetamine (10,447) or LSD (5,126). 78% of ED cases involving ecstasy also involved other drugs. In 1999, these other drugs included: alcohol (47% of ecstasy cases); marijuana (28%); cocaine (18%); GHB (16%); LSD (11%); methamphetamine
(6%); and ketamine (5%). 80% of cases involved individuals of 25 years or younger. 74% of cases were identified as white/Caucasian.

Figure 6.1: Emergency Department (ED) cases involving MDMA

![Graph showing ED mentions from 1994 to 1999.]


Estimating the Frequency of Emergency Department Visits After Ecstasy Use

As described in a previous section, the Monitoring the Future Survey provides annual estimates of the prevalence of ecstasy use among young adults in the United States. Given these data and DAWN estimated ecstasy-related ED cases, it is possible to estimate the frequency with which episodes of ecstasy use result in ED visits. In 1999, 1923 ecstasy ED cases involved individuals of 18-25 years of age, while 347 cases involved younger individuals and 578 involved older adults. The Population Estimates Program of the U.S. Census Bureau states that there were about 26 million individuals age 18-24 in the U.S. in 1999. This suggests that there were almost 30 million 18-25 year-olds in 1999. According to the 1999 Monitoring the Future Survey, 3.6% of adults, ages 19-28, used ecstasy in the last year. Although frequency of ecstasy use is not published in further detail for this group, it is available for 12th grade high school students (see Table 3.3). If one assumes that the distribution of annual ecstasy exposures is similar for young adults, then the total number of ecstasy exposures among young adults in 1999 can be estimated. However, there is a need to make assumptions about both novice users and very frequent users. Two estimates are therefore presented. In the low estimate, it is assumed that everyone reporting 1-2 ecstasy exposures in the year only used once and that no individual used more than 40 times in 1999. In the high estimate, it is assumed that individuals reporting 1-2 ecstasy exposures in the year used twice and that no individual used more than 100 times in 1999. It follows that there were approximately 5.4 (low estimate) to 6.7 (high estimate) million episodes of ecstasy use among young adults (ages 18-25) in the United States in 1999. Since there were 1923
ED visits for this age group, this implies that 2.9 to 3.6 in 10,000 ecstasy exposures resulted in an ED visit in 1999.

This estimate is limited by a number of factors. Most importantly, the number of ecstasy-related ED visits reported by DAWN may be over or under-estimated. Toxicology screens vary in their ability to detect MDMA. In a recent survey, approximately 1/3 of 2734 laboratories failed to detect MDMA that was present (Poklis 1999). Second, estimated ecstasy exposures for young adults were derived from patterns reported by 12th graders, and may be inaccurate.

This number must also be interpreted cautiously. First, it is important to recognize that this estimate does not provide a measure of risk for the individual young adult. ED visits are probably not randomly distributed among ecstasy users and some populations are likely at higher risk of adverse event. For example, individuals using higher doses are likely at greater risk of some adverse events. A subsequent section discusses this issue. Second, not all ecstasy-related health problems are treated at an ED. Most obviously, ecstasy-related deaths may not result in ED visits. The use of other health care facilities by ecstasy users is discussed in a following section. Third, the relationship between ecstasy exposures and ED visits reflects the drug use patterns and behaviors of the changing user population as well as the pharmacological characteristics of MDMA. This estimate cannot be seen as a characteristic of the drug in general.

<table>
<thead>
<tr>
<th>Users</th>
<th>No. of days used in 6 mo.</th>
<th>Possible episodes of ecstasy use in 6 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>37% of 329</td>
<td>1</td>
<td>1 to 1</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>1 to 6</td>
</tr>
<tr>
<td>33% of 329</td>
<td>108</td>
<td>7 to 12</td>
</tr>
<tr>
<td>19% of 329</td>
<td>62</td>
<td>13 to 24</td>
</tr>
<tr>
<td>12% of 329</td>
<td>37</td>
<td>25 to 100</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>100 to 100</td>
</tr>
</tbody>
</table>

Total users: 329
Total episodes: 2708 to 7305
Minimum no. of ED visits: 8 to 8
Minimum rate of ED visits per 10,000 episodes: 29.5 to 11.0

Data taken from Topp et al. 1999. Italicized numbers were directly stated by the authors. Unitalicized numbers show the range of possibilities. It is assumed that each day on which ecstasy was used is a separate episode of use.

This estimate can be compared to the results of a survey of 329 polydrug-using ecstasy users in Australia (Topp et al. 1999). In the survey, users were recruited through
“snowball’ sampling and were required to have used ecstasy at least three times in the last 12 months and at least once in the last 6 months. Thus, novice or very infrequent ecstasy users were excluded, in contrast to the nationwide U.S. data relied on for the above estimate. The researchers found that 8 of 329 users had presented to an ED with an ecstasy-related problem in the previous 6 months. Given the data in this report, it can be calculated (see Table 6.1) that there were at most 7305 episodes of ecstasy use by these users in this period. Because there were at least 8 ED visits in this time, we can conclude that there were the equivalent of at least 11 ED visits per 10,000 episodes of ecstasy use in this population.

Thus, data from these Australian ecstasy users suggest that the previous estimate of 2.9 to 3.6 ED visits in 10,000 ecstasy exposures is realistic, perhaps even low. There are insufficient data to determine to what extent differences between these estimates are due to the comparison of Australian and U.S. ecstasy users, exclusion of novice and infrequent users from the Australian sample, or the inherent inaccuracy in the estimates.

What Types of Adverse Events Are Most Common?

The adverse case report literature provides data on the range of adverse events in ecstasy users but it does not indicate the true frequency of these events since published case reports over-represent “interesting” or unusual cases. The distribution of different types of acute adverse events after ecstasy use is better estimated by counting consecutive cases from emergency departments (ED) or phone calls to poison control centers. Table 6.2 summarizes signs and symptoms from a series of 48 ecstasy-related cases presenting in an ED (Williams et al. 1998b). As can be seen, the most common complaints were: feeling strange/unwell/dizzy/weak (31.2% of users); collapse/loss of consciousness (22.9%); and panic/anxiety/restlessness (18.8%). High temperature (defined as >37.1°C) was documented in 18.8% of cases. Dehydration occurred in 4.2%. Management of these ecstasy-related ED cases varied:

After an initial assessment, 41 (85.4%) cases had an electrocardiogram or continuous cardiac monitoring. In 30 cases (62.5%) the patient received a further period of observation and monitoring (mean 9 hours, range 1-12 hours) in the A&E department. Fifteen cases (31.3%) received fluids (oral eight/intravenous seven) while six (12.5%) had some form of medication administered (diazepam, two, and one each naloxone, activated charcoal, metoclopramide, and antibiotics/paracetamol). Advice/reassurance was recorded as having been given in 14 (29.%) cases. Full resuscitation and intubation were required in one case.

Of these 48 cases, seven required hospital admission, while most were discharged after a period of observation in the ED.
### Table 6.2: Features of 48 Sequential Ecstasy-related ED Visits

#### Clinical features associated with ecstasy only (n=16)

<table>
<thead>
<tr>
<th>Complaint/symptom</th>
<th>No (%)</th>
<th>Clinical findings/sign</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strange/unwell/dizzy/weak</td>
<td>7 (43.8)</td>
<td>High pulse rate (&gt;100 beats/min)</td>
<td>13 (81.3)</td>
</tr>
<tr>
<td>Collapsed/loss of consciousness</td>
<td>1 (6.3)</td>
<td>Dilated pupils</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>5 (31.3)</td>
<td>Hyperventilation (&gt;20 breaths/min)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>Panic/anxiety/restlessness</td>
<td>5 (31.3)</td>
<td>Anxiety/agitation/disturbed behavior</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>6 (37.5)</td>
<td>High temperature (&gt;37.1°C)</td>
<td>5 (31.5)</td>
</tr>
<tr>
<td>Hot/cold (feeling hot/cold)</td>
<td>4 (25.0)</td>
<td>High blood pressure (&gt;160/95 mm Hg)</td>
<td>0</td>
</tr>
<tr>
<td>Strange/unwell/dizzy/weak</td>
<td>7 (43.8)</td>
<td>Drowsiness</td>
<td>0</td>
</tr>
<tr>
<td>Shaking</td>
<td>2 (12.5)</td>
<td>Dehydration</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (12.5)</td>
<td>Shivering</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (6.3)</td>
<td>Seizure</td>
<td>0</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>2 (12.5)</td>
<td>Nystagmus</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (18.8)</td>
<td>Hallucinating</td>
<td>0</td>
</tr>
<tr>
<td>Muscle aches/pains</td>
<td>1 (6.3)</td>
<td>Sweating</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>2 (12.5)</td>
<td>Unconscious</td>
<td>0</td>
</tr>
<tr>
<td>Thirst</td>
<td>2 (12.5)</td>
<td>Tremulousness</td>
<td>0</td>
</tr>
<tr>
<td>Seizure</td>
<td>0</td>
<td>No abnormality found</td>
<td>0</td>
</tr>
<tr>
<td>Twitching</td>
<td>0</td>
<td>Other</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (25.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Clinical features associated with ecstasy and other drugs and/or alcohol (n=32)

<table>
<thead>
<tr>
<th>Complaint/symptom</th>
<th>No (%)</th>
<th>Clinical findings/sign</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strange/unwell/dizzy/weak</td>
<td>8 (25.0)</td>
<td>High pulse rate (&gt;100 beats/min)</td>
<td>19 (59.4)</td>
</tr>
<tr>
<td>Collapsed/loss of consciousness</td>
<td>10 (31.1)</td>
<td>Dilated pupils</td>
<td>12 (37.5)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>6 (18.8)</td>
<td>Hyperventilation (&gt;20 breaths/min)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Panic/anxiety/restlessness</td>
<td>4 (12.5)</td>
<td>Anxiety/agitation/disturbed behavior</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>6 (18.8)</td>
<td>High temperature (&gt;37.1°C)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Hot/cold (feeling hot/cold)</td>
<td>3 (9.4)</td>
<td>High blood pressure (&gt;160/95 mm Hg)</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Strange/unwell/dizzy/weak</td>
<td>8 (25.0)</td>
<td>Drowsiness</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Shaking</td>
<td>4 (12.5)</td>
<td>Dehydration</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (12.5)</td>
<td>Shivering</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (9.4)</td>
<td>Seizure</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>2 (6.3)</td>
<td>Nystagmus</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (3.1)</td>
<td>Hallucinating</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Muscle aches/pains</td>
<td>3 (9.4)</td>
<td>Sweating</td>
<td>0</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>1 (3.1)</td>
<td>Unconscious</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Thirst</td>
<td>1 (3.1)</td>
<td>Tremulousness</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (9.4)</td>
<td>No abnormality found</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Twitching</td>
<td>1 (3.1)</td>
<td>Other</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (9.4)</td>
<td>Missing data</td>
<td>1 (3.1)</td>
</tr>
</tbody>
</table>

*Table reproduced from (Williams et al. 1998b)*

Page 152 of 367
Two publications have described ecstasy-related calls to a poison control center. The earlier report describes 37 consecutive ecstasy-related calls to the National Poisons Information Centre in Ireland from January 1991 to June 1992 (Cregg and Tracey 1993). Symptoms were described as relatively mild in most cases, although 1 death due to ecstasy-related congestive heart failure in a 17-year-old male was recorded. Serious signs and symptoms included coma (5.4% of cases), hypokalaemia (2.7%), convulsions (2.7%), and cardiorespiratory arrest (2.7%). In a retrospective survey of 191 ecstasy-related calls handled by the New York City Poison Control Center from 1993-1999 (Rella et al. 2000), 73% of calls involved minor or no toxicity. Of the 27% (52/191) of calls involving moderate to major toxicity, 7 patients were hyperthermic (one died) and three had electrolyte abnormalities, including hyponatremia.

These three reports suggest that most acute adverse events involving ecstasy are modest in severity. Aside from typical MDMA effects (such as dilated pupils, hypertension, tachycardia, and excitement), symptoms and signs of ecstasy toxicity are varied. From these reports, no single mechanism or syndrome seems obviously responsible for the majority of ecstasy-related ED visits. From these reports, signs and symptoms of ecstasy toxicity appear fairly similar to those reported from amphetamines (Chan et al. 1994; Derlet et al. 1989; Richards et al. 1999). One exception to this may be hyponatremia, which is relatively common in ecstasy users but does not appear to be associated with other amphetamines. There are limitations to using EDs and poison control centers as sources of information. Both types of facilities likely also treat more acute, rather than chronic, problems. Therefore it is important to consider use of other types of health care facilities by ecstasy users.

Use of Other Health Care Services by Ecstasy Users

Ecstasy users are likely to use health care services other than EDs for some ecstasy-related problems. In particular, ecstasy-related problems that are chronic in nature and are not life-threatening are likely to be treated at other facilities. The incidence of these chronic problems is difficult to assess. In the survey of 329 Australian polydrug-using ecstasy users, 22% had received formal assistance for an ecstasy-related health problem, although other drugs were also involved in most (58%) of these cases (Topp et al. 1999). When only those problems which were considered ecstasy-related are included, the percentages of users in this survey accessing non-emergency health care services were: 8.8% for a general practitioner, 3.3% for a ‘natural therapist’, and 1.5% for a psychiatrist. Thus, this survey suggests that a substantial minority of ecstasy users seek health care for ecstasy-related problems.

Although the specific reasons for seeking health care are not given, the incidence of various potentially ecstasy-related problems is given for the overall sample in this study. Significant minorities of users reported symptoms lasting beyond the short-term recovery period such as weight loss (17.3% of users), depression (24.3%), irritability (20.4%), energy loss (19.4%), difficulty sleeping (16.1%), anxiety (14.0%), and dental problems (12.2%). Of course, it cannot be conclusively established that these symptoms were caused by ecstasy use. The individuals in this survey also may not be representative of
ecstasy users in general. In addition to seeking relief from possible ecstasy effects, users may have also sought formal health care for assistance in decreasing ecstasy use. 25% of users in this survey wanted to reduce their ecstasy use. Ecstasy dependence is discussed in a subsequent section.

Deaths After Ecstasy Use

There are few available data on MDMA-related deaths in the United States. DAWN collects data on drug-related deaths from medical examiners in large metropolitan areas. However, participation in this program is voluntary and is not based on a statistical sampling. Furthermore, for comparing data across years, DAWN only includes reports from medical examiners who provided data for at least 10 months in every relevant year. Therefore, DAWN counts of MDMA-related deaths do not represent the U.S. as a whole, merely a consistent but unrepresentative subset. DAWN recently reported that 27 deaths involving MDMA occurred between 1994 and 1998 (DAWN 3/2000 update). MDMA-related deaths ranged from 1 in 1994 to 9 in 1998, with no apparent trend in numbers after 1995 when 6 deaths were reported. These numbers may be useful for illustrating potential trends, but are clearly not comprehensive.

Table 6.3: Estimated Annual Ecstasy-related Death Rate in England and Scotland

<table>
<thead>
<tr>
<th></th>
<th>Scotland</th>
<th>England</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of ecstasy-related deaths</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total in 1995-97 for Scotland, and in 1995-96 for England</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Annual</td>
<td>3.7</td>
<td>9.0</td>
</tr>
<tr>
<td><strong>Population (age 15-24)</strong></td>
<td>600 x 10^3</td>
<td>6000 x 10^3</td>
</tr>
<tr>
<td><strong>Number of ecstasy users (age 15-24) in 1996</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>42 x 10^3</td>
<td>420 x 10^3</td>
</tr>
<tr>
<td>Regular users</td>
<td>18 x 10^3</td>
<td>180 x 10^3</td>
</tr>
<tr>
<td>Sporadic users</td>
<td>24 x 10^3</td>
<td>240 x 10^3</td>
</tr>
<tr>
<td>First-time users (estimate A)</td>
<td>7 x 10^3</td>
<td>70 x 10^3</td>
</tr>
<tr>
<td>First-time users (estimate B)</td>
<td>12.8 x 10^3</td>
<td>128 x 10^3</td>
</tr>
<tr>
<td><strong>Annual ecstasy-related death rate per 10,000 users</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All users</td>
<td>0.87</td>
<td>0.21</td>
</tr>
<tr>
<td>Sporadic users</td>
<td>1.54</td>
<td>0.38</td>
</tr>
<tr>
<td>First-time users (estimate A)</td>
<td>5.29</td>
<td>1.29</td>
</tr>
<tr>
<td>First-time users (estimate B)</td>
<td>2.89</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Table adapted from Gore, 1999.
Estimate A assumes the number of new first-time users was constant each year. Estimate B assumes that number increased.

Because reliable data are not available on ecstasy/MDMA-related deaths, it is not possible to estimate the death rate of ecstasy users in the U.S. There are apparently more complete data available on ecstasy-related deaths in Scotland and England. By 1996, at least 53 ecstasy-related deaths had occurred in the U.K. (anonymous 1996). One publication (Gore 1999) has ventured estimates of death rates in young ecstasy users in Scotland and England. These estimates are reproduced in Table 6.3. It must be cautioned that, as always, estimated ecstasy-related deaths may over or under-estimate actual MDMA-related deaths. Letters responding to the calculation by Gore have pointed
out difficulties in such estimates, including the varying and unknown contents of illicit ecstasy pills (Lind et al. 1999; Ramsey et al. 1999).

**Hyperthermia**

The most commonly reported category of ecstasy-related adverse event involved hyperthermia (overheating). Any case in which body temperature equaled or exceeded 38°C or was stated as involving hyperthermia was classified in this category. Hyperthermia occurred in 25.1% (50/199) of the cases identified in the literature. The presence of MDMA was confirmed in the majority of these cases (70.0%). Of the 50 cases involving hyperthermia in the ecstasy literature, 62.0% (31/50) occurred in a dance or party setting. Hyperthermia occurred in other settings in 14% (7/50) of cases. Location was unknown in 24% (12/50) of cases. This section will discuss possible mechanisms and risk factors for ecstasy-related hyperthermia, including dose-dependant drug effects, setting of use, and user behaviors. Three rare, potentially relevant, drug-induced hyperthermic syndromes will be discussed. Finally, symptoms that can be caused by sustained hyperthermia, such as rhabdomyolysis, acute renal failure, and disseminated intravascular coagulation, will be mentioned.

Hyperthermia in the presence of neurologic disturbance, such as delirium, stupor, or convulsions, has high risk of mortality or lasting morbidity. Mortality rates from heat stroke vary from 30-80%, depending on the maximum temperature reached, the durations of hyperthermia and unconsciousness, and the health of the individual. Mortality occurred in 42.0% (21/50) of cases of ecstasy-related hyperthermia. Of the 49 cases where body temperature is available in the literature, individuals who recovered from ecstasy-related hyperthermia tended to have lower body temperature than fatalities. Initially recorded body temperatures were 41.1° ± 1.8° C in fatalities versus 40.3° ± 1.5° C in survivors. However, this difference is not statistically significant, partially because data are skewed by case reports describing unusually high body temperatures in survivors (Logan et al. 1993; Mallick and Bodenham 1997).

Many cases of ecstasy-related hyperthermia are likely the result of an interaction of drug effects, setting of use, and user behavior. In rodent studies, MDMA has been shown to dose-dependently impair thermoregulation, leading to hyperthermia in most settings (Broening et al. 1995; Colado et al. 1995; Dafters 1994; 1995; Daws et al. 2000; Gordon et al. 1991). Drug-induced vasoconstriction likely plays a role in hyperthermia by slowing heat loss from the body (Fitzgerald and Reid 1994; Gordon et al. 1991). High ambient temperatures (as can be sometimes found at dance events) and exercise can be expected to increase body temperature. Ambient temperature has been linked to risk of death in overdose from other stimulants. A retrospective review of cocaine overdoses in New York City analyzed the maximum daily temperature and the number of unintentional cocaine overdoses over a three-year period. It found a threshold peak temperature of about 31.1°C (88°F) above which daily deaths from cocaine overdose increased dramatically (Marzuk et al. 1998). A number of studies of athletes and amphetamines suggest that these drugs can prolong ability to exercise, possibly by delaying fatigue or masking pain (Clarkson and Thompson 1997). MDMA may also
increase desire or ability to exercise beyond one’s normal limits. MDMA has been shown to decrease fluid consumption when fluid-deprived animals are given access to water (Dafters 1995) or sweetened ethanol solution (Bilsky et al. 1990). Thus, MDMA intoxication may mask thirst, preventing dehydrated individuals from rehydrating. Dehydration impairs sweating and therefore cooling. In a rat study, dehydration increased MDMA-induced hyperthermia (Dafters 1995).

However, it does not appear that ecstasy-related hyperthermia can be entirely attributed to warm settings, dance, and dehydration. 14.0% (7/50) of cases of ecstasy-related hyperthermia described in the literature occurred in settings other than dances or parties. These other settings included homes (5 cases), pubs (1 case), and jail (1 case). Dehydration is also not necessary for hyperthermia. In the 48 ecstasy-related ED cases summarized by Williams et al. (1998), high temperature was reported in 18.8% of cases, while dehydration occurred in only 4.2%.

A number of case reports describe hyperthermic syndromes that rapidly developed after ecstasy ingestion in individuals who were apparently not exercising (Brown and Osterloh 1987; Demirkiran et al. 1996; Henry et al. 1992). In one case, blood concentration of MDMA was very high (6.5 mg/L), suggesting impaired MDMA metabolism or overdose, despite the modest estimated dose of 100-150 mg MDMA (Brown and Osterloh 1987). In another case, adverse symptoms began within 15 minutes of drug ingestion and resembled neuroleptic malignant syndrome (Demirkiran et al. 1996). Although MDMA was not specifically identified in biofluids, it was detected in another tablet reportedly from the same batch consumed by the patient. These cases suggest that ecstasy hyperthermia may sometimes be one of several rare drug-induced hyperthermic syndromes. These syndromes are all described below.

**Malignant Hyperthermia (MH).** Malignant hyperthermia is a hypermetabolic state that is due to one of several inherited muscle-cell membrane disorders. MH has varied clinical presentation including rhabdomyolysis, muscle pain, and markedly elevated core temperature. When triggered in a clinical setting by anesthetics, signs of MH include tachycardia, dysrhythmia, cyanosis, generalized muscle rigidity, and (of course) hyperthermia. In addition to anesthetics, other possible triggers of MH are exercise in heat, infections, and neuroleptic drugs. MH is triggered by a rapid and sustained increase in myoplasmic Ca\(^{2+}\). Ca\(^{2+}\) is stored in the sarcoplasmic reticulum and released in a process controlled by at least three structural proteins. The amount of released Ca\(^{2+}\) controls the strength of skeletal muscle contraction. In MH, regulation of Ca\(^{2+}\) fails and sustained increases in free Ca\(^{2+}\) lead to muscle tension and heat production. Testing for susceptibility to MH involves taking muscle fibers from the thigh by biopsy and measuring their response to halothane and, separately, caffeine. Although several gene mutations have been associated with MH, others have yet to be discovered. It is therefore not possible to screen for MH susceptibility by DNA testing. Treatment of MH typically involves ice, fans, cooling blankets, and dantrolene (a drug that decreases heat production by relaxing muscles through blocking myoplasmic Ca\(^{2+}\) release).
Serotonin Syndrome. Serotonin syndrome is a potentially fatal toxic syndrome that is thought to result from excessive 5HT release with common symptoms including restlessness, confusion, myoclonus, hyporeflexia, hyperthermia, sweating, shivering, tremor, and diarrhea. In animal studies, increased extracellular 5HT does not necessarily lead to serotonin syndrome, suggesting other neurotransmitters may be involved. 5HT$_{1A}$ and, to a lesser extent, 5HT$_{2}$ receptors are thought to mediate many symptoms of serotonin syndrome since drugs acting as antagonists at these receptors decrease these effects in animals. It has also been suggested that serotonin syndrome may be due to 5HT release inhibiting DA release, leading to NMS, although this hypothesis has not been confirmed. Serotonin syndrome occurs most commonly when two agents that increase serotonin levels by different mechanisms are taken together. For example, simultaneous administration of a monoamine oxidase inhibitor and L-tryptophan has led to serotonin syndrome in many cases. Less often, a high dose of a single serotonergic agent may also cause serotonin syndrome. Treatment of serotonin syndrome is primarily supportive. Although animal studies suggest that nonspecific 5HT antagonists or propranolol (a β-andrenergic blocker that is also a 5HT$_{1A}$ antagonist) may be useful, results have been mixed in humans.

Neuroleptic Malignant Syndrome (NMS). NMS is a very rare potentially fatal extrapyramidal syndrome associated with muscle (“lead pipe”) rigidity, autonomic dysfunction, and altered mental state. NMS typically develops when a drug blocks dopamine receptors or decreases extracellular dopamine levels. Decreased dopaminergic levels in the striatum causes muscle tension, which, along with altered hypothalamic functions, leads to hyperthermia. Most commonly, NMS occurs during the administration of neuroleptics. In addition to dose-related variables, risk factors for developing NMS are thought to include high ambient temperature, dehydration, and agitation. Treatment of NMS involves dopamine agonists such as bromocriptine or apomorphine.

There is not sufficient evidence to establish whether cases of ecstasy-related hyperthermia are sometimes one of these three drug-induced hyperthermic syndromes. There is overlap in the symptoms of these syndromes and correct diagnosis ultimately relies on understanding the cause of the syndrome, which remains unknown in cases involving ecstasy. Based on the pharmacology of MDMA, which includes increased synthesis and release of dopamine, serotonin syndrome seems more likely than NMS. Demirkiran et al. (1996) discuss this issue and conclude that ecstasy-related hyperthermia is more likely serotonin syndrome than NMS. Among other considerations, serotonin syndrome has a more rapid onset after drug administration than NMS, which often occurs in clinical practice 3 to 9 days after a patient’s medication is changed. Testing for malignant hyperthermia proved negative in a case of MDE-related hyperthermia (Tehan et al. 1993).

On the other hand, two reports analyzing muscle changes in ecstasy users presenting with hyperthermia have drawn conflicting conclusions. One report describes an ecstasy user presenting with pain and swelling in the left buttock, oliguria, and elevated CK. The authors conclude that the microscopic muscle changes in this user were characteristic of
NMS (Behan et al. 2000). However, it is not clear why NMS should lead to localized muscle swelling, since muscle contractions are due to CNS abnormalities. Another report described muscle changes in three deceased hyperthermic MDMA or MDE users that were considered typical of malignant hyperthermia (Fineschi et al. 1999). In these individuals, immunohistochemistry revealed hypercontracted fibers with disruption of cell architecture. Given the divergent conclusions in these two reports, it does not appear that hyperthermic syndromes can be diagnosed by microscopic muscle changes. Finally, an in vitro study found that MDMA poteniated halothane- or caffeine-induced muscle contractions (Denborough and Hopkinson 1997). However, the concentrations of MDMA (2 mM) used were very high and of questionable physiological relevance (Hall 1997a). Overall, it remains unclear whether some cases of ecstasy-related hyperthermia are due to serotonin syndrome, NMS, or malignant hyperthermia. It is possible, perhaps even likely, that fulminant ecstasy-related hyperthermia has different causes in different individuals.

Treatment of ecstasy-related hyperthermia is discussed in several publications (Dar and McBrien 1996; Henry 2000; MacConnachie 1997; Rochester and Kirchner 1999; Walubo and Seger 1999). This typically involves supportive measures and facilitation of cooling with fans, ice, etc. Intravenous saline solution is used to correct hypovolemia, which often corrects tachycardia and hypotension. Anticonvulsants, such as diazepam, are sometimes required. The use of dantrolene is controversial and it is not clear if it is effective (Hall 1997a; Singarajah and Lavies 1992; Stone 1993; Tehan 1993; Watson et al. 1993; Webb and Williams 1993).

Sustained hyperthermia can lead to multiple organ and system failure. In adverse case reports, hyperthermic ecstasy users commonly present with or develop tachycardia, hypotension, rhabdomyolysis, acute renal failure, and disseminated intravascular coagulation (DIC). These last three syndromes are discussed below.

**Rhabdomyolysis.** Rhabdomyolysis is a clinical syndrome resulting from muscle degeneration and the release of muscle proteins into the extracellular fluid. In ecstasy users, muscle degeneration is probably most often due to sustained hyperthermia or prolonged exercise but can also be caused by muscle compression in an unconscious individual. Rhabdomyolysis was reported in 38.0% (19/50) of hyperthermic ecstasy users. In addition, rhabdomyolysis was identified in three users who were not known to have been hyperthermic (Bertram et al. 1999; Sultana and Byrne 1996; Williams and Unwin 1997), although hyperthermia may have occurred before these individuals received medical assistance. Mortality occurred in 36.4% (8/22) of cases of ecstasy-related rhabdomyolysis. Possible risk factors for rhabdomyolysis in methamphetamine users are discussed by Richards et al. (1999) and include hyperthermia, decreased nutrition, dehydration, exhaustive physical exercise, tobacco smoking, and alcoholism. These may also be risk factors in ecstasy users. Symptoms of rhabdomyolysis include muscle pain, weakness, and brown (“Coca-Cola” colored) urine. The release of damaged muscle contents can lead to potentially fatal electrolyte imbalance, acute renal failure, and disseminated intravascular coagulation. Rhabdomyolysis was associated with acute
renal failure in 50.0% (11/22), and with disseminated intravascular coagulation in 63.6% (14/22), of published cases.

**Acute Renal Failure (ARF).** Acute renal failure can occur when myoglobin that was released from damaged muscles precipitates and blocks renal tubules. Dehydration facilitates the development of ARF. ARF leads to an accumulation of metabolic waste products, damaging tissues and impairing organ functioning. ARF occurred in 24.0% (12/50) of cases of ecstasy-related hyperthermia. ARF also occurred in one case in which there was rhabdomyolysis but no evidence of hyperthermia (Bertram et al. 1999). Chronic renal failure led to death in one ecstasy user who was treated too late to detect possible hyperthermia (Bingham et al. 1998). Treatment of ARF in ecstasy users is discussed by Cunningham (1997).

**Disseminated intravascular coagulation (DIC).** DIC is a systemic blood coagulation disorder involving the generation of intravascular fibrin and the consumption of procoagulants and platelets. In DIC, endothelial or tissue injury leads to release of procoagulant cytokines and tissue factors. When these factors are exhausted, coagulation is no longer possible and generalized bleeding occurs. Acute DIC is characterized by generalized bleeding, which leads to hypoperfusion, infarction, and end-organ damage. Fever and a shock–like syndrome with tachycardia and hypotension may occur. Symptoms of DIC include bleeding nose or gums, cough, shortness of breath or difficulty breathing, confusion, and fever. DIC occurred in 50.0% (25/50) of cases of ecstasy-related hyperthermia. Mortality occurred in 60.0% (15/25) of cases of ecstasy-related DIC.

**Psychiatric Problems in Ecstasy Users**

Psychiatric problems were reported in 22.1% (44/199) of case reports. The presence of MDMA was confirmed in only a minority of psychiatric case reports (9.1%, 4/44), generally due to the elapsed time between last ecstasy exposure and psychiatric assessment. For purposes of analysis, psychiatric problems in ecstasy users may be categorized into psychotic and affective symptoms (such as panic, anxiety, or depressed mood). However, not all case reports can be easily categorized as cases mood or anxiety disorders or psychosis because some cases have atypical symptoms. In addition, cases in which symptoms were absent until after ecstasy use could be reasonably classified as organic mental disorders.

Interpreting the role of MDMA in case reports of psychiatric problems in ecstasy users is difficult. When psychiatric complications occur in ecstasy users, it is impossible to determine whether ecstasy use nonspecifically triggered the onset of psychiatric complications in vulnerable individuals in whom problems could have been triggered by other stressors. Alternatively, certain patterns of ecstasy exposure could cause psychiatric complications in healthy individuals with no other risk factors. Finally, early symptoms of an undiagnosed psychiatric disorder could lead individuals to use ecstasy. It is impossible to fully separate the relative contributions of individual vulnerability and drug exposure in most case reports.
Given repeatedly, other amphetamines are able to cause psychotic symptoms or frank psychosis in volunteers who have been screened for pre-existing psychotic disorders (Angrist 1994). The symptoms of stimulant psychosis typically disappear or greatly diminish with withdrawal from drug use, but are likely to re-occur if drug use is reinitiated. MDMA may cause acute psychotic symptoms in some cases. In rodents, some patterns of MDMA administration cause behavioral sensitization, which is considered to be an animal model of stimulant psychosis (Kalivas et al. 1998; Spanos and Yamamoto 1989).

Psychotic symptoms were the most commonly reported psychiatric complication in the literature, occurring in 66.0% (29/44) of cases. Psychotic symptoms commonly included delusions of persecution, ideas of reference, depersonalization, and derealization. Most cases (79.3%, 29/38) with psychotic symptoms occurred in “regular” or “experienced” users, and only 2 cases were known to involve new users. In 48.3% (14/29) of cases with psychotic symptoms, a personal and/or family history of psychiatric problems was documented. Outcome has generally been poor in cases of psychotic symptoms in ecstasy users. In 34.5% (10/29), full recovery was reported. In 20.7% (6/29), symptoms were only partially controlled or the patient was known to have relapsed. No improvement was evident in 17.2% (5/29). Outcome was not stated in 27.6% (8/29) of cases. History of psychiatric illness did not appear to predict outcome. While 50% of those fully recovering had known personal and/or family history of psychiatric illness, none of the 5 cases without improvement had any known history.

In a few cases, psychotic symptoms resembled those of stimulant psychosis. Stimulant psychosis is typically a paranoid psychosis with ideas of reference, delusions of persecution, and auditory and visual hallucinations, in a setting of clear consciousness, although atypical symptoms (such as clouding of consciousness) may occur. For example, Alciati et al. described three cases of delirium in ecstasy users concurrently using ecstasy and cocaine that resolved within five days (Alciati et al. 1999). These could be regarded as cases of atypical stimulant psychosis.

Many cases with psychotic symptoms were not typical of stimulant psychosis. Persisting symptoms after drug discontinuation are not expected in stimulant psychosis. Full recovery was only reported in 34.5% of ecstasy users with psychotic symptoms. McGuire et al. (1994) compared 8 ecstasy users with psychosis to 40 substance naïve psychotic patients. While ecstasy users reported less depression than other patients, this difference was no longer significant after correction for multiple comparisons. In other reports, patients had atypical symptoms. One research group has reported an association between chocolate craving and psychotic symptoms in ecstasy users. In a series of 50 ecstasy users presenting at an addiction treatment unit, chocolate craving was found in 7 of 16 patients with psychopathology (Schifano and Magni 1994). All 7 of these patients, who had psychotic symptoms, reportedly developed chocolate craving after beginning ecstasy use.

In 2 ecstasy users (cases 3 and 11 from McGuire et al., 1994), symptoms more closely
resembled post-hallucinogen persisting perceptual disorder than atypical psychosis. In these cases, patients had full preservation of insight and reported persisting (rather than episodic) hallucinations and illusions. For example, an 18-year-old female who was reportedly a regular ecstasy user experienced persisting visual illusions and hallucinations (McGuire et al. 1994). Brain MRI was normal, and no neurological or ophthalmological signs were noted. While chlorpromazine and dothiepin were ineffective, counseling resulted in some improvement.

Affective symptoms were reported in 54.5% (24/44) of psychiatric case reports. The most common affective symptoms were anxiety disorders, which occurred in 40.9% (18/44) of these cases. While anxiety – usually acute panic response or chronic panic disorder – was the sole diagnosis in 38.9% (7/18) of cases, it sometimes occurred in cases with psychotic symptoms (38.9%, 7/18) or depression (16.7 %, 3/18). In some cases, an acute panic attack during ecstasy intoxication rapidly resolved (Whitaker-Azmitia and Aronson 1989). For example, a 25-year-old male with 6 previous ecstasy exposures had a panic attack approximately 30 minutes after ecstasy ingestion while riding on a subway. He experienced “unnatural fear”, spatial disorientation, need to escape, tachycardia, sweaty palms, tenseness, hypervigilance, ideas of reference, and difficulty speaking. After recovery, he reportedly used ecstasy without further problems. Persisting anxiety or panic attacks after ecstasy intoxication occurred in several cases (McCann and Ricaurte 1992). For example, a 21-year-old male had panic attacks for 1 mo after consuming 6 ecstasy tablets. He was successfully treated with paroxetine and counseling (Windhaber et al. 1998). Outcome is generally good in cases of pure anxiety disorders in ecstasy users. Full recovery was reported in 6 of 7 cases, and the outcome was not reported in the remaining case.

Depression was diagnosed in 18.2% (8/44) cases with psychiatric symptoms, and a larger number of cases had symptoms of depression but were not diagnosed with it. For example, a 17-year-old male became acutely depressed, agitated, and confused during what was thought to be his first ecstasy exposure, and committed suicide two days later (Cohen 1996). Because this individual was not examined by a clinician, diagnosis cannot be made. Two ecstasy users with depression had psychotic symptoms (case 5 in McGuire et al., 1994, and case 5 in Schifano and Magni, 1994) and 3 had anxiety disorders (case 1 in McCann and Ricaurte, 1991, and cases 2 and 7 in Schifano and Magni, 1994). Full recovery was reported in 2 cases, and partial recovery in 3 cases. Outcome was not available in 2 cases. The case with no improvement was complicated by atypical psychosis in addition to depression (Schifano and Magni 1994).

Several reports have found a relationship between greater ecstasy exposure and likelihood of psychopathology. However, the direction of causality cannot be determined and psychiatric symptoms may have led to increased ecstasy use rather than the other way around. In a comparison of 150 polydrug-using ecstasy users in treatment for substance abuse, ecstasy users with psychiatric problems had significantly earlier age of first ecstasy use (t test, p < 0.001), higher lifetime total ecstasy dose (Mann-Whitney test, p < 0.001), greater frequency (Mann-Whitney test, p < 0.001) and duration of use (Mann-Whitney test, p < 0.001), and higher largest single dose (Mann-Whitney test, p < 0.001)
than ecstasy users without psychiatric problems (Schifano 2000). In a Spanish-language review of case reports of ecstasy-related psychiatric complications published from 1985-1997, patients with psychotic symptoms were compared to those with affective symptoms (Bango et al. 1998). Patients with psychotic symptoms had significantly higher incidence of family history of psychiatric problems than patients with other symptoms (9/11 vs. 10/25, X² = 3.8, p = 0.05). Patients with psychotic symptoms also tended to have greater ecstasy exposures than those with other symptoms, but this difference was not statistically significant.

The mechanisms by which MDMA could produce or even trigger psychopathology are largely unknown. Stimulant psychosis can be produced by drugs that are not neurotoxic, such as cocaine and l-amphetamine. Similarly, psychiatric symptoms in ecstasy users may not necessarily be produced by serotonergic neurotoxicity, although neurotoxicity may contribute to problems. It is also not known if serotonergic neurotoxicity contributes to affective symptoms seen in ecstasy users. Because serotonergic drugs are useful in affective disorders and serotonergic abnormalities can be seen in many patients with affective disorders, some have speculated that serotonergic neurotoxicity may increase risk of affective disorder. This makes sense based on our limited understanding of serotonin, but it has not been demonstrated. Animal studies show that neurotoxicity begins to occur several hours after MDMA administration. Therefore, adverse reactions occurring earlier are likely due to an interaction of the pharmacological effects of MDMA and the individual’s susceptibility. McCann and Ricaurte (1992) suggest that panic disorder occurring in a 23-year-old male ecstasy user was likely triggered by the pharmacological effects of MDMA rather than serotonergic neurotoxicity.

**Hepatotoxicity in Ecstasy Users**

16.1% (32/199) of case reports involved ecstasy-related hepatotoxicity (liver damage). Ecstasy has been reported to be the second most frequent cause of hepatotoxicity in Spanish individuals younger than age 25 (Andreu et al. 1998). It has been further suggested that many cases of subclinical hepatotoxicity occur in ecstasy users and escape detection (Jones and Simpson 1999). There is more than one pattern of ecstasy-related hepatotoxicity. Acute liver failure or hepatitis has occurred after reported ingestion of a single ecstasy tablet (Dykhuizen et al. 1995; Ellis et al. 1996; Henry et al. 1992). In other cases, hepatotoxicity has occurred after regular ecstasy use for months (Andreu et al. 1998). Common symptoms of hepatotoxicity in ecstasy users include jaundice, anorexia, nausea, vomiting, lethargy, dark urine, and pale stools. The delay between ecstasy exposure and onset of hepatic injury varies. Acute liver failure may occur shortly after ecstasy ingestion, while hepatitis may develop as long as four weeks after drug exposure (Dykhuizen et al. 1995; Gorard et al. 1992). There is no clear relationship between the extent of liver damage and duration of ecstasy use or estimated cumulative dose. Although MDMA has been specifically identified in very few of these cases (5.7%, 3/53), it is clear that MDMA or some common ingredient in illicit ecstasy pills is causing hepatotoxicity. Several ecstasy users who have been treated for hepatotoxicity develop new liver damage when they returned to using ecstasy (Khakoo et al. 1995; Shearman et al. 1992). Although evidence of liver damage was not seen in dogs and rats following
28-days of daily dosing with MDMA in one study (Frith et al. 1987), three \textit{in vitro} studies demonstrate that MDMA can impair liver cell viability and that hyperthermia potentiates this impairment.

Acute liver failure has developed in individuals experiencing ecstasy-related hyperthermia. Liver damage is known to occur in heat stroke as well. It appears that the liver damage in these cases is partially due to hyperthermia but that ecstasy plays an additional role. An \textit{in vitro} study using mice hepatocytes showed that MDMA increases the lipid peroxidation and loss of cell viability produced by hyperthermic conditions (Carvalho et al. 2001). 1.6 mM MDMA slightly but significantly decreased cell viability but did not affect lipid peroxidation over 60 to 180 min under normothermic (37° C) conditions. When temperature was raised to 41° C, the hepatotoxicity of MDMA was dramatically increased. At this temperature, 1.6 mM MDMA approximately doubled lipid peroxidation after 180 min and decreased cell viability after as little as 60 minutes. A lower concentration, 0.8 mM MDMA, also decreased cell viability after 180 min at 41° C. Amphetamines, and perhaps ecstasy, may make liver cells vulnerable to heat damage by impairing expression of heat shock protein, which normally helps cells survive heating (Lu and Das 1993). Thus, both hyperthermia and MDMA appear able to contribute to hepatotoxicity.

Not all ecstasy-related hepatotoxicity can be explained by heat stroke. Ecstasy-related acute liver failure has also occurred in individuals without evidence of hyperthermia (Ellis et al. 1996; Henry et al. 1992). In these cases, there are at least two main possibilities. First, a concentration-dependant toxic effect of MDMA may have occurred. Second, an idiosyncratic reaction, with a possible immunological mechanism, may have occurred. These two possibilities will now be discussed.

Two further \textit{in vitro} studies have confirmed that high concentration or extended-duration exposure to MDMA may be directly toxic to liver cells. In one study, MDMA caused increases in ALT, AST, and LDH activities in rat hepatocytes (Beitia et al. 2000). These increases were statistically significant with high concentrations of MDMA (1 mM for six hours) or lower concentrations for prolonged exposures (0.1 mM for 24 hours). Further evidence of MDMA-induced toxicity to hepatocytes came from moderate decreases in ATP (after three, but not one, hour incubation with 0.1 mM MDMA). Beitia et al. suggest that this impairment in liver cell viability may be due to MDMA effects on intracellular calcium ions (Ca$^{2+}$). In the same publication, the researchers reported that MDMA dose-dependently increased intracellular Ca$^{2+}$, which is well known as a cause of cell damage. Maximum increase in cytosolic free Ca$^{2+}$ occurred after 3 mM MDMA. The researchers suggest that MDMA may increase Ca$^{2+}$ influx as well as cause release of Ca$^{2+}$ from intracellular stores.

A third \textit{in vitro} study examined the possible pro-fibrogenic effects of MDMA on the liver by measuring expression of procollagen mRNA in a cell line of hepatic stellate cells (Varela-Rey et al. 1999). These cells produce the collagen characteristics of a fibrotic liver. Expression of \(\alpha_1(1)\) procollagen mRNA was significantly increased by 0.5, but not 0.1, mM MDMA for 24 hr. This effect required sustained exposures, as 1 mM MDMA
for 8 hr did not increase mRNA expression. This pro-fibrogenic effect of MDMA may have been mediated by oxidative stress. Pretreatment with the antioxidants glutathione monoethyl ester or deferoxamine prevented the pro-fibrogenic effect.

All three in vitro studies have found that MDMA depletes intracellular glutathione. Glutathione is an important antioxidant produced mainly by the liver. Beitia et al. found that glutathione was depleted after one hour of 0.3 mM MDMA. This depletion was not due to oxidation of glutathione as the potentiation of MDMA-induced glutathione depletion by hyperthermia did not lead to increases in the product of glutathione oxidation, GSSG (Varela-Rey et al. 1999). One possibility is that metabolites of MDMA bind to glutathione, forming conjugates.

The drug exposures in these studies are unlikely to occur in a clinical setting but may occur in illicit settings, especially during ‘binges’ when repeated doses are taken. The lowest concentration used in the study by Beitia et al. (0.1mM or ~19.3 mg/l MDMA) decreased ATP after 3 but not 1 hour and affected indices of cell viability after 24 hr, but not 6 hr. This same concentration had no significant pro-fibrogenic effect after 24 hr in the other study. This concentration is approximately 40 times higher than the highest plasma level reported in a clinical study, 486.9 µg/l MDMA after 150 mg (de la Torre et al. 2000a), and has only been approached in adverse case reports involving very high doses (see Tables 6.5 and 6.6). Liver exposure to drugs is often higher than blood levels. In an autopsy of a deceased ecstasy user, liver MDMA concentration was 7.2 times higher than femoral blood MDMA concentration (Rohrig and Prouty 1992). Thus, the peak liver exposure to MDMA in a clinical setting may be one-fifth the concentration shown to impair cell viability in these studies. Therefore it is unlikely that MDMA exposures in clinical studies will approach those demonstrated in these studies to impair rat liver cell viability or induce procollagen mRNA. On the other hand, it is possible that illicit users achieve hepatotoxic MDMA exposures.

These in vitro studies suggest that ecstasy-related hepatotoxicity should be exposure dependant. This has not been consistently observed in case reports. In at least 5 cases, hepatotoxicity has occurred after reported ingestion of a single ecstasy pill (Behan et al. 2000; Brauer et al. 1997; Ellis et al. 1996; Henry et al. 1992; Schirren et al. 1999). However, it must be noted that the presence of MDMA was not confirmed in any of these cases. One of these cases was reported to have symptoms of NMS, but temperature was not reported (Behan et al. 2000). One possible explanation for the apparent lack of exposure-dependence is that repeated ecstasy exposure produces asymptomatic hepatotoxicity that can become symptomatic after a modest dose. Only 9.4% (3/32) of cases of hepatotoxicity were known to have occurred in novice users, while at least 56.3% (18/32) occurred in “regular” or experienced users.

Alternatively, an idiosyncratic toxic reaction to MDMA (or a contaminant) may have occurred. Genetic deficiency in CYP2D6 activity has been hypothesized to influence susceptibility to ecstasy-related hepatotoxicity. However, Schwab et al. (1999) phenotyped three individuals presenting with ecstasy-related hepatitis and determined that all had extensive CYP2D6 activity. Furthermore, the importance of CYP2D6 in
MDMA metabolism may be less than previously thought, since MDMA inhibits CYP2D6 activity (Brady et al. 1986; Delaforge et al. 1999; Wu et al. 1997).

Immunological mechanisms may play a role in ecstasy hepatotoxicity (Jones and Simpson 1999). This suggestion is based on reports that re-exposure to ecstasy produces further liver damage in some patients with a history of ecstasy-related hepatotoxicity (Khakoo et al. 1995; Shearman et al. 1992). Also, liver biopsy in at least one patient showed features (such as eosinophils) of an autoimmune hepatitis-like injury which resolved spontaneously when ecstasy use stopped (Fidler et al. 1996).

Jones and Simpson (1999) discuss treatment of ecstasy-related hepatotoxicity. As always, it is important to eliminate other possible causes of hepatotoxicity such as viruses or alcohol abuse. Treatment of acute hepatic failure is often complicated by other symptoms such as hyperthermia. Theoretically, N-acetyl-cysteine may be useful in acute hepatic failure if in vitro studies are correct in suggesting a role for glutathione depletion and oxidative stress. Jones and Simpson state that high dose steroid therapy, such as prednisolone, should be considered in cases thought to have an immunological mechanism. While some cases of ecstasy-related hepatotoxicity have spontaneously resolved, auxiliary or complete liver transplant has been necessary in some cases. Survival rate for cases requiring liver transplant is very poor.

Hyponatremia in Ecstasy Users

Hyponatremia is a term for abnormally low plasma sodium concentration and can lead to serious neurological symptoms and death. Beginning in 1993 (Maxwell et al. 1993), at least 19 individuals with ecstasy-related hyponatremia have been described in medical case reports. The presence of MDMA was confirmed in 63.2% (12/19) of these case reports. Many more cases of this syndrome have occurred in ecstasy users but not been fully described in medical reports. For example, between August 1994 and December 1995, 15 cases of ecstasy-related hyponatremia were identified by the London National Poison Information Service (Henry 2000). This adverse event does not appear to be dose-related and has been documented after reported ingestion of one half of an MDMA-containing tablet by an experienced user who had been dancing (Nuvials et al. 1997). Blood levels of MDMA in hyponatremic ecstasy users are often modest. Most of these individuals appear to have been drinking large amounts of water. However, excessive fluids cannot be entirely blamed for cases of ecstasy-related hyponatremia as MDMA specifically increases risk of hyponatremia by inducing antidiuretic hormone release.

Although hyponatremia may occur without symptoms, symptoms are more likely when hyponatremia develops quickly, as occurs in ecstasy users. In acute hyponatremia, symptoms occur when serum sodium falls below approximately 120 mEq/L. The development of symptoms indicates a medical emergency and leads to death in over 15% of hyponatremia cases (Ayus and Arieff 1996). Clinical signs and symptoms of hyponatremia are summarized in Table 6.4. In ecstasy-related hyponatremia, individuals frequently show bizarre behavior and vomiting followed by drowsiness and agitation, with epileptiform convulsions in some cases. Death occurred in 15.8% of cases of
ecstasy-related hyponatremia.

Symptoms of hyponatremia are due to the effects of low plasma sodium on the brain. When plasma sodium (and thus osmolality) starts to fall, osmotic pressure immediately causes water to move into cells. In the brain, a number of mechanisms decrease intracellular solutes in an attempt to prevent cell swelling. One important mechanism is the Na⁺-K⁺ ATPase pump. This pump system can release sodium into the subarachnoid space, causing water to diffuse from the brain into the cerebral spinal fluid. If this and other mechanisms are unable to compensate for hyponatremia, there will be increased intracranial pressure, cerebral edema, brainstem herniation, compression of the midbrain, and possibly death.

Premenopausal women have a greater risk of dying or developing permanent brain damage from hyponatremia than men, probably due to the effects of sex hormones on brain Na⁺-K⁺ ATPase (Ayus and Arieff 1996). Indeed 84% of the published ecstasy-related hyponatremia cases have been female, even though most cases identified in the literature are male. Thus, while men make up a much greater proportion of the ecstasy case reports, women are significantly more likely to be diagnosed with hyponatremia (chi-square, x²=227, p < 0.001).

Risk of hyponatremia is due to the pharmacological effects of MDMA. MDMA has been shown to induce antidiuretic hormone release in volunteers after doses as low as 40 mg (Henry et al. 1998). This is consistent with a rat study that found MDMA increased basal aldosterone levels (Burns et al. 1996). One case report of ecstasy-related hyponatremia measured antidiuretic hormone, and confirmed it was elevated (Holden and Jackson 1996). In some case reports, laboratory findings and history are more consistent with a syndrome of inappropriate antidiuretic hormone secretion rather than excessive water consumption (Ajaelo et al. 1998; Gomez-Balaguer et al. 2000; Sharma and Nelson 2000). Overall, it appears that MDMA may lead to syndrome of inappropriate antidiuretic hormone and thus, hyponatremia, in the absence of either excessive sweating or extensive fluid intake.

However, factors other than the effects of MDMA contribute to risk of ecstasy-related hyponatremia. Sustained dancing may increase risk of hyponatremia. Exercise without drug use can lead to hyponatremia when solute-free water is ingested. In a recent prospective study, 18% of 605 marathon runners developed hyponatremia (Speedy et al. 1999). Biochemical analyses in some ecstasy-related cases (Matthai et al. 1996) have suggested to some that hyponatremia was triggered by excessive consumption of water and failure to replace lost sodium (Wilkins 1996). In some case reports, witnesses reported that the individual consumed large amounts of water (Box et al. 1997; Holmes et al. 1999; Lehmann et al. 1995; O'Connor et al. 1999; Parr et al. 1997). Thus, ecstasy-related hyponatremia may be partially due to user beliefs that water consumption reduces ecstasy toxicity.
users are often advised to consume sports drinks or salty foods along with fluids. When

| Early* | Anorexia                  |
|        | Headache                  |
|        | Nausea                    |
|        | Emesis                    |
|        | Muscular cramps           |
|        | Weakness                  |
| Advanced* | Impaired response to verbal stimuli |
|          | Impaired response to painful stimuli |
|          | Bizarre (inappropriate) behavior |
|          | Hallucinations (auditory or visual) |
|          | Asterixis                 |
|          | Obtundation               |
|          | Incontinence (urinary or fecal) |
|          | Respiratory insufficiency |
| Far Advanced* | Decorticate and/or decerebrate posturing |
|              | Bradycardia               |
|              | Hyper- or hypotension     |
|              | Altered temperature regulation (hypoor hyperthermia) |
|              | Dilated pupils            |
|              | Seizure activity (usually grand mal) |
|              | Respiratory arrest        |
|              | Coma                      |
|              | Polyuria (secondary to central diabetes insipidus) |

*Any manifestation may be observed at any stage, and some patients will have only minimal symptoms. Table reproduced from (Fraser and Arieff 1997)

Health care workers now caution ecstasy users that water is not a panacea for ecstasy toxicity, given the apparently increased risk of hyponatremia in ecstasy users (Finch et al. 1996). In addition, it has been emphasized that it can be dangerous to let semi-conscious ecstasy users "sleep it off" since impaired consciousness may indicate hyponatremia (Matthai et al. 1996).

It may be possible to develop guidelines for ecstasy users based on the American College of Sports Medicine position stand on Exercise and Fluid Replacement (Convertino et al. 1996). One suggestion from this document is that athletes (read as “ecstasy users”) drink about 500 mL (about 17 oz) about 2 hr before exercise (“dosing”) to promote adequate hydration while allowing time for excretion of excess fluids. In other words, individuals should assure that they are adequately hydrated before exercise or ecstasy exposure. Further fluid consumption should be directed towards replacing water lost through sweat (or vomiting). Because solute-free water may increase risk of hyponatremia, ecstasy users are often advised to consume sports drinks or salty foods along with fluids. When
exercise lasts more than 1 hr, the position stand on fluid replacement recommends
drinking 600-1200 mL/hr (20-40 oz/hr) of cool fluids containing 4% to 8% carbohydrates
and 0.5-0.7 g sodium/L water. This fluid replacement recommendation was developed
for athletes engaging in sustained sweat-inducing exercise and suggests volumes that are
likely excessive for ecstasy users who are not exercising or losing fluids through sweat or
vomit.

Management of patients with hyponatremia is discussed in the ecstasy literature
(Zenenberg and Goldfarb 2000) and elsewhere (Fraser and Arieff 1997). Treatment of
hyponatremia depends on the severity of symptoms. In symptomatic patients, therapy
with hypertonic saline solution is often indicated after a secure airway has been obtained.
Because inappropriate treatment of hyponatremia can lead to brain damage and patients
require constant monitoring, only trained medical personnel should attempt treatment.

Cardiovascular-Related Complications

At the doses used in published clinical reports, MDMA typically produces robust but
clinically insignificant increases in heart rate and blood pressure as well as
vasoconstriction. In illicit users, a number of serious adverse events have been due to
these cardiovascular effects, including hypertensive emergencies and dysrhythmias.

Drug-induced hypertension may lead to damage in numerous organs, usually when
diastolic blood pressure exceeds 130 mmHg. Ecstasy-induced hypertension has been
linked to several of these organ dysfunctions, including acute renal failure (Woodrow et
al. 1995), aortic dissection (Duflou and Mark 2000), gastric artery perforation (Williams
et al. 1998a), retinal hemorrhage (Jacks and Hykin 1998), myocardial infarction
(Dowling et al. 1987; Milroy et al. 1996), and cerebral hemorrhage (Gledhill et al. 1993;
Henry et al. 1992; Manchanda and Connolly 1993; Selmi et al. 1995). Although the
presence of MDMA was rarely confirmed in these cases, these types of events are all well
established complications of hypertension and can occur after use of other amphetamines.

While the cardiovascular effects of MDMA have largely resolved in clinical studies by
post 6 hrs, dysrhythmias have occurred the day after illicit ecstasy use in two case
reports. One individual presented with hyperthermia, 200/110 mmHg BP, sinus
tachycardia, agitation, and dehydration, 5 hrs after taking an ecstasy tablet (MDMA was
not confirmed). ECG monitoring revealed QT prolongation lasting at least 30 hrs after
drug ingestion (Drake and Broadhurst 1996). QT prolongation after ecstasy use has been
reported in one other case report (Maxwell et al. 1993). Prolonged QT indicates the
cardiac action potential has been prolonged, an event that is associated with torsades de
pointes, a polymorphous ventricular arrhythmia that may cause syncope and degenerate
into ventricular fibrillation.

Ventricular fibrillation leading to death has been documented in at least two ecstasy
users. One case involved a previously healthy 18-year-old female who collapsed 60-90
minutes after consuming 1.5 ecstasy tablets with ethanol (Dowling et al. 1987).
Postmortem analysis of blood revealed relatively high concentrations of MDMA (1.0
mg/L). In a second case, an individual with Wolff-Parkinson-White Syndrome (a cardiac disorder increasing risk of dysrhythmia) used ecstasy one morning, complained of palpitations that evening, and experienced ventricular fibrillation early the next morning (Suarez and Riemersma 1988). MDMA was confirmed in blood.

In a series of autopsies of 7 ecstasy users, Milroy et al. (1996) found focal or contraction band cardiac necrosis in 4 of 5 cases with confirmed MDMA involvement, including a hyperthermic individual (case 1) in whom cardiac arrest was the cause of death, and a normothermic individual (case 6) in whom sudden death occurred. These cardiac changes resembled those seen in catecholamine-induced injury.

Management of ecstasy-related cardiovascular complications is discussed by Ghuran and Nolan (2000). Given the lack of specific information on treating cardiovascular complications of MDMA, it may be useful to note that the alpha-antagonist, phentolamine, has been recommended for treatment of toxicity from the MDMA-analogue, MDA (Simpson and Rumack 1981).

**Cerebrovascular Problems in Ecstasy Users**

Ecstasy use has preceded cerebral hemorrhage or infarction in at least five cases. Such cerebrovascular accidents are well-established adverse effects of sympathomimetic psychostimulants (Hughes et al. 1993; Kaku and Lowenstein 1990; Perez et al. 1999). Cerebral hemorrhage after psychostimulant use is likely due to drug-induced hypertension (causing rupture of blood vessels in the brain), with possible contributions from vasculitis in chronic drug users. Cerebral infarction may be due to vasospasm or vasoconstriction-induced ischemia or clot formation (possibly related to dehydration or drug-induced coagulopathy). One case of cerebral venous sinus thrombosis has been reported in a 22-year-old female who became dehydrated after dancing for 8 hr without drinking fluids (Rothwell and Grant 1993).

Three cases of ecstasy-related cerebral hemorrhage have been identified in the medical literature. Hemorrhage locations were subarachnoid (Gledhill et al. 1993; Henry et al. 1992), left frontal cerebral (Selmi et al. 1995), and left frontal parietal cerebral (Manchanda and Connolly 1993). In two of these cases (Gledhill et al. 1993; Selmi et al. 1995) a previously existing underlying arteriovenous malformation appeared to play a role in the event. Both individuals had reportedly used ecstasy on previous occasions without apparent adverse event. In one case, symptoms appear approximately 1 hr after ecstasy ingestion (Gledhill et al. 1993; Henry et al. 1992), as would be expected from a hypertension-related event. In another case, however, onset was over 36 hr after ecstasy ingestion, while the patient was smoking cannabis (Manchanda and Connolly 1993).

**Other Neurological Problems in Ecstasy Users**

Possible neurological effects of ecstasy exposure have been examined in several studies and case reports. The studies suggest that brain atrophy or ischemic lesions are not common in ecstasy users. However, illicit ecstasy use appears to frequently have
detectable effects on parietal white matter and global brain volume. These studies are summarized below. Other studies have specifically looked for evidence of serotonergic changes that could be the result of selective serotonergic neurotoxicity. These studies, which are discussed in detail in the previous chapter, have generally found that illicit ecstasy use is associated with long-term serotonergic alterations.

In a study comparing 22 ecstasy users and 37 nonusers, MRI found no evidence of brain atrophy or white matter lesions (Chang et al. 1999). Proton magnetic resonance spectroscopy (1H MRS) measures of cerebral metabolites in the same individuals generally supported this conclusion, finding unaltered lactate and N-acetyl-aspartate levels. However, myo-inositol was elevated in parietal white matter, suggesting glial activation, possibly due to damage or pharmacological effects of MDMA. Myo-inositol in parietal white matter (r = 0.48, P = 0.04) and occipital gray matter (r = 0.68, P = 0.002) was correlated with the logarithm of cumulative lifetime MDMA dose.

In a study of cerebral blood flow using many of the same volunteers, 21 ecstasy users were compared to 21 nonusers using single photon emission computed tomography (SPECT) and MRI. Although no significant differences were found between ecstasy users and nonusers, duration of ecstasy use negatively correlated with global brain volume, even when co-varied with age (r = -0.57, P = 0.02). In this same report, regional and global cerebral blood flow was measured in 10 ecstasy users before and after administration of MDMA in a clinical study. The results of this prospective study, which are discussed in the section on human neurotoxicity, indicate that MDMA exposure can alter cerebral blood flow for at least several weeks.

Two reports have identified bilateral lesions in the globus pallidus of ecstasy users. In one case, these lesions were identified during autopsy (Squier et al. 1995). In another case they were identified during magnetic resonance imaging (MRI) of a 26-year-old female who lost consciousness and developed lasting and severe impairment of episodic memory three days after ingesting half an ecstasy tablet (Spatt et al. 1997). Squier et al. (1995) speculate that local release of serotonin led to prolonged vasospasm and necrosis of the globus pallidus. The authors of the second report suggest that lesioning of the globus pallidus was “clinically silent” and not the cause of the patient’s amnesic syndrome, which they hypothesize may have been due to hippocampal toxicity not detected with MRI.

Parkinsonism has been reported in one ecstasy user (Mintzer et al. 1999). Onset of symptoms was three months after last ecstasy use. After excluding other possible causes, the authors hypothesized that delayed MDMA-induced dopaminergic neurotoxicity had occurred, although several letter writers disputed this theory (Baggott et al. 1999; Sewell and Cozzi 1999), including the patient (Borg 1999). Among other points, it was argued that MDMA is not a selective dopaminergic neurotoxin in primates and that the time course of symptoms was not consistent with drug-induced neurotoxicity. Subsequent analysis of the brain of a deceased chronic ecstasy user found no evidence of dopaminergic neurotoxicity (Kish et al. 2000), suggesting that any link between ecstasy use and parkinsonism is not due to dose-dependent dopaminergic neurotoxicity.
Two cases of white matter lesions with different symptoms and outcomes have been reported in ecstasy users (Bertram et al. 1999; Bitsch et al. 1996). In the first case, a 22-year-old male developed fever and gradual loss of vigilance and orientation beginning the day after using a larger dose of ecstasy than was typical for him (Bitsch et al. 1996). After 5 days of worsening symptoms, a generalized seizure occurred, upon which he was taken for medical assistance. Laboratory tests revealed signs of inflammation in blood and CSF. T₂-weighted MRI showed hyperintense white matter lesions throughout the brain. The patient recovered after 7 days of treatment and a MRI at 14 days after onset revealed a reduction in lesions. The authors note that cerebral vasculitis has been reported as a rare complication of amphetamine use.

In a second case, a 19-year-old male with a history of opiate and benzodiazepine abuse lost consciousness the morning after reportedly using ecstasy for the first time (Bertram et al. 1999). On examination, the patient was comatose with respiratory insufficiency and evidence of liver and renal failure, rhabdomyolysis, and pneumomediastinum. Benzodiazepines and unspecified amphetamines were identified in biofluids. Although initial computed tomography was normal, repeated measures at 2, 3, and 4 weeks after admission revealed bilateral hypodense lesions of white matter, which were also detected with MRI. The patient was in a persistent vegetative state and had not recovered when the case report was written. The authors suggest that selective damage to myelinated tracts may have been due to accumulation of lipophilic drug and localized oxidative stress. However, it is not clear why the patient was vulnerable to this severe idiosyncratic complication.

In one case report, a reportedly first-time ecstasy user developed lasting neurological and psychiatric symptoms and was subsequently diagnosed as having suicidal depression and possibly temporal lobe epilepsy (Cohen and Cocores 1997). Because the patient had no previous symptoms, personal or family psychiatric history, or other drug use, and symptoms developed with ecstasy exposure, the authors suggest ecstasy may have caused or triggered the onset of this condition.

**Hematological Problems in Ecstasy Users**

Most hematological problems in ecstasy users have been coagulation disorders occurring in the context of hyperthermia. Disseminated intravascular coagulation (DIC) has already been discussed in the section on hyperthermia. DIC occurred in 25 case reports, 60.0% (15/25) of which were fatal. In addition to these cases, 3 cases of aplastic anemia and 1 case of thrombotic thrombocytopenic purpura have been reported in ecstasy users.

Three cases of aplastic anemia have been reported in ecstasy users (Clark and Butt 1997; Marsh et al. 1994). Aplastic anemia is a rare disorder in which blood cell production is suppressed. It can be caused by viruses or drug exposure, although the cause goes unrecognized in most cases. In cases involving ecstasy users, the link between ecstasy use and the disorder was made by excluding other possible causes. The period from last ecstasy exposure to symptoms was 1 to several weeks. In two cases the condition
resolved spontaneously 7 to 9 weeks after presentation (Marsh et al. 1994), while the third case required bone marrow transplant (Clark and Butt 1997).

Thrombotic thrombocytopenic purpura was diagnosed in a 20-year-old male recovering from ecstasy-related acute liver failure (Schirren et al. 1999). Thrombotic thrombocytopenic purpura is a blood disorder characterized by low platelets and red blood cell fragmentation (caused by premature breakdown of the cells). Platelet clumping leads to transient ischemia of organ systems. In the CNS this can produce behavioral disturbances, headache, or even coma. Bleeding beneath the skin produces characteristic red rashes or bruises.

**Ecstasy-Related Pneumomediastinum and Subcutaneous Emphysema**

Six cases of pneumomediastinum and one case of cervical emphysema have been reported in ecstasy users. Pneumomediastinum is a condition in which air is present in the mediastinum, the space in the chest between the lungs. Symptoms include chest pain, crackling sounds in the chest and throat, and altered voice. Most cases of non-traumatic mediastinal and cervical emphysema are thought to be due to rupture of the alveolus after a sudden increase in pressure such as during the valsalva maneuver or vomiting. In published cases, emphysema may have been caused by vomiting or retching (Levine et al. 1993; Rezvani et al. 1996), repeatedly blowing a whistle (Pittman and Pounsford 1997), and possibly severe exercise (Quin et al. 1999; Rezvani et al. 1996), although the cause has not always been clear (Bertram et al. 1999; Onwudike 1996; Quin et al. 1999; Rezvani et al. 1996). In most cases, pneumomediastinum has been the sole complaint, although it occurred in one case in conjunction with liver and renal failure, rhabdomyolysis, and neurological symptoms (Bertram et al. 1999). Patients presenting solely with emphysema have recovered with conservative management in these published cases.

**Ophthalmic Problems in Ecstasy Users**

A 17-year-old male developed double vision due to bilateral sixth nerve palsy approximately 24 hr after taking 2 ecstasy tablets. The patient recovered within 5 days (Schroeder and Brieden 2000). Two cases of corneal epitheliopathy have also been reported in ecstasy users, with corneal exposure thought to be the likely cause (O’Neill and Dart 1993).

**Dermatitis in Ecstasy Users**

Two cases of dermatitis have been reported in ecstasy users (Wollina et al. 1998). In one case, evidence of altered liver function was seen. Dermatitis has been previously reported as a rare complication of amphetamines (Kauvar et al. 1943).
Dental Problems in Ecstasy Users

A case report (Murray and Wilson 1998), a survey (Topp et al. 1999), and a study (Milosevic et al. 1999; Redfearn et al. 1998) suggest that ecstasy use may lead to dental problems. One review has discussed this issue (Duxbury 1993). In a study of 30 ecstasy users and 28 nonusers, ecstasy was associated with significantly increased wear of the occlusal surfaces (molars and premolars) due to bruxism (jaw clenching) (Milosevic et al. 1999; Redfearn et al. 1998). This erosion of the biting surfaces of the back teeth contrasts to the usual pattern of tooth wear affecting the front teeth. The researchers suggest that ingestion of carbonated and acidic beverages during ecstasy use may contribute to this problem. In a survey of 329 polydrug-using ecstasy users recruited by snowball sampling, 14.6% reported teeth problems that were considered to be only related to ecstasy use (Topp et al. 1999). It is not clear what proportion of this number is due to lasting dental problems because it also includes acute bruxism and mouth ulcers from excessive chewing.

Ecstasy Use During Pregnancy

Ecstasy use during pregnancy may increase risk of birth defect. While alcohol is universally recognized as impairing fetal development, amphetamine has also been associated with adverse outcomes such as clefting, cardiac anomalies, and fetal growth rate deficits (Plessinger 1998). The pharmacological and structural similarities between amphetamines and MDMA raise the possibility that ecstasy might produce similar malformations. This issue has been addressed in two studies of ecstasy users. These studies have not been large enough to draw conclusions, but serve to raise concerns about possible problems. Three animal studies reported only few effects of prenatal or newborn MDMA exposure, while a recent study of newborn rats found that repeated MDMA exposure dose-dependently impaired learning and memory.

The U.K. National Teratology Information Service conducted a prospective follow-up study on 78 infants whose mothers had used ecstasy during pregnancy (McElhatton et al. 1999). There was a significantly higher rate of congenital anomalies (15.4% in these women) than expected in the general population (2-3%). The authors concluded that this small case sample had insufficient statistical power to confirm a causal relation with any particular disorder. This study did not control for effects of inadequate prenatal care such as poor nutrition and use of tobacco. For example, one case of neonatal death involved a mother who had been taking ecstasy, heroin, and methadone throughout pregnancy. Although an earlier Dutch study (available in English only in abstract form) failed to find an effect of ecstasy use on fetal development (van Tonningen-van Driel et al. 1999), this earlier study was smaller and also lacked statistical power to detect rare events. The earlier study examined 36 live births from women who had taken ecstasy (and often other drugs) during pregnancy. In any case, caution dictates that pregnant women should not use ecstasy.

While earlier animal studies found few effects of prenatal MDMA exposure, a recent study of newborn rats found that repeated MDMA exposure dose-dependently impaired
sequential learning and spatial learning and memory (Broening et al. 2001). MDMA was administered twice daily for ten days, with individual doses of 5 to 20 mg/kg. Because of interspecies differences, newborn rats are thought to be the developmental equivalent of a 3rd trimester human fetus. Thus, the newborn rats were exposed to MDMA during the equivalent of the third-trimester in humans. Some rats were administered MDMA during the equivalent of the early part of the third trimester, while others were exposed during the late part of this period. MDMA decreased body weight for both groups. In behavioral tests beginning at least 1 mo after MDMA exposure, rats exposed in the late (but not early) third trimester had significantly impaired learning and memory. These impairments were not correlated to the serotonergic neurotoxicity seen in both groups, which was measured as a 20% or less depletion of hippocampal serotonin.

Previous studies found more subtle effects of MDMA exposure. A rat study found that a repeated administration of 10 mg/kg MDMA, once or twice daily, for 4 days, decreased the extent to which young rats cried when separated from their mother (Winslow and Insel 1990). This effect was only seen in rats exposed to MDMA shortly after birth (the human equivalent of early trimester) and not earlier. This effect was only monitored for 2 wks after drug exposure. Concurrent measures of locomotion, geotaxis, and weight gain were not altered. Another animal study found only subtle behavioral alterations in offspring after pregnant rats were treated with 2.5 or 10 mg/kg MDMA (St Omer et al. 1991). MDMA treatment increased olfactory discrimination in male and female offspring, and female pups displayed negative geotaxis. No evidence for a “substantial effect” of prenatal MDMA exposure upon offspring was reportedly found. In another study, the administration of MDMA (8, 16, or 32 mg/kg egg wt) or amphetamine to chicken embryos had no significant adverse effect on hatchability or hatch weight (Bronson et al. 1994). Overall, it appears that the effects of prenatal MDMA exposure may depend on the developmental stage of the fetus.

Traffic Accidents and Dangerous Behavior in Ecstasy Users

A number of reports have suggested that ecstasy use may impair driving or otherwise lead to motor vehicle accidents. MDMA concentrations associated with impaired motor vehicle operations are summarized in Table 6.5. The table excludes cases of MDMA users who were injured as pedestrians or passengers (Henry et al. 1992; Hooft and van de Voorde 1994). Several reports offer insufficient information from which to draw strong conclusions. For example, one letter (Davies et al. 1998) mentioned 16 ecstasy abusers who were injured as a result of “reckless driving”, but did not differentiate drivers from passengers, provide blood or urine levels, or comment on the presence of other drugs. Henry et al. (1992) cited 5 cases of road accidents, but only one of these fatalities involved a driver. Dowling reported a case of a driver who died in an accident while under the influence of the related analogue MDE, although this fatality was attributed to atherosclerotic cardiovascular disease rather than the accident itself (Dowling et al. 1987). Similarly, it is not known to what extent MDMA impairment of driving ability may be attributable to seizures or other ecstasy-induced medical conditions, as opposed
Table 6.5. Traffic Accidents Involving Drivers Under the Influence of MDMA

<table>
<thead>
<tr>
<th>Population</th>
<th>MDMA Level:</th>
<th>Other Substances Confirmed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 cases</td>
<td>0.18 ± 0.14 mg/l blood</td>
<td></td>
<td>(Omtzigt cited in Crifasi et al. 1999)</td>
</tr>
<tr>
<td>18-yr-old male driver killed in collision</td>
<td>0.1 mg/l plasma postmortem.</td>
<td>None mentioned in text, although Crisfasi (1996) states this case was complicated “by the presence of other drugs”</td>
<td>(Henry et al. 1992) Case 17 of 24.</td>
</tr>
<tr>
<td>29-yr-old male driver killed in collision</td>
<td>2.32 mg/L blood postmortem</td>
<td>MDA</td>
<td>(Crifasi and Long 1996)</td>
</tr>
<tr>
<td>18 cases of impaired driving in Germany</td>
<td>Median 76 (range: 1-514) ng/mL serum</td>
<td>Alcohol, Amphetamine, Cannabis, Codeine, and Bromazepam, MDA and/or MDEA were also reported in sample from which these cases are a subset.</td>
<td>(Moeller and Hartung 1997)</td>
</tr>
<tr>
<td>136 “drugged drivers” in Norway.</td>
<td>“64% of the MDMA positive samples presented drug concentrations equal to or lower than the blood concentrations obtained after intake of a ‘standard dose’ of 100 mg MDMA.”</td>
<td>“Frequent presence of other drugs in the samples.”</td>
<td>(Morland 2000)</td>
</tr>
</tbody>
</table>

To a decrement in such mundane factors as reaction time, spatial/temporal perception, cognitive judgment, or emotional equilibrium.

Dangerous behavior during ecstasy use has resulted in injury. Ecstasy-intoxicated individuals have received serious burns (Cadier and Clarke 1993), been electrocuted and fallen to their death (Dowling et al. 1987), and been killed while attempting to stand on top of a moving vehicle (Hooft and van de Voorde 1994). In these cases, drug intoxication may have impaired judgment and facilitated risky behavior or may have impaired ability to successfully complete risky behaviors.
Is Risk of Ecstasy-Related Toxicity Dose Dependant?

It is commonly said that ecstasy toxicity in humans is not dose-related. Originally this statement was intended to convey that many ecstasy-related emergencies did not occur because the patient consumed an unusually large dose of ecstasy. More recently, harm reduction advocates have additionally suggested that toxicity can be explained by the use of ecstasy in a risky manner (e.g. high ambient temperature, exercise, too little or too much fluid consumption) rather than “overdose”. Blood concentration of MDMA in published case reports confirm that survival is not closely related to MDMA concentration (see Tables 6.6 and 6.7). A danger of stating that ecstasy toxicity is not dose-related lies in the possibility that the reader will interpret this to mean that ecstasy toxicity is never dose-related.

Perhaps the most accurate statement would be that high dose is a risk factor for some types of ecstasy toxicity, but it is only one of several risk factors. Other probable risk factors include exercise, dehydration, over hydration, and hot or humid settings. More frequent use or greater total lifetime dose may be risk factors for psychological problems. For example, psychiatric disturbances appear more likely in individuals who have used more ecstasy. Still other risk factors remain unknown. While rare, serious ecstasy toxicity cannot be predicted beforehand, and in many specific cases cannot be explained afterwards. Serious adverse reactions or even death can occur after modest amounts of ecstasy in the absence of known risk factors.

Several reports provide evidence that common adverse effects of ecstasy are related to dose. In a survey of 100 ecstasy users, the severity of side effects reported was positively correlated with both the total number of doses consumed ($r = 0.34$, $p < 0.05$) and the frequency of use ($r = 0.50$, $p < 0.01$) (Solowij et al. 1992). Topp et al. (1999) found that those who had binged on ecstasy reported increased physical (nine versus seven; $t_{344} = -5.3; p < 0.001$) and psychological side-effects (five versus four; $t_{319} = -3.6; p < 0.001$). As described below, Topp et al. found that recent bingeing on ecstasy and the quantity of ecstasy typically used were associated with physical side effects in a regression analysis.

Bingeing was also identified as a risk factor for adverse effects by van de Wijngaart et al. (1999). In a comparison of polydrug-using ecstasy users and drug-free volunteers, Parrott et al. (2000b) found that ecstasy users with an average of 6.8 (range: 1–20) ecstasy exposures differed from non-drug users in self-reported measures of paranoid ideation and psychotism. Individuals with an average of 371 (range: 30–1000) ecstasy exposures had more self-reported anxiety, paranoid ideation, and appetite than less experienced users. This study is limited because volunteers were only asked to not use ecstasy on the day of testing. Therefore it is not clear whether these differences are due to preexisting differences, acute ecstasy withdrawal, longer lasting ecstasy effects, or the effects of other drugs.
Table 6.6: Blood Concentrations of MDMA in Published Fatalities

<table>
<thead>
<tr>
<th>Identity</th>
<th>MDMA mg/L</th>
<th>Diagnosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 M</td>
<td>7.15</td>
<td>Hyperthermia; DIC</td>
<td>Fineschi et al., 1999</td>
</tr>
<tr>
<td>32 M</td>
<td>4.56</td>
<td>MDMA-Ritonavir interaction</td>
<td>Henry &amp; Hill, 1998</td>
</tr>
<tr>
<td>21 M</td>
<td>4.2</td>
<td>Cardiac arrest</td>
<td>Milroy et al., 1996</td>
</tr>
<tr>
<td>53 M</td>
<td>3.71</td>
<td>Hyperthermic syndrome</td>
<td>Walubo &amp; Seger, 1999 *</td>
</tr>
<tr>
<td>20 M</td>
<td>2.8</td>
<td>Acute poisoning due to insufflation of MDMA, cocaine, and heroin</td>
<td>Moore et al., 1996</td>
</tr>
<tr>
<td>20 F</td>
<td>2.3</td>
<td>Hyperthermic syndrome</td>
<td>Mueller &amp; Korey, 1998</td>
</tr>
<tr>
<td>17 M</td>
<td>2.3</td>
<td>Gross pulmonary edema, amphetamine abuse</td>
<td>Dar and McBrien, 1996</td>
</tr>
<tr>
<td>21 M</td>
<td>2.1</td>
<td>Inhalation of vomit</td>
<td>Milroy et al., 1996; Forrest et al., 1994 *</td>
</tr>
<tr>
<td>18 M</td>
<td>1.53</td>
<td>Hyperthermic syndrome</td>
<td>Henry et al., 1992</td>
</tr>
<tr>
<td>20 M</td>
<td>1.41</td>
<td>Hyperthermic syndrome</td>
<td>Henry et al., 1992</td>
</tr>
<tr>
<td>32 M</td>
<td>1.1</td>
<td>Asthma</td>
<td>Dowling et al., 1987</td>
</tr>
<tr>
<td>18 F</td>
<td>1</td>
<td>Acute MDMA intoxication</td>
<td>Dowling et al., 1987</td>
</tr>
<tr>
<td>26 F</td>
<td>0.82</td>
<td>hyperthermia; terminal cardiac arrest</td>
<td>Byard, et al., 1998</td>
</tr>
<tr>
<td>22 M</td>
<td>0.55</td>
<td>Hyperthermic syndrome</td>
<td>Cox &amp; Williams, 1996</td>
</tr>
<tr>
<td>16 F</td>
<td>0.516</td>
<td>Hyperthermic syndrome</td>
<td>Henry et al., 1992</td>
</tr>
<tr>
<td>16 F</td>
<td>0.424</td>
<td>Hyperthermic syndrome</td>
<td>Chadwick et al., 1991</td>
</tr>
<tr>
<td>18 M</td>
<td>0.44</td>
<td>Hyperthermia, Cardiac Arrest</td>
<td>Henry et al., 1992</td>
</tr>
<tr>
<td>22 F</td>
<td>0.3</td>
<td>Hyperthermic syndrome</td>
<td>Byard, et al., 1998 *</td>
</tr>
<tr>
<td>34 M</td>
<td>0.2</td>
<td>Sudden cardiac death</td>
<td>Suarez &amp; Riemersma, 1988 **</td>
</tr>
<tr>
<td>20 M</td>
<td>0.185</td>
<td>Hyperthermic syndrome</td>
<td>Fineschi and Masti, 1996</td>
</tr>
<tr>
<td>27 F</td>
<td>0.219</td>
<td>Hyponatremia</td>
<td>O'Connor, et al., 1999</td>
</tr>
<tr>
<td>20 M</td>
<td>0.18</td>
<td>Hyperthermic syndrome</td>
<td>Fineschi et al., 1999 *</td>
</tr>
<tr>
<td>21 F</td>
<td>0.13</td>
<td>Hyperthermic syndrome</td>
<td>Henry et al., 1992</td>
</tr>
<tr>
<td>21 F</td>
<td>0.134</td>
<td>Hyperacute liver failure; Hyperthermic syndrome</td>
<td>Ellis et al., 1996</td>
</tr>
<tr>
<td>15 F</td>
<td>0.05</td>
<td>Hyponatraemia</td>
<td>Parr et al., 1997</td>
</tr>
<tr>
<td>20 M</td>
<td>0.04</td>
<td>Hyponatraemia</td>
<td>Milroy et al., 1996</td>
</tr>
</tbody>
</table>

* sample taken postmortem ** units unclear (given as “mg%” in paper)

When necessary, plasma/serum concentrations were converted to blood levels using a hematocrit of 0.45 and partitioning data from Garrett et al. (1994).

Abbreviations: DIC – disseminated intravascular coagulation.
<table>
<thead>
<tr>
<th>Identity</th>
<th>MDMA mg/L</th>
<th>Diagnosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 F</td>
<td>7.9</td>
<td>Toxic psychosis; hyperthermia</td>
<td>Hayner &amp; McKinney, 1986</td>
</tr>
<tr>
<td>32 F</td>
<td>6.5</td>
<td>Hyperthermia; multiple severe complications</td>
<td>Brown &amp; Osterloh, 1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>from ingestion of MDMA</td>
<td></td>
</tr>
<tr>
<td>19 M</td>
<td>5.2</td>
<td>Confusion, central depression</td>
<td>Regenthal et al., 1999</td>
</tr>
<tr>
<td>20 M</td>
<td>4.92</td>
<td>Hyperthermia, vomiting, convulsions</td>
<td>Roberts and Wright, 1993</td>
</tr>
<tr>
<td>30 M</td>
<td>1.2</td>
<td>Unconsciousness, apnea, convulsions</td>
<td>Ramcharan et al., 1998</td>
</tr>
<tr>
<td>19 F</td>
<td>1.2</td>
<td>Hyperthermia, Thrombocytopenia</td>
<td>Henry et al., 1992</td>
</tr>
<tr>
<td>21 M</td>
<td>0.91</td>
<td>Hyperthermia; DIC; severe multiple organ failure</td>
<td>Murthy et al., 1997a,b</td>
</tr>
<tr>
<td>13 month M</td>
<td>0.9</td>
<td>Agitation, twitching, convulsions</td>
<td>Bedford Russell et al., 1992; Henry et al., 1992</td>
</tr>
<tr>
<td>19 M</td>
<td>0.46</td>
<td>Hyperthermia; DIC; acute liver damage</td>
<td>Ellis et al., 1996</td>
</tr>
<tr>
<td>20 M</td>
<td>0.29</td>
<td>Hyperthermia; DIC; rhabdomyolysis, ARF</td>
<td>Henry et al., 1992</td>
</tr>
<tr>
<td>25 F</td>
<td>0.26</td>
<td>Subarachnoid hemorrhage</td>
<td>Henry et al., 1992; Gledhill et al., 1993</td>
</tr>
<tr>
<td>23 M</td>
<td>0.2</td>
<td>Hyperthermia, DIC, ARF, rhabdomyolysis; impaired liver function</td>
<td>Barrett and Taylor, 1993</td>
</tr>
<tr>
<td>23 M</td>
<td>0.2</td>
<td>Hyperthermia, DIC, ARF, rhabdomyolysis</td>
<td>Henry et al., 1992</td>
</tr>
<tr>
<td>23 M</td>
<td>0.2</td>
<td>Hyperthermia, acute renal failure</td>
<td>Fahal et al., 1992</td>
</tr>
<tr>
<td>24 F</td>
<td>0.06</td>
<td>Hyponatraemia</td>
<td>Satchell &amp; Connaughton, 1997</td>
</tr>
<tr>
<td>17 F</td>
<td>0.061</td>
<td>Hyponatraemia</td>
<td>Maxwell et al., 1993</td>
</tr>
<tr>
<td>36 M</td>
<td>0.016</td>
<td>Hyponatraemia with hyperthermia then delayed severe rhabdomyolysis</td>
<td>Lehmann, et al., 1995</td>
</tr>
</tbody>
</table>

When necessary, plasma/serum concentrations were converted to blood levels using a hemacrit of 0.45 and partitioning data from Garrett et al. (1994)

Abbreviations: DIC – disseminated intravascular coagulation; ARF – acute renal failure.
The adverse effects of described in the previous paragraph are self-reported. Such self-reported common adverse effects cannot necessarily be equated with more serious adverse events requiring medical intervention. Evidence that serious adverse events are related to ecstasy dose or exposures is limited to the report by Schifano et al. (1998, 2000) that found that polydrug-using inpatient ecstasy users with psychiatric problems had used significantly more ecstasy than those without problems. In this sample, those who had used more than 11 tablets were 17.4 times more likely to have experienced psychiatric problems than those who had taken it once or twice. As stated before, causality cannot be demonstrated this study and it is possible that individuals with psychiatric problems tend to use ecstasy more than others.

There are a number of considerations that help us understand why ecstasy toxicity does not appear to be dose dependant. These considerations, which are discussed below, include tolerance to the effects of MDMA, the influence of environment on amphetamine lethality, and the triphasic dose-lethality curves of some amphetamines.

**Tolerance to the Effects of MDMA.** Extensive anecdotal evidence suggests that ecstasy users develop tolerance to the euphoric effects of ecstasy. Animal studies confirm that high dose regimens of MDMA decrease the ability of the animal to distinguish between a lower dose of MDMA and placebo. An ascending dose regimen produced long-term tolerance to the effects of MDMA on performance of various behavioral tasks by nonhuman primates (Frederick et al. 1995). Ecstasy users may also develop tolerance to the physiological effects of ecstasy, allowing them to self-administer doses that would be toxic to novice users.

**The Influence of Environment on Amphetamine Lethality.** A large literature has established that many amphetamines, including MDMA, have increased lethality when test animals are housed in groups rather than individually. In individually housed male albino mice, the 24 hr LD50 for IP MDMA is 97.6 (95% CI: 82.8 – 115.0) mg/kg, while in group-housed mice the LD50 is lowered to 19.9 (11.9 – 33.2) mg/kg (Davis and Borne 1984). Thus the lethality of MDMA is increased almost five-fold when mice are group-housed. This increase may be partially due to the stress of the novel physical and social environment, since acclimation reduces the effect of group housing on \(d\)-amphetamine lethality (Vargas-Rivera et al. 1990).

**Triphasic Dose-Lethality Curves of Some Amphetamines.** Several studies have found certain amphetamines to have complex, triphasic dose-response curves for lethality. The percent of animals killed within 24 hr of a dose does not increase smoothly as dose is increased. Instead, lethality may decrease at some doses, producing valleys in the dose-lethality curve. While MDMA does not appear to have been examined in this regard, researchers have investigated the lethality of MDA and MMDA (3-methoxy-4, 5-methylenedioxyamphetamine which is structurally 5-methoxy-MDA, although its functional groups are conventionally numbered differently) (Davis et al. 1977). The researchers found evidence of a triphasic lethality pattern for MMDA in both individually and group-housed mice and for MDA in individually housed mice only. MMDA was
also noteworthy for the steepness of its dose-lethality curve, with doses spaced by 0.05 log units. If MDMA were to have a similar steep and triphasic dose-toxicity curve, toxicity would likely appear dose-independent under the varied conditions of illicit ecstasy use.

Factors in addition to ecstasy exposure have been linked to risk of adverse effects in ecstasy users. In the survey of 329 Australian polydrug-using ecstasy users (Topp et al. 1999), adverse psychological effects were predicted by being female ($\beta = 0.91; p < 0.001$), recent bingeing on stimulants ($\beta = 0.58; p < 0.05$), number of drugs typically used when recovering from ecstasy ($\beta = 0.41; p < 0.001$), and more extensive recent polydrug use ($\beta = 0.15; p < 0.05$). This model accounted for a relatively small proportion of variance (16%) and does not indicate the direction of causality. In the same report, adverse physical effects were predicted by being female ($\beta = 1.6; p < 0.001$), being younger ($\beta = -0.20; p < 0.001$), number of drugs typically used when recovering from ecstasy ($\beta = 0.88; p < 0.001$), recent bingeing on ecstasy ($\beta = 1.4; p < 0.005$), quantity of ecstasy typically used ($\beta = 0.52; p < 0.01$) and unemployment ($\beta = -1.2; p < 0.05$) were independently associated with more physical side-effects. This model accounted for 29% of the variance. Another study interviewed individuals before and after a series of dance events (1121 participants before, of whom 768 returned afterward) (van de Wijngaart et al. 1999). 81% of participants had used ecstasy, 64% on the night of the study. Results of regression analysis (not actually described in the publication) were used to create “risk profiles” of dance events attendees. In these profiles, risk factors for having adverse events at parties included: having less experience with drug use; lacking a social safety net; being female; bingeing; and regularly buying “fake” ecstasy pills. Observations and objective measurements of temperature, humidity, and other variables were also made. The researchers reported that a regression analysis found that ambient conditions, such as temperature and humidity, played “virtually no role” in the incidence of self-reported complaints and illness. This finding is limited by the fact that adverse events were self-reported and that users experiencing serious adverse events were unlikely to be available for after-events interviews. This possible bias appears serious when one considers that 353 participants were interviewed before but not after the dance events.

When one considers the risk factors identified in these two studies, it seems likely that not all of these risk factors actually cause adverse events. For example, the number of drugs typically used when recovering from ecstasy is likely higher in individuals who suffer more severe adverse effects. Thus the use of drugs to recover from ecstasy is likely an effect of toxicity, not a cause. Controlled clinical trials suggest that females may experience more anxiety and dysphoric reactions and physical side effects than men (Liechti et al. 2001a). This increased sensitivity may be further amplified by the fact that females tend to weigh less than men and thus may often receive a larger dose (in mg/kg) from an equivalent number of pills. It is not clearer if regularly buying fake ecstasy pills is a risk factor merely because users ascribe adverse effects to fake ecstasy or if fake ecstasy actually causes more toxicity than MDMA.

It is possible that some drug combinations increase risk of ecstasy toxicity. In addition to MDMA, 78% of ecstasy-related emergency department cases in 1999 involved other
drugs, most commonly ethanol. In the series of cases reported by Williams et al. (1998), two-thirds (32/48) involved a substance in addition to ecstasy. Unfortunately, there are insufficient data to conclude that some combinations involving ecstasy and other illicit substances are more dangerous than others.

Drugs that are known to have potential for adverse interactions with sympathomimetic amphetamines may adversely interact with MDMA. For example, case reports describe apparent adverse interactions between ecstasy and MAO inhibitors (Kaskey 1992; Smilkstein et al. 1987). It can also be speculated that there might be pharmacological interactions between MDMA and other drugs that are also substrates for cytochrome P-450 isoenzymes 2D6, 1A2, 3A4, or 2B6 (Kreth et al. 2000; Maurer et al. 2000). Such a pharmacological interaction may have occurred with the protease inhibitor, ritonavir (Henry and Hill 1998).

Contents of Ecstasy Pills

Published data suggest that most illicit ecstasy pills contain MDMA. For example, Schifano (2000) reports that about 85-90% of the over 20,000 ecstasy pills seized in northeast Italy over a 5 year period contained MDMA. In an analysis of the first 107 ecstasy pills submitted to the DanceSafe testing program in the United States, Baggott et al. (2000) reported that 63% contained some MDMA or an analogue (MDA or MDE). However, there are also many pills containing other substances (see Table 6.9). Analysis of biofluids of individuals who had reportedly taken ecstasy has revealed other compounds such as amphetamine (Cox and Williams 1996; Hughes et al. 1993; Smit et al. 1996) and PMA (Byard et al. 1998; White et al. 1997). In an attempt to capitalize on the popularity of MDMA, other intoxicants such as gamma-hydroxybutyrate (GHB) and Ephedra extracts have been marketed using names like “Liquid Ecstasy” [sic] and “Herbal Ecstasy” [sic].

<table>
<thead>
<tr>
<th>Report</th>
<th>0-25 mg</th>
<th>26-75 mg</th>
<th>76-125 mg</th>
<th>126-159 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bean &amp; Pearson 1993 §</td>
<td>6 (50%)</td>
<td>3 (25%)</td>
<td>3 (25%)</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Milroy et al 1996</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Saunders 1995</td>
<td>1 (5%)</td>
<td>10 (45%)</td>
<td>0</td>
<td>11 (50%)</td>
<td>22</td>
</tr>
<tr>
<td>Sherlock 1999</td>
<td>3 (25%)</td>
<td>2 (17%)</td>
<td>5 (42%)</td>
<td>2 (17%)</td>
<td>12</td>
</tr>
<tr>
<td>Category totals</td>
<td>12</td>
<td>16</td>
<td>8</td>
<td>13</td>
<td>49</td>
</tr>
</tbody>
</table>

Adapted from (Sherlock et al. 1999). § Bean declined to confirm findings from his unpublished 1993 report, which was cited by Sherlock.
Few reports present quantitative information on the contents of ecstasy pills. The amount of MDMA found in ecstasy pills often seems to be lower than many authors assume. In neurotoxicity studies, it is commonly assumed that each pill contains 100 mg. In contrast, Sherlock et al. reported a 70-fold quantitative range of MDMA in illicit ecstasy pills. In one study of illicit ecstasy pills seized in Ireland, the quantity ranged from “not detectable” to 180 mg per pill (O'Connell and Heffron 2000).

Is Ecstasy Addictive?

Early reports found no evidence of ecstasy dependence. For example, Siegel interviewed 44 ecstasy users and determined that none engaged in compulsive use, although two had periods of intensified use during which they used ecstasy daily, ostensibly for therapeutic reasons (Siegel 1986).

However, increasing reports indicate that a minority of users engages in an out-of-control pattern of ecstasy use that leads to significant problems. Such behavior may fit the standard definition of substance dependence. The criteria for substance dependence in the most widely used psychiatric system in the United States, the Diagnostic and Statistical Manual of Mental Disorders, version IV (DSM-IV), are shown in Table 6.10. Individuals meeting three or more of these criteria within a 12-month period are considered dependent. Although the DSM-IV is not uniformly used internationally, criteria for substance dependence are almost identical in other widely used systems.

A few dependent ecstasy users have been described in the medical literature. For example, Jansen (1999) presented three case reports of dependent ecstasy users. In addition, case reports have described ecstasy users who developed ecstasy-related hepatotoxicity and, after treatment, continued to use ecstasy despite evidence of new liver damage (Khakoo et al. 1995; Shearman et al. 1992). While there is not sufficient information to diagnose these individuals as dependent, it seems likely that they would be so diagnosed if sufficient information were available.

Although the incidence of ecstasy dependence cannot be stated with certainty, recent surveys suggest that a substantial minority of ecstasy users may be dependent. In the survey of 329 polydrug-using ecstasy users in Australia, 25% wished to reduce ecstasy consumption (Topp et al. 1999). Their motivations for wanting to reduce usage were financial difficulties (57% of users), physical health problems (45%), psychological health problems (35%), occupational problems (37%), desire to improve quality of life (28%), relationship problems (17%), and feeling dependent on ecstasy (16%). Three of the 329 individuals had attended a detoxification program to reduce ecstasy use and three individuals (possibly the same ones) had attended Narcotics Anonymous for that reason. While these users cannot be conclusively classified as dependent based on this information, it seems likely that many would be considered dependent if sufficient information was available.
Table 6.9. Non-MDMA Contents of Ecstasy Pills

<table>
<thead>
<tr>
<th>Content</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA</td>
<td>(Curran 2000; Milroy et al. 1996; O’Connell and Heffron 2000; Renfroe 1986; Solowij et al. 1992; Sondermann and Kovar 1999; Winstock and King 1996)</td>
</tr>
<tr>
<td>MDEA or MDE</td>
<td>(Boggott et al. 2000; Curran 2000; Milroy et al. 1996; O’Connell and Heffron 2000; Saunders and Doblin 1996; Sherlock et al. 1999; Winstock and King 1996; Wolff et al. 1995)</td>
</tr>
<tr>
<td>MBDB</td>
<td>(Winstock and King 1996)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>(Sherlock et al. 1999)</td>
</tr>
<tr>
<td>Paramethoxyamphetamine</td>
<td>(Felgate et al. 1998)</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>(Curran 2000; Milroy et al. 1996; O’Connell and Heffron 2000; Sherlock et al. 1999; Winstock and King 1996; Wolff et al. 1995)</td>
</tr>
<tr>
<td>“Amphetamine compound”</td>
<td>(Renfroe 1986)</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>(Boggott et al. 2000; O’Connell and Heffron 2000; Saunders and Doblin 1996; Shewan and Dalgarno 1996)</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>(Boggott et al. 2000; Milroy et al. 1996; O’Connell and Heffron 2000)</td>
</tr>
<tr>
<td>Procaine</td>
<td>(Shewan and Dalgarno 1996)</td>
</tr>
<tr>
<td>Caffeine</td>
<td>(Boggott et al. 2000; Milroy et al. 1996; O’Connell and Heffron 2000; Saunders and Doblin 1996; Sherlock et al. 1999; Sondermann and Kovar 1999; Winstock and King 1996; Wolff et al. 1995)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>(Curran 2000; Sherlock et al. 1999; Shewan and Dalgarno 1996; Wolff et al. 1995)</td>
</tr>
<tr>
<td>Triprolidine</td>
<td>(Milroy et al. 1996)</td>
</tr>
<tr>
<td>N-methyl-1-phenylethylamine</td>
<td>(O’Connell and Heffron 2000)</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>(Saunders and Doblin 1996)</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>(Boggott et al. 2000; Saunders and Doblin 1996)</td>
</tr>
<tr>
<td>Selegiline</td>
<td>(Shewan and Dalgarno 1996)</td>
</tr>
<tr>
<td>Glyceryl guaiacolate</td>
<td>(Saunders and Doblin 1996)</td>
</tr>
<tr>
<td>1-Phenylethlamine</td>
<td>(Winstock and King 1996)</td>
</tr>
<tr>
<td>Methylaine</td>
<td>(Renfroe 1986)</td>
</tr>
<tr>
<td>Salicylates</td>
<td>(Boggott et al. 2000; O’Connell and Heffron 2000)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>(O’Connell and Heffron 2000; Sherlock et al. 1999; Wolff et al. 1995)</td>
</tr>
</tbody>
</table>

Additional drugs may have been detected in three reports that we have not yet been able to obtain (Bohn et al. 1993; Frost et al. 1996; Rashed et al. 2000).
Table 6.10. DSM-IV Criteria for Substance Dependence

<table>
<thead>
<tr>
<th>Substance Dependence: A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12 month period:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tolerance, as defined by either of the following:</td>
</tr>
<tr>
<td>a. a need for markedly increased amounts of the substance to achieve intoxication or desired effect</td>
</tr>
<tr>
<td>b. markedly diminished effect with continued use of the same amount of the substance.</td>
</tr>
<tr>
<td>2. Withdrawal, as manifested by either of the following:</td>
</tr>
<tr>
<td>a. the characteristic withdrawal syndrome for the substance</td>
</tr>
<tr>
<td>b. the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.</td>
</tr>
<tr>
<td>3. The substance is often taken in larger amounts or over a longer period than was intended.</td>
</tr>
<tr>
<td>4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.</td>
</tr>
<tr>
<td>5. A great deal of time is spent in activities necessary to obtain the substance, or recover from its effects.</td>
</tr>
<tr>
<td>6. Important social, occupational, or recreational activities are given up or reduced because of substance use.</td>
</tr>
<tr>
<td>7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.</td>
</tr>
</tbody>
</table>

The fact that a minority of users appear to develop ecstasy dependence should not be misinterpreted as evidence that MDMA has high abuse liability as the term is commonly understood with regard to drugs such as heroin. In the survey of partygoers in the Netherlands, ecstasy was not among the top three substances that participants found it most difficult to do without (van de Wijngaart et al. 1999). These substances were tobacco, cannabis, and alcohol.

Given the widespread illicit use of ecstasy, it seems almost redundant to mention studies demonstrating that animals will self-administer MDMA or find its effects rewarding. Two primate studies found that animals trained to self-inject cocaine will subsequently take MDMA. In one study, three of four rhesus monkeys self-administered MDMA (Beardsley et al. 1986). In the second primate study, three baboons self-administered MDMA at doses of 0.32 to 3.2 mg/kg per injection (Lamb and Griffiths 1987). Self-administration of cocaine occurred at a higher rate than MDMA in both studies. MDMA also makes rats more likely to electrically stimulate electrodes implanted in the median forebrain bundle or other areas of the brain thought to be involved in pleasure and drug-taking (Hubner et al. 1988; Lin et al. 1993; Lin et al. 1997a; Reid et al. 1995). The dose-dependent rewarding effects of MDMA can be further seen in conditioned place preference experiments. In these studies, animals administered MDMA will subsequently prefer the physical location in which they experienced the drug (Bilsky et
The increasing evidence of ecstasy dependence in a minority of users follows a pattern seen with the non-medical use of other drugs, such as cocaine and amphetamines. When a drug is first used non-medically, reports of serious toxicity are rare and dependence is seldom recognized. However, as more people use the drug, serious toxicity and dependence syndromes may be reported. This is likely due to the changing user population and patterns of drug use as well as the fact that rare adverse events can only be detected in large samples.
References


Berger UV, Gritzann R, Molliver ME (1992a) The neurotoxic effects of p-chloroamphetamine in rat brain are blocked by prior depletion of serotonin. Brain Res 578: 177-85,


Bjorklund A, Stenevi U (1979) Regeneration of monoaminergic and cholinergic neurons in the mammalian central nervous system. Physiol Rev 59: 62-100,


Boys ALSNK (1997) Polydrug use at raves by a Western Australian sample. Drug & Alcohol Review 16: 227-234,


Chait LD, Uhlenhuth EH, Johanson CE (1986) The discriminative stimulus and subjective effects of d-amphetamine, phenmetrazine and fenfluramine in humans. Psychopharmacology 89: 301-6,


Davis GC, Williams AC, Markey SP, Ebert MH, Caine ED, Reichert CM, Kopin IJ (1979) Chronic Parkinsonism secondary to intravenous injection of meperidine analogues. Psychiatry Res 1: 249-54,


Evenden JL (1999) Varieties of impulsivity. Psychopharmacology 146: 348-361,


Faraj BA, Ołkowski ZL, Jackson RT (1994) Active [3H]-dopamine uptake by human lymphocytes: correlates with serotonin transporter activity. Pharmacology 48: 320-7,


Gasser P (1994) Psycholytic Therapy with MDMA and LSD in Switzerland. MAPS Newsletter 5: 3-7,


Grob CS, Poland RE, others (In preparation) Psychological, physiological and neuroendocrine effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") in healthy humans:
Haertzen CA (1966) Development of Scales Based on Patterns of Drug Effects, Using the Addiction Research Center Inventory (Arci). Psychological Reports 18: 163-194,

Page 199 of 367
Hekmatpanah CR, McKenna DJ, Peroutka SJ (1989) Reserpine does not prevent 3,4-methylenedioxymethamphetamine-induced neurotoxicity in the rat. Neurosci Lett 104: 178-82,
Hensley D, Cody JT (1999) Simultaneous determination of amphetamine, methamphetamine, methylenedioxymethamphetamine (MDA), methylenedioxymethamphetamine (MDMA), and methylenedioxymethylamphetamine (MDEA) enantiomers by GC-MS. J Anal Toxicol 23: 518-23,
Hervias I, Lasheras B, Aguirre N (2000) 2-Deoxy-D-glucose prevents and nicotinamide potentiates 3,4-methylenedioxymethamphetamine-induced serotonin neurotoxicity. J Neurochem 75: 982-90,
Heym J, Gladfelter WE (1982) Locomotor activity and ingestive behavior after damage to ascending serotonergic systems. Physiol Behav 29: 459-67,
Hiratsuka A, Chu TY, Distefano EW, Lin LY, Schmitz DA, Cho AK (1995) Inactivation of constitutive hepatic cytochromes P450 by phenylcyclohexine in the rat. Drug Metab Dispos 23: 201-6,


Layton JM, Wykle MH (1990) A validity study of four empathy instruments. Research in Nursing & Health 13: 319-325,


Lin JH (1998) Applications and limitations of interspecies scaling and in vitro extrapolation in pharmacokinetics. Drug Metab Dispos 26: 1202-12,


Logan AS, Stickle B, O'Keefe N, Hewitson H (1993) Survival following 'Ecstasy' ingestion with a peak temperature of 42 degrees C. Anaesthesia 48: 1017-8,


Malberg JE, Seiden LS (1998) Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat. J Neurosci 18: 5086-94,

Mallick A, Bodenham AR (1997) MDMA induced hyperthermia: a survivor with an initial body temperature of 42.9 degrees C. J Accid Emerg Med 14: 336-8,

Manchee GR, Eddershaw PJ, Ranshaw LE, Herriott D, Park GR, Bayliss MK, Tarbit MH (1996) The aliphatic oxidation of salmeterol to alpha-hydroxysalmeterol in human liver microsomes is catalyzed by CYP3A. Drug Metab Dispos 24: 555-9,
Masters R, Houston J (1972) Mind Games: The Guide to Inner Space. Dell, Dell,
McCann UD, Ricartue GA (1993) Reinforcing subjective effects of (+/-)3,4-methylenedioxyamphetamine ("ecstasy") may be separable from its neurotoxic actions:


Mechan AO, O'Shea E, Elliott JM, Colado MI, Green AR (2001) A neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) to rats results in a long term defect in thermoregulation. Psychopharmacology (Berl) on-line publication.


Oswald I, Thacore VR (1963) Amphetamine and phentramine addiction, physiological abnormalities in the abstinence syndrome. British Medical Journal 2: 427-431,


Schmidt CJ, Fadayel GM, Sullivan CK, Taylor VL (1992b) 5HT₂ receptors exert a state-dependent regulation of dopaminergic function: studies with MDL 100,907 and the amphetamine analogue,
Spanos LJ, Yamamoto BK (1989) Acute and subchronic effects of methylenedioxymethamphetamine [(+/-)MDMA] on locomotion and serotonin syndrome behavior in the rat [published erratum appears in

Page 215 of 367


van Tonningen-van Driel MM, Garbis-Berkvens JM, Reuvers-Lodewijks WE (1999) [Pregnancy outcome after ecstasy use; 43 cases followed by the Teratology Information Service of the National Institute for Public Health and Environment (RIVM)]. Ned Tijdschr Geneeskd 143: 27-31,


Whitaker-Azmitia PM, Aronson TA (1989) "Ecstasy" (MDMA)-induced panic. Am J Psychiatry 146: 119, 


Widmer S (1997) Listening into the heart of things: The awakening of love: On MDMA and LSD: The 
undesired psychotherapy. Basic Editions, Basic Editions,

utilization in the rat. Neuropharmacology 28: 1129-38, 

Wilkins B (1996) Cerebral oedema after MDMA ("ecstasy") and unrestricted water intake. Hyponatraemia 
must be treated with low water input. Bmj 313: 689-90; discussion 690, 

Med 91: 541-2, 

Williams A, Unwin R (1997) Prolonged elevation of serum creatine kinase (CK) without renal failure after 
ingestion of ecstasy. Nephrol Dial Transplant 12: 361-2, 

Williams H, Dratcu L, Taylor R, Roberts M, Oyefeso A (1998b) "Saturday night fever": ecstasy related 
problems in a London accident and emergency department. J Accid Emerg Med 15: 322-6, 

Williams JH, Azmitia EC (1981) Hippocampal serotonin re-uptake and nocturnal locomotor activity after 
microinjections of 5,7-DHT in the fornix-fimbria. Brain Res 207: 95-107,

drugs in a community sample of drug users. Drug Alcohol Depend 44: 87-94, 

Wilson JM, Kalasinsky KS, Levey AI, Bergeron C, Reiber G, Anthony RM, Schmunk GA, Shannak K, 
Haycock JW, Kish SJ (1996) Striatal dopamine nerve terminal markers in human, chronic 
methamphetamine users. Nat Med 2: 699-703,

11: 18-34,

Wilson MA, Ricautre GA, Molliver ME (1989) Distinct morphologic classes of serotonergic axons in 
primates exhibit differential vulnerability to the psychotrophic drug 3,4- 
methylenedioxymethamphetamine. Neuroscience 28: 121-37, 

Windhaber J, Maierhofer D, Dantendorfer K (1998) Panic disorder induced by large doses of 3,4- 
methylenedioxymethamphetamine resolved by paroxetine. J Clin Psychopharmacol 18: 95-6, 

Winslow JT, Insel TR (1990) Serotonergic modulation of rat pup ultrasonic vocal development: studies 
with 3,4-methylenedioxymethamphetamine. J Pharmacol Exp Ther 254: 212-20, 

Winstock AR, King LA (1996) Ecstasy and neurodegeneration. Tablets often contain substances in addition 
to, or instead of, ecstasy... BMJ 313: 423-4, 


Wolfson PE (1985) Testimony of Philip E. Wolfson, M.D. In the Matter of MDMA Scheduling. Docket 
No. 84-48. (United States Department of Justice, Drug Enforcement Administration.)

Wolfson PE (1986) Meetings at the edge with Adam: A man for all seasons? Journal of Psychoactive Drugs 
18: 329-333, 

dermatosis. Dermatology 197: 171-3, 

ingestion of 3,4-methylenedioxymethamphetamine ('ecstasy'). Nephrol Dial Transplant 10: 399-400, 

Wright JD, Pearl L (1990) Knowledge and experience of young people regarding drug abuse, 1969-89. Bmj 
300: 99-103, 


Wu C, Singh SK, Dias P, Kumar S, Mann DM (1999) Activated astrocytes display increased 5HT2A receptor expression in pathological states. Exp Neurol 158: 529-33,


Appendix A: Structured Abstracts of Reports on Clinical MDMA Research

Lisa Jerome, Ph.D., and Matthew Baggott, B.A.

Contains: summaries of all available studies (34 published and unpublished as of June 1, 2001) in the English-language literature in which MDMA was administered to humans.

Anderson et al. (1978). Absolute configuration and psychotomimetic activity.


**Purpose:** Pharmacological, psychological; Comparison of effects of the R and S isomers of MDMA, and argument for placing MDMA in a classification separate from the classic hallucinogens on the basis of the profile of these isomers.

**Design:** Non-experimental uncontrolled within-subjects design, wherein all volunteers received at least one dose of each form of MDMA; racemate, R-MDMA and S-MDMA, at doses including those of 40-200 mg. (Also performed comparative studies on rabbits wherein hyperthermic response to racemate and each isomer of MDMA was compared with response to the phenethylamine classic hallucinogen, DOM).

**Subjects:** Unspecified number (perhaps 6 (6 x 5)?) of human volunteers, probably including the authors, gender and ages of volunteers not provided. Information on subject recruitment not provided. **Criteria for Inclusion** – Prior experience with psychedelic drugs. (An unspecified number of rabbits were used in studies of drug-induced hyperthermia).

**Measures:** An author-constructed five-point rating scale for overall drug effects, with rating dependent upon degree and intensity / intrusiveness (described as “disruptiveness”) of subjective drug effects, and open-ended narratives wherein volunteers described drug effects. (Rectal hyperthermia in rabbits).

**Analyses:** No formal analyses were performed. Comparative drug effects of racemic MDMA, R-MDMA and S-MDMA are presented in descriptive form.

**Results:** Volunteers reported that racemic MDMA was active at 5 mg – 150 mg. S-MDMA was reported to be effective at doses of 80 mg – 120 mg. The effective doses for R-MDMA were far higher, and even 200 mg. R-MDMA did not produce the full intoxication obtained with racemic MDMA. Most of the emotional and sensory effects reported with the racemate are present with S-MDMA, but volunteers reported that they preferred the racemate to S-MDMA alone. The physiological effects of the racemate were also present with S-MDMA, including dilated pupils (mydriasis) and jaw clenching. R-MDMA did not produce these physiological effects. However, 2 / 6 or 2 / 35 reported “color enhancement” with R-MDMA but not with S-MDMA. (These volunteers reported experiencing color enhancement with racemic MDMA). The authors conclude that the effects found with each isomer, alone or summed, did not account for the effects of racemic MDMA. (In rabbits, S-MDMA produced greater elevation in body temperature (rectal hyperthermia) than either R-MDMA or racemic MDMA).

**Overall Effects:** S-MDMA was far more active than the R-enantiomer and moderately more active than the racemate. S-MDMA had a lower effective dose than the R-enantiomer and it seemed to produce most or all of the effects associated with racemic MDMA, including psychological effects and side effects. R-MDMA was found to have a much higher effective dose range, and it did not produce an intoxication comparable to racemic MDMA even after 200 mg R-MDMA. With the possible exception of altered perception of color, S-MDMA appeared to possess most of the effects of the racemate. Nevertheless, volunteers preferred the effects of the racemate to either R-MDMA or S-MDMA, and the authors conclude that racemic MDMA produces effects that are not simply the sum of the effects produced by each enantiomer alone. The authors argue that because the R-enantiomers of hallucinogens are typically
more potent than S-enantiomers and MDMA was more active as the S-enantiomer, MDMA should not be classed as a hallucinogen. (As with humans, studies with rabbits indicated that the S-enantiomer of MDMA was more active than the R-enantiomer, when hyperthermia is used as a test of activity).

**Adverse Effects:** See above; an unspecified number of volunteers reported sweating and jaw clenching with racemic MDMA and with S-MDMA.

**Comments:** This paper is the second published report of the effects of MDMA in humans, and the only report at present that describes the individual effects of the MDMA enantiomers in humans. It is unclear how many volunteers were involved in these trials or how many doses were sampled for each compound. However, this paper does offer some preliminary information about the effects of racemic MDMA and the effects R-MDMA and S-MDMA. On the basis of their findings, the authors propose that MDMA should not be classified as a hallucinogen.

**Boone et al. (In Preparation). Neuropsychological Effects of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy).**


**Purpose:** Neuropsychological, assessment of cognitive performance; “This current study evaluates...possible chronic and subacute effects of MDMA on brain function as measured by neuropsychological tests.” (p. 2 in manuscript).

**Design:** Randomized, double-blind, placebo-controlled within-subjects design used to compare performance on neuropsychological test battery before receiving 2 separate doses of up to 2.5 mg / kg, MDMA (combined dose =0.75-4.75 mg/kg) with performance after receiving 2 doses of MDMA from 0.75 up to 2.5 mg/kg., with all volunteers assessed pre-drug and approximately 2 wks post-drug. (Study also compares MDMA-experienced subjects’ performance on a (baseline) neuropsychological test battery with published norms matched for subject sample age or education, with comparison conducted on 14 volunteers + an additional 10 volunteers who did not take part in the pre-drug / post-drug study.)

**Subjects:** 24 MDMA-experienced subjects, 16 men, 8 women, average age 38, underwent baseline assessment only. 14 / 24 subjects, gender and age not provided, underwent baseline and post-drug assessment 2 wks after 2 doses of MDMA. (Volunteers in pre-test / post-test study belong to same sample reported on in Grob et al., 1996, Grob, 2000). All volunteers recruited via local advertisements.

**Criteria for Inclusion** – Good health as assessed through medical examination, psychiatric interview and neurological examination. Lack of personal or family history of major medical or psychiatric illness. No history of substance abuse (except for MDMA or nicotine) and no history of head trauma with loss of consciousness over 30 min. At least 1 mo free of psychoactive medications or illicit drugs, and pre-sessiion urine screen free of marijuana, barbiturates, cocaine, benzodiazepines or amphetamines. Not pregnant.

**Measures:** MRI – Performed via clinical 1.5 Tesla scanner. Neuropsychological Assessment – Test battery administered at baseline for 24 / 24 subjects, conducted 193 + / - 225.3 days after last use of MDMA / ecstasy (range 7.5-780 days). Baseline assessment contained measures of intelligence (WAIS-R), attention (digit span), information processing (Stroop, Digit Symbol), language (Boston Naming Test), constructional ability (Rey-Osterrieth Complex Figure), Memory, Verbal (Logical Memory sub-test of WMS-R, Warrington Recognition Memory Test, Words, RAVLT), Memory, nonverbal (Visual Reproduction sub-test of WMS-R, Warrington Recognition Memory Test-Faces, Rey-Osterrieth Figure, 3 minute delayed, Continuous Visual Memory Test), and executive function (Stroop, Auditory Consonant Trigrams, WCST, Controlled Oral Word Association Test - Fluency. 14 / 24 volunteers assessed again with a less extensive test battery. Post-drug assessment included Digit Span, (Attention), Auditory Consonant Trigrams (Executive function), alternate forms of
RAVLT (verbal memory), Controlled Oral Word Association – Fluency (executive function) and Continuous Visual Memory (visual memory). Post-drug assessment conducted approximately 2 wk after receiving the second of 2 doses of MDMA as part of a controlled, laboratory study.

**Analysis:** Performance on each test scored for 24 volunteers at baseline and for 14 / 24 volunteers post-drug. Pre-drug performance compared with post-drug performance on each test via paired t-test. (24 / 24 performance scores on baseline test battery compared with published norms for each test, matched for sample age group, except for Copy and Recall scores for Rey-Osterrieth figure, matched for sample education. Spearman correlation coefficient used to assess relationship between MDMA user parameters (duration, frequency and recency of use) and performance on each assessment employed in baseline test battery.)

**Results:** MRI – MRI scans normal for all subjects. Neuropsychological Assessment – Post-drug performance did not differ from baseline. MDMA did not reduce performance scores on measures of digit span, RAVLT, continuous visual memory, auditory trigrams, or verbal fluency when post-drug assessment was compared with baseline. (When baseline test performance matched with age-appropriate norms, MDMA users (24 / 24 subjects) found to score within normal range (25th – 74th percentile or higher) for all tests except WCST. Volunteers scored <25th percentile on several WCST scores, including trials to identifying category, failure to maintain set (FTM and number of categories. Frequency of MDMA use negatively correlated with scores on tests of visual memory and verbal recognition memory, and frequency of use positively correlated with speed in test of mental speed and cognitive inhibition. Length of abstinence prior to assessment positively correlated with performance on measures of divided attention / working memory and visual memory).

**Overall Effects:** Recent administration of MDMA in controlled setting did not reduce performance on tasks involving attention, memory and executive function. Test battery scores attained at least 2 weeks after receiving the second of 2 doses of MDMA were no lower than scores attained at baseline. However, frequent use of MDMA was associated with poorer performance at baseline on tasks involving memory, with visual memory being particularly affected, and more recent use of MDMA was associated with poorer performance at baseline on a test of divided attention and working memory. At baseline, MDMA users also performed below norm on the WCST, a test of executive function. On the other hand, frequency of use is associated with faster performance on a test of mental speed.

**Adverse Effects:** Not reported in this paper; see Grob, 2000 dose-response study).

**Comments:** This is the first investigation into MDMA’s effects on cognitive performance that uses a prospective design. Previous comparisons between MDMA users and MDMA-naïve controls have used retrospective designs. Their findings are subject to confounding factors that may arise when two self-selected groups are compared. While Boone and Grob’s research probably will not settle the debate concerning MDMA’s effects on cognitive function, this prospective study suggests that reductions in cognitive function will not arise after a small number of doses of MDMA. Instead, it may be chronic, frequent use of illicit ecstasy that is associated with cognitive deficits. These findings suggest that a few doses of MDMA can be administered in controlled settings without producing a decline in cognitive function.

**Cami et al. (2000). Human pharmacology of 3,4-methylenedioxymethamphetamine (“Ecstasy”); psychomotor performance and subjective effects.**


**Purpose:** Neuropsychological, psychopharmacological; “…to assess the abuse liability of MDMA as compared with amphetamine and placebo.” (p. 88). Study examined MDMA’s effects on psychomotor performance and subjective effects, compared with amphetamine and placebo.
Design: Randomized, double-blind placebo controlled crossover (i.e. within subjects) design, with drug (placebo, 40 mg amphetamine, 75 mg MDMA or 125 mg MDMA) as a factor. all volunteers took part in all 4 conditions (placebo, amphetamine, 75 mg MDMA and 125 mg MDMA, with each session scheduled at least 1 wk after previous session.

Subjects: 14 MDMA-experienced men, with data presented for 8 / 14 men, aged 21-30, mean = 26.5. (same sample used in Mas et al., 1999).

Criteria for Inclusion - Lack of major psychiatric or medical illness as assessed through interview and physical examination, routine laboratory tests, urinalysis and ECG. Lack of substance abuse (except for nicotine dependence). Past use of MDMA (or ecstasy) at least five times in the past. Urinary drug screens for opioids, cocaine, amphetamines conducted before and after study; all were negative. Identified as extensive metabolizers (measure of CYP2D6) via dextromethorphan / dextorphan assay.

Measures: Mood – Measured via POMS, with POMS administered at 0, 1, 2, 4, 6, 8, 10 and 24 h post-drug administration.

Drug Effects, Alterations in Consciousness – Measured with Spanish-language ARCI and author-constructed visual analog scales (VAS), with both measures administered at 0, 15, 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 10, 12 and 24 h post-drug.

Psychomotor Performance – Psychomotor performance measured via Digit Symbol Substitution Test (DSST), simple RT task and Maddox-Wing device. DSST = a test of visual pattern recognition; volunteers respond to patterns presented on screen, scored as % of correct patterns keyed into computer in 90 sec. Simple RT task = measure of sensory-motor performance, scored as speed of response after stimulus and Maddox-Wing device = measure of extraocular muscular movement, scored as either exophoria (tendency of eyes to move apart from each other, divergent squint), normal activity or esophoria (tendency for eyes to move toward each other, convergent squint). Measures of psychomotor performance administered at 0, 30, 60, 90 min and 2, 3, 4, 6, 8, 10, 12 and 24 h post-drug.

Drug Class Identification – Questionnaire administered 10 h post-drug in each condition; volunteers indicated which drug they thought they had received from the following list; benzodiazepines, alcohol, stimulants (like amphetamine), designer drugs (ecstasy-like), cocaine, hallucinogen, cannabis or others.

Analysis: Psychomotor performance scores, ARCI, POMS and visual analog scale scores transformed into differences from baseline. Peak effect within 6 h (maximum change from baseline) and AUC calculated via trapezoidal rule.

Mood – POMS analyzed via 1-way repeated measures ANOVA, with drug (placebo, amphetamine, 75 mg MDMA, 125 mg MDMA) as factor.

Drug Effects, Alterations in Consciousness – 1-way repeated measures ANOVA performed on ARCI and VAS, with drug condition as factor.

Psychomotor Performance – Scores on RT, DSST and Maddox-Wing tasks analyzed via 1-way repeated measures ANOVA (described above), with drug condition as factor,

All Data - Post-hoc comparisons made via Tukey’s test. Significance, p. = .05.

Results: Mood – Maximum change in mood generally occurred 90 min – 2 h post-drug and returned to baseline 4 h post-drug. Only 125 mg MDMA increased POMS “elation,” “positive mood” and “confusion” scales compared with placebo or amphetamine.

Drug Effects, Alterations in Consciousness – Maximal alterations in consciousness occurred 90 min – 2 h post-drug and declined to baseline at 4 h post-drug.

Drug Effects, ARCI – All drugs (amphetamine, 75 and 125 mg MDMA) increased A (d-amphetamine-sensitive) scores. MDMA (at both doses) increased MBG (euphoria) and LSD (dysphoria) scores compared with placebo. Only amphetamine increased BG (energy, intellectual efficiency) score and only 125 mg. MDMA increased PGAG (sedation) score compared with placebo.

Drug Effects, VAS – Amphetamine and MDMA (75 mg, 125 mg) increased scores for “liking,” “any effect,” “stimulated” and “good effects” compared with placebo. 75 mg. And 125 mg. MDMA increased “drunken” rating compared with placebo, amphetamine. 125 mg. MDMA increased ratings of “high,” “drunken” and “confusion” compared with placebo or amphetamine, and 125 mg MDMA increased “high” and “confusion” more than 75 mg MDMA. 125 mg. MDMA increased ratings of “changes in
shapes,” “changes in lights,” “changes in hearing,” “different, changed unreal body feelings” and “different or unreal surroundings.” Colors rated brighter, sounds sharper. 75 mg. MDMA only increased ratings of “different, changed unreal body feelings.” No hallucinations reported. Amphetamine did not increase ratings of changed perception.

**Psychomotor Performance** – Maximal effects on performance seen 1 – 2 h post-drug. DSST – During peak effects, amphetamine and 75 mg. MDMA did not affect DSST performance, but 125 mg. MDMA slightly increased errors and reduced number of correct responses. Amphetamine slightly increased performance on DSST; improvement not statistically significant. RT Task – No changes in simple reaction time with any drug (amphetamine, 75 mg. MDMA or 125 mg. MDMA); amphetamine slightly decreased RT, effect not significant. Maddox-Wing Device – 125 mg. MDMA (and no other treatment) produced esophoria (convergent squint).

**Drug Class Identification** – 6 / 8 identified both doses (75 mg., 125 mg.) of MDMA as designer drug (“ecstasy-like.”) 1 / 8 identified 125 mg. MDMA as a stimulant and 1 / 8 identified 125 mg. MDMA as a benzodiazipine. 1 / 8 identified 75 mg. MDMA as placebo, and 1 / 8 identified 75 mg. MDMA as a benzodiazipine. 6 / 8 correctly identified amphetamine as stimulant (other identifications not reported). 7 / 8 correctly identified placebo; 1 / 8 identified placebo as benzodiazipine.

**Overall Effects:** While MDMA appeared to share some effects with the stimulant amphetamine, as reflected in similar values for “stimulated,” “good effects” and ARCI A (d-amphetamine sensitive) scale, MDMA produced a unique psychological profile. Both 75 and 125 mg MDMA increased positive mood, “drunken” feeling, “euphoria (ARCI MBG) and “dysphoria” (ARCI LSD). The higher (125 mg) dose of MDMA significantly altered perception in several modalities (without causing hallucinations) and increased ratings of “sedation” (ARCI PGAG) and “confusion.” 125 mg MDMA also slightly impaired performance on the DSST, a test of visual pattern recognition. 125 mg. MDMA, but not 75 mg. MDMA or 40 mg amphetamine, produced a convergent squint (esophoria). Most volunteers correctly identified MDMA and successfully differentiated it from amphetamine. As noted below, both doses of MDMA were safely administered without producing severe psychological or physiological distress.

**Adverse Effects**: None reported in paper; authors indicate that none of the volunteers experienced severe adverse effects, and there was no need for clinical intervention for any subject in any of the drug conditions.

**Comments:** This is a companion paper to Mas et al’s (1999) study of the cardiovascular effects and pharmacokinetics of MDMA in humans. This study is notable in identifying peak drug effects through multiple administration of psychometric and performance measures rather than administering measures at a pre-determined time when peak effects are expected to occur. By employing different measures of psychomotor performance, the authors are also able to draw more specific conclusions about MDMA’s effects on attention; simple attending was less affected by MDMA than complex attending. Cami et al. interpret high ratings on the ARCI MBG scale as indicative of high abuse potential. However, both doses of MDMA also received high ratings (compared to placebo) on the ARCI LSD scale, said to measure “dysphoria.” The findings in this paper seem to support placing MDMA in a separate class of drugs, entactogens, on the basis of its differential effects on psychological measures.

**Chang et al. (2000). Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow; A co-registered SPECT and MRI study.**


**Purpose:** Neurophysiological, brain imaging: “This study evaluates the chronic and sub-acute effects of MDMA on brain function as measured by regional cerebral blood flow.” (p. 16). Study compared pre-
MDMA scans with post-MDMA scans and also compared scans of MDMA users with scans from controls with no history of MDMA use.

**Design:** Randomized, double-blind, placebo-controlled within-subjects design for comparing SPECT scans made before receiving 2 separate doses of MDMA, (combined dose range = 2.25 to 4.75 mg / kg, mean 3.5 + / - .8 mg / kg) with SPECT scans made after volunteers received MDMA. All volunteers received pre-drug and post-drug scans. (Study also used between-subjects design to compare scans of MDMA-experienced volunteers (drug-free for at least 1 mo.) with MDMA-naive controls.)

**Subjects:** 10 MDMA-experienced subjects, 6 men, 4 women, average age 38.4 + / - 12.5 (from a sample of 21 MDMA users, 17 men, 4 women, aged 43.4 + / - 12.5). MDMA-experienced is defined here as having used MDMA at least 6 times for at least one year. Volunteers recruited through local advertisements (in California area).

**Criteria for Inclusion** – Reported using low doses of MDMA, with low doses defined as (< 3 mg / kg per session), at least 6 times a year for at least one year, as assessed through screening questionnaire. Good health as assessed through medical examination, psychiatric interview and neurological examination. Lack of personal or family history of major medical or psychiatric illness. No history of substance abuse (except for MDMA or nicotine) and no history of head trauma with loss of consciousness for more than 30 min. At least 1 month free of psychoactive medications or illicit drugs, and pre-session urine screen free of marijuana, barbiturates, cocaine, benzodiazepines or amphetamines (MDMA would register if used within 48 h.) Not pregnant, and without metallic objects in body.

**Measures:** Imaging – 2 [99mTc]-HMPAO SPECT scans co-registered with MRI scans, with MRI and SPECT scan occurring before MDMA administration and another pair of scans (1 MRI, 1 SPECT) approximately 21 days after two separate doses of MDMA. 8 / 10 received scans approximately 2 weeks post-drug and 2 / 10 received scans approximately 2 months post-drug.

**Analysis:** Regions of interest (ROIs) selected by investigator blinded to drug use condition. 8 / 10 subjects’ data analyzed via 3-way repeated measures ANOVA, with scan time (baseline, post-drug), brain hemisphere and brain region as within-subjects variables. Post-drug scans also compared with scans of 8 matched (non-MDMA user) controls via 3-way mixed measures ANOVA, with drug use as a between-subjects variable, and brain hemisphere and brain region as within-subjects variables. Effects of time since MDMA administration and combined dose of MDMA on measures of rCBF assessed through linear regression. Overall p. values corrected for multiple comparisons with Huynh-Feldt test. Post-hoc comparisons conducted with Fisher’s PLSD with Bonferroni correction. (Scans of 21 MDMA users and 21 controls also compared).

**Results:** Global and, in most regions, regional CBF decreased post-MDMA when compared to pre-MDMA scans or when compared with scans of 8 MDMA-naïve controls who never received MDMA in study. There was a trend toward overall drug effect (p < .07) and a significant MDMA x region effect when comparing pre-drug with post-drug scans. Post-hoc comparisons between pre-drug and post-drug scans found significantly decreased CBF post-drug in the following regions; L, R visual cortex, L, R caudate, L, R superior parietal region and L, R dorsolateral frontal region. When compared with matched controls, post-drug scans show decreased rCBF in most regions examined, with greatest decreases in caudate (L, R), superior parietal region (L, R) and right dorsolateral frontal cortex (R only). Higher doses of MDMA were positively correlated with greater decrease in rCBF post-drug (compared to pre-drug), and recency of MDMA administration also correlated with decreased rCBF post-MDMA. Increased CBF found in post-drug scans of 2 / 20 volunteers who received scans 2 mo. after MDMA. (Overall study found no significant differences between 21 MDMA-using volunteers and 21 non-using controls in scans taken at baseline.

**Overall Effects:** There appeared to be no differences in rCBF (either increase or decrease) associated with low to moderate MDMA use, as SPECT scans from 21 MDMA-experienced volunteers did not differ from scans of 21 age and gender-matched MDMA-naïve controls. However, MDMA sub-acutely reduced rCBF in several brain regions, with reductions seen when baseline scans were compared with post-drug scans made 2 wks after MDMA administration and when post-drug scans were compared with scans of matched controls (who never received MDMA during course of study). CBF reduced in the
following regions bilaterally in post-drug scans; caudate, superior parietal region and dorsolateral frontal regions. CBF also appeared to be reduced in these and other areas when comparing post-drug scans to those of matched controls.

**Adverse Effects:** None reported in this study,

**Comments:** This is the first prospective study of MDMA’s effects on rCBF, with measures taken both before and volunteers received MDMA. Unlike the majority of retrospective comparisons between MDMA users and non-users, the authors of this study can also be certain that the compound producing the differences in CBF is MDMA rather than a contaminant of illicit ecstasy or another compound entirely sold as ecstasy. Authors relate their study findings to a postulated enhancement of 5HT-induced vasoconstriction produced by MDMA or by one of its metabolites. These findings could support other hypotheses, such as neurotoxicity, transient changes in receptor activity after alteration by serotonin release, or sub-acute serotonin depletion. The paper is part of an ongoing examination of the psychological, physiological and neuroendocrine responses to different doses of MDMA in a placebo-controlled study, wherein a range of doses of MDMA were administered to MDMA-experienced subjects.

**De la Torre et al. (2000). Non-linear pharmacokinetics of MDMA (“Ecstasy”) in humans.**


**Purpose:** Pharmacokinetic; A further investigation into an “unexpected observation” suggesting “nonlinear pharmacokinetics of MDMA.” (p. 105).

**Design:** Pilot: Between-subjects single-dose study (no placebo control), wherein volunteers evenly divided into groups receiving 50, 100 and 150 mg MDMA (2 per cell). **Final study:** Randomized, placebo-controlled within-subjects design; with all volunteers taking part in all 4 conditions (placebo, 40 mg. amphetamine, 75 mg. MDMA, 125 mg MDMA).

**Subjects:** 14 MDMA-experienced men, aged 21-31, weight 66-83 kg), 6 in pilot study and 8 in final study. Volunteers recruited by word of mouth.

**Criteria for Inclusion** – Healthy as assessed through psychiatric interview, medical examination, ECG, and routine blood, urine analysis. Used MDMA / ecstasy at least 5 times, but no history of substance abuse (save nicotine dependence). Identified as extensive metabolizers (measure of CYP2D6) via dextromethorphan / dextorphan assay. (Same sample used in Mas et al., 1999, Cami et al., 2000).

**Measures:** Concentration of the following measured in plasma and urine; MDMA, MDA, HMMA, HMA, using solid-liquid extraction and gas chromatography with nitrogen specific detection. Measures of substances either made directly or after hydrolysis of glucuronide conjugates. AUC, Cmax, Tmax renal and non-renal clearance calculated for MDMA and MDA. “Blank” urine samples collected pre-drug to verify absence of MDMA metabolites.

**Plasma** – MDMA and metabolites measured in blood, with measures taken at baseline, .25, .5, .75, 1, 1.5, 2, 3, 4, 6, 8, 10, 24 h post-drug.

**Urine** – MDMA and metabolites measured in urine sampled at 0-8 h and 8-24 h post—drug in pilot study and in final study at 0-4 h, 4-8 h and 8-24 h post-drug.

**Other Measures** – Cardiovascular and psychological measures taken; relationship of plasma MDMA to diastolic BP reported here.

**Analysis:** Pharmacological statistics (Tmax, Cmax, AUC) calculated with pharmacokinetics software. Within-subjects comparisons at final study performed with student’s t test. A 1-way between subjects ANOVA used to compare across all doses, including pilot study and final study. Plasma MDMA plotted against measures of diastolic BP.

**Results:** AUC for 125 mg MDMA significantly different from AUC for 75 mg MDMA (paired t test). When combined with pilot studies, authors found that while doses used in study (50 mg, 75 mg, 100 mg, 125 mg & 150 mg) varied by factor of 3, differences in AUC varied by factor of 10. A non-parametric
test comparing 100 mg MDMA to other doses found marginally significant differences between doses (50, 75, 125 and 150 mg, all versus 100 mg). 125 mg MDMA is not bioequivalent to 75 mg. MDMA. Plasma – (Non-renal) clearance dose-dependent. Comparing 8 final study subjects, found 125 mg MDMA non-renal clearance reduced by .5 compared with 75 mg MDMA. Plasma samples compared across 5 subjects, 1 subject per dose, specifically examining HMMA and MDMA. While HMMA is major plasma product at doses of 50, 75 and 100 mg, this ratio reversed at 125 and 150 mg doses, with MDMA superseding HMMA as major plasma product. When plasma MDMA concentrations increase (with higher dose), so does measure of diastolic BP. Urine – MDA and HMA only minor metabolites in urinary recovery study; HMMA and MDMA major metabolites. 50% recovery for MDMA in urine occurred, independent of MDMA dose administered. (Renal) clearance constant. Urine concentration of MDMA increased nonproportionally over doses. Doses increased by factor of 3 but MDMA concentrations increase by factor of 20. Overall Effects: Increasing the dose of MDMA by a factor of 3 increased AUC by a factor of 10 and increased urine MDMA by a factor of 20. When MDMA and metabolites are compared with each other in plasma and urine, and when plasma and urine MDMA and metabolite concentrations are compared across dose, it appeared that while MDMA clearance in urine did not vary greatly with dose, it did vary dose-dependently in plasma. MDA and HMA were only minor metabolites, and unchanged MDMA and HMMA were major constituents in plasma and urine. HMMA was more common than MDMA in plasma at lower doses of MDMA, whereas MDMA was more common in plasma at higher doses. Higher doses of MDMA appeared to be metabolized differently than lower doses of MDMA, with metabolism possibly inhibited by MDMA itself at higher doses. The supralinear increase in plasma MDMA concentration was accompanied by similarly elevated diastolic BP. Adverse Effects: None specifically reported in this paper; however, authors note that at 150 mg MDMA, volunteers experienced psychological and physiological (cardiovascular) effects that precluded using this dose in final study. For more details, see Cami et al., 2000 and Mas et al., 1999. Comments: This paper presents direct evidence for a non-linear relationship between MDMA dose and its clearance in humans. The paper uses the same sample of MDMA-experienced males utilized in other papers by the Spanish team (e.g. Cami et al., 2000 and Mas et al., 1999). The authors believe that their data indicates that MDMA inhibits demethylation, both by acting as a substrate for CYP2D6 and by possibly inhibiting CYP2D6 activity (as suggested by in vitro studies). The findings in this paper, particularly those from the final study suggests that care should be taken when using larger doses of MDMA, as the magnitude of drug effects may not be predictable from those of smaller doses. Specifically, larger doses may produce a non-proportionately higher elevation in diastolic BP. De la Torre’s sample size is small enough to warrant further replication before their conclusions can be treated as representing the general population. However, the nonlinear pharmacokinetics found both across doses and in a smaller within-subjects comparison offer good support for these apparently nonlinear pharmacodynamics.

De la Torre et al. (2000). Pharmacology of MDMA in humans.


Purpose: Neuroendocrine, pharmacological, physiological; Examines and summarizes the effects of various doses of MDMA in humans, including physiological, cardiovascular, psychomotor performance and neuroendocrine responses. Also analyzes metabolism and pharmacokinetics of MDMA. Most of the data presented in this paper has appeared in previous publications, except for a complete chart of
physiological responses for all doses of MDMA investigated and measurements of responses after 100 mg MDMA.

**Design:** All subjects – A randomized, double-blind placebo controlled design was used, wherein each subject received either placebo or a specific dose of MDMA. Doses used were 50 mg (2 / 27), 75 mg (10 / 27), 100 mg (13 / 27), 125 mg (8 / 27) or 150 mg (2 / 27). **Dose Comparison - 8 / 27** participated in a study with a within-subjects design, with each subject taking part in three sessions; placebo, 75 mg MDMA and 125 mg MDMA.

**Subjects:** 27 MDMA-experienced men, ages not provided here. Recruitment information not provided here, but all previous studies conducted by this team recruited subjects via “word of mouth.”

**Criteria for Inclusion –** Healthy, presumably assessed via medical and psychiatric examination, no history of substance abuse other than nicotine dependence, having used MDMA at least 5 times, and absence of any past medical or psychiatric adverse reactions to MDMA. Previous publications indicated that subjects were typed for CYP2D6 activity and found to be extensive metabolizers.

**Measures:** Vital signs, physiological measures – HR, systolic and diastolic BP and oral temperature were measured via vital signs monitor. Pupillary diameter was assessed with a pupil gauge. Schedule of measures not reported. In previous studies, physiological responses to MDMA were assessed at 15, 30, 45, 60 and 90 minutes after drug administration, and after 2, 3, 4, 6, 8, 10, and 24 hours after drug administration. All subjects also underwent continuous ECG throughout the study.

**Psychomotor Performance –** Attention and reaction time assessed via a simple reaction time task. Decision making and attention assessed with the Digit-Symbol task (DSST), a test of visual pattern recognition. Extra-ocular muscle movement was measured via the Maddox-Wing device. Schedule of assessments not reported here, but Cami et al, 2000 indicates measures of psychomotor performance administered at 0, 30, 60, 90 min and 2, 3, 4, 6, 8, 10, 12 and 24 h post-drug.

**Neuroendocrine Response –** Hormone analyses were conducted on blood drawn at the time of drug administration and at 30, 60 and 90 minutes after drug administration, and at 3, 4, and 6 hours after drug administration. Hormone analysis was apparently only measured in subjects who received 75 mg, 100 mg and 125 mg MDMA. Serum cortisol concentration was measured with fluorescence polarization immunoassay, and serum prolactin concentration was determined via microparticle enzyme immunoassay (MEIA).

**Pharmacokinetics –** Detection of MDMA and its metabolites (MDA, HMMA and HMA) were measured in blood drawn at 0, 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 10 and 24 hours after drug administration. Samples were analyzed for MDMA and metabolites with gas chromatography coupled to a nitrogen phosphorus detector.

**Analyses:** MDMA and Metabolites – Cmax (peak concentration), time taken to reach peak concentration (Tmax) and area under the concentration-time curve (AUC) were calculated for MDMA and its metabolites in plasma.

**Results:** Vital signs, physiological measures – All doses above the 50 mg dose increased systolic and diastolic BP, pulse rate and pupillary diameter. Some individuals met criteria for hypertension or sinus tachycardia at doses at or above 75 mg MDMA (Reported in Mas et al, 1999). While all doses where statistical comparisons employed (75, 100 and 125 mg) increased systolic and diastolic BP at 1 and 2 h post-drug, only doses above 75 mg increased systolic BP at 4 h post-drug, and only the 100 mg dose continued to increase diastolic BP at 4 h post-drug. Pulse rate remained significantly elevated (compared with placebo) up to 4 h after drug administration, but only 100 mg and 125 mg MDMA maintained significantly elevated pulse at 8 h after drug administration. Pupillary diameter remained increased for 75 mg, 100 mg and 125 mg MDMA up to 8 h post-drug. Changes in BT were biphasic, with a slight
range .8 mg /lb – 1.9 mg / lb, mean = 1.14 mg / lb. Baseline-after MDMA comparisons made for some decrease at 1 h post-drug and a slight increase at 2 and 4 h post-drug. BT was no longer significantly elevated at 8 h post-drug, when compared with placebo.

**Psychomotor Performance** – MDMA did not significantly affect reaction time at any dose measured, though there was a slight increase in reaction time with doses above 50 mg. MDMA impaired performance on the DSST in a dose-dependent manner. MDMA induced esophoria (convergent squint) as measured via Maddox-Wing device. Impairment on the DSST was significantly different from placebo for 125 mg MDMA at 1 h post-drug. MDMA produced longest decision reaction times and most errors at 1 h and 2 h post-drug.

**Neuroendocrine Response** – Serum cortisol and prolactin concentrations were elevated after all doses of MDMA measured (75 mg, 100 mg, 125 mg), with peak concentration of both hormones appearing at 2 h after drug administration. Plasma MDMA in subjects receiving 100 mg MDMA reached Tmax at 2 h post-drug. Elimination half-life for MDMA was measured at 8 – 9 h. MDA appeared in plasma slowly after MDMA administration, reaching Cmax (13.1 ng / ml) at 5 – 7 h after drug administration, and elimination half-life for MDA estimated at 25 h. Plasma HMMA concentration followed similar pattern as plasma MDMA, and plasma HMA concentration pattern similar to that of MDA.

**Overall Effects**: MDMA increased systolic and diastolic blood pressure and produced elevated pulse rate, particularly at doses above 50 mg. Pupillary diameter was also enlarged after MDMA. The authors found a slight decrease in BT at 1 h after MDMA administration, with BT elevated at 2 and 4 h after MDMA administration, a finding that indicates that the effects of MDMA on body temperature may be complex. The decrease in body temperature occurring 1 h after drug administration is explained as the result of mucocutaneous vasoconstriction. While MDMA produced little or no impairment on a reaction time task, performance on a more complex task requiring decisions about visual patterns was impaired. MDMA produced convergent squint (esophoria), an effect compared with the divergent squint (exophoria) produced by sedatives. MDMA at 75, 100 and 125 mg, increased plasma concentrations of cortisol and prolactin. HMMA (reported as main metabolite in previous papers) in plasma paralleled MDMA concentration, and HMA paralleled that of MDA. As previously noted, the elimination half life of MDMA was measured at 8 – 9 hours while the half-life of MDA was 25 h.

**Adverse Effects**: None specifically measured or reported in this paper beyond individuals who met criteria for hypertension or sinus tachycardia during study and impairment on the DSST.

**Comments**: A large portion of this paper is devoted to summarizing findings already presented in other papers. However, the authors also present information for all measures taken at the 50 mg and the 150 mg doses of MDMA, and the paper describes the effects of MDMA in a larger sample given 100 mg MDMA. This paper is notable in finding that fluctuation in body temperature changes across time after MDMA administration, with an apparent dip in temperature preceding the more familiar rise in body temperature. The authors explain this as the result of altered peripheral vasoconstriction experienced 1 h after drug administration. Otherwise, the data presented in this paper are comparable to findings presented in other papers concerning the physiological and neuroendocrine effects of MDMA in humans.

**Downing (1986). The psychological and physiological effects of MDMA on normal volunteers.**


**Purpose**: Exploratory; pilot study of the acute and sub-acute psychological, neuropsychological and physiological effects of MDMA in humans. “…a pilot study of the effects of a single exposure to MDMA in 21 healthy volunteers…” (p. 336).

**Design**: Uncontrolled single dose one-session design, with drug dosage self-selected by each subject; range .8 mg /lb – 1.9 mg / lb, mean = 1.14 mg / lb. Baseline-after MDMA comparisons made for some
physiological and neuropsychological measures. Additional data gathered via retrospective self-report survey.

**Subjects:** 21 MDMA-experienced volunteers (13 men, 8 women) aged 20-58. No information on subject recruitment provided; author states volunteers were “well known” to clinic staff, so perhaps recruited via “word of mouth.”

Criteria for Inclusion – At least 1 previous experience with MDMA, and good mental and physical health as assessed through self-report and by clinic staff. “…subjects personally known to a member of the research staff, stated that they were in good health (with two exceptions), and were considered mentally stable, both by their own account and by the staff.” (p. 336). Health exceptions: glaucoma (1 woman), legal blindness (1 man).

**Measures:** Alterations in Consciousness – Alertness, lucidity of thought, as assessed by clinicians, who assayed subject’s orientation in time, evidence for perceptual alterations, quality of thinking. Observers requested self-reports from patients during or after peak effects of MDMA.

Neuropsychological function – Digit repetition, unspecified memory task, multiplication task (possibly mental multiplication), hypothetical decision making task and finger to nose task, with at least memory task and finger to nose task conducted at baseline and again during peak effects of MDMA.

Physiological Effects / Vital Signs – BP and pulse measured in all 21 subjects, with measures taken during baseline, 30 minutes, 1, 2, 3, 4, 5, 6, and 24 h post-drug. Pupillary diameter measured in 10 / 21 subjects. ECGs were performed on 5 of 21 subjects.

Adverse Effects – Measured during session for 10 / 21 subjects, probably via observation of volunteers and requests for information about subjective effects by staff.

Blood Chemistry - A 25-item standard panel, including total protein, albumin, globulin, albumin / globulin ratio, bilirubin, total, direct and indirect serum glutamic oxalotransminase, alkaline phosphatase, gamma-glutamyl peptidase, serum glutamic-pyruvic transaminase, lactic dehydrogenase, blood urea nitrogen, creatinine, blood urea nitrogen / creatinine ratio, uric acid, calcium, phosphorous, cholesterol, triglycerides, glucose, sodium, potassium and chloride. 11/ 21 volunteers provided blood samples at preingestion, 6 h post drug and 24 h post drug, 16 / 21 provided preingestion and 6 h post drug samples. MDMA Experience Survey – 14 / 21 completed a survey containing items on subject demographics, features of past MDMA experience, general health, use of other psychoactive drugs, adverse effects of MDMA, possible effects of MDMA on social adjustment, preferred frequency of MDMA use and recommendations for legal status.

Analyses: No formal analysis performed. Baseline measures were compared with on-drug and post-drug measures without using tests of significance or effect size. Blood chemistry panels assessed via comparison with published norms. Number of responses counted on survey.

Results: Alterations in Consciousness – Volunteers reported experiencing euphoria, physical and emotional energy. No evidence of confused thinking or hallucinations (visual or auditory) and subjects’ attention focused on present rather than past or future. Euphoria, time focus diminished at 3 h post-drug. No depression / crash observed 24 h after dose (in 12 / 21 returning 24 h post-drug). 2/ 12 reported more sleep than usual; no insomnia. Several (unspecified) reported slight enhancement of mood at 24 h.

Neuropsychological Function – 10 / 21 volunteers examined during peak drug effects. Digit repetition and short term memory test scores did not differ between baseline and peak drug effects. 3 / 10 volunteers had difficulty with multiplication during peak drug effects; volunteers stated they had “difficulty focusing on” task. 4 / 10 volunteers gave idiosyncratic responses to decision-making task (implying impaired judgment), and 2 / 10 volunteers had trouble with finger to nose task.

Physiological Effects – BP and pulse increased in all 21 subjects. Mean peak increase in BP occurs within an hour of ingestion. One case (at 1 mg / lb) of diastolic BP at 200 / 120 in woman, aged 58. Subject on highest dose (1.9 mg / lb) had strongest cardiovascular responses (increase in pulse and BP) but no physical discomfort during session. 14 / 21 volunteers remained after 6 h post-drug, and BP fell below pre-drug levels in 9 / 14 subjects. 12 volunteers measured at 24 h, 5 / 12 still below pre-drug levels. Pupil dilation measured in 10 / 21 subjects; pupillary dilation increased from baseline to peak
drug effects for 9 / 10 volunteers (no change in blind subject). 5 / 21 volunteers given ECGs; all ECGs normal.

Blood Chemistry Panel – No positive findings in the blood chemistry panel. Glucose elevated in 6 subjects, and potassium and sodium in 5 subjects, but difficult to interpret these differences due to study’s lack of controls for pre-session food or drink consumption.

MDMA Experience Survey – 14 / 21 volunteers responded; responses to selected items listed here.

General Health – All volunteers considered themselves healthy. Woman with glaucoma had used MDMA 13 times previous to study with no ill effects. 70% (10 / 14) reported that MDMA had no effects on health and 4 did not respond. MDMA bad for health in own opinion? 5 / 14 reported “good,” 1 / 14 “bad” and 6 did not respond. Negative Effects – 80% reported jaw clenching, 60% reported headaches and 20% eyelid twitches. No one objected to these effects. Reported mental deficits “during or after MDMA” not described, reported as “minimal and hard to describe.” Possible Effect on Social Adjustment – 6 / 14 reported major life change after MDMA experience(s); two marriages, two divorces, also reported finding better jobs. All (14) wished to continue using MDMA and 90% stated relationships improved after MDMA use. 10% either didn’t answer or reported no change in relationships after MDMA and none reported relationships worse after MDMA. Preferred Use, Legal Status – Preferred frequency of use: range monthly – every 4 months, mean 2.2 mo. Preferred dose; range, 75-200 mg, mean 158 mg, (near mean dose, 165 mg, chosen for study). Legal status: 11/ 14 answered, answers open-ended. Either “MDMA used with therapists and spiritual leaders only,” “prescription only” and “over the counter,” with 8 / 11 supporting legal controls and 3 / 11 supporting over the counter use. 3 / 11 supported “prescription,” 1 / 11 “therapist only” and 4 / 11 both “prescription” and “therapist.”

Overall Effects: MDMA reliably increased mood, emotional and physical energy, blood pressure and pulse. MDMA did not produce abnormal cardiac activity, as assessed through ECG. While volunteers did not become confused, did not hallucinate and retained short term memory, observers reported that people had some difficulty concentrating during peak drug effects and judgment was impaired in some subjects. People experienced some adverse effects but were not troubled by them. MDMA did not affect blood chemistry. Most volunteers personally felt MDMA good for them, with only one dissenter. People reported that MDMA had little or no effects on their social adjustment, and reported some apparent life benefits to MDMA use. While all preferred legal MDMA, most also preferred legal controls on use of MDMA.

Adverse Effects: During Session – 3 / 10 volunteers experienced nystagmus in all directions, 6 / 10 reported jaw clench, increase in jaw reflex, deep tendon reflexes enhanced in 8 / 10 subjects, finger-to-nose test impaired in 2 / 10 subjects, gait affected in 7 / 10 subjects, difficulty concentrating (as assessed through multiplication task) in 3 / 10 subjects, judgment impaired (as assessed through decision making in hypothetical situations) in 4 / 10 subjects, 1 / 10 reported nausea and vomiting. Appetite suppressed in 10 / 10 individuals (or perhaps all 21 individuals). Apparent hypertension in one subject. No evidence of insomnia (but author notes that study began in the morning, so not good for assessing distortions in sleep function).

Self-report – Data gathered from 14 / 21 subjects. 80% of sub-sample reported jaw clenching, 60% headaches and 20% eyelid twitches.

Comments: This is one of the first studies attempting to record the acute and sub-acute effects of MDMA, and it does contain one of the most extensive arrays of measures (from subjective experience to blood chemistry). It may be the first paper attempting to assess MDMA’s effects on organ function in humans with a prospective design and using blood chemistry panels. While impressive for its breadth, the study can only be viewed as exploratory due to a number of methodological flaws. No formal analysis is used for comparing baseline with on-drug scores, observation is used rather than objective measures in some cases and in other cases, the objective measures used are not specified (as with the measure of short-term memory or judgment). Different assessments are performed on different sub-samples of volunteers without any means for associating responses on one measure with responses on another measure, since composition of each sub-sample is unknown. Furthermore, it is an uncontrolled, single-dose study with no placebo condition. Nevertheless, the paper does indicate that even when
minimal inclusionary criteria are used, MDMA can be administered without serious psychological or physical distress.

Fallon et al. (1999). Stereospecific analysis and enantiomeric disposition of 3,4-methylenedioxyamphetamine (Ecstasy) in humans.


Purpose: Pharmacokinetic. To investigate “the pharmacokinetic properties of the enantiomers of MDMA in humans” (p. 1059).

Design: Single dose, non-blind within-subjects design. All volunteers took part in treatment condition, receiving 47.5 mg. MDMA hydrochloride (equivalent to 40 mg. MDMA base), with pharmacokinetic parameters calculated from blood sampled over a 24 h period and urine collected over a 72 h period.

Subjects: 8 MDMA-naïve males, ages 22-32, 7 Caucasian, 1 Asian. No information on subject recruitment provided.

Criteria for Inclusion – Healthy, as assessed through physical examination. Normal HR, BP and liver function as assessed through laboratory tests. Not currently receiving any drugs for medical condition and not recently involved in “any other study of a similar nature.” (p. 1060).

Measures: Plasma – Plasma levels of MDMA (both R and S isomers) and metabolites performed through capillary gas chromatography (CG). Plasma concentrations measured from blood collected at .5, 1, 2, 4, 6, 8, and 24 h post-drug (MDMA).

Urine - Urine levels of MDMA (R and S forms) and metabolites measured through CG. Metabolites measured in urine sampled at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 and 24-48 and 48-72 h post-drug. (Authors also sought to validate method and assess its sensitivity through measuring accuracy across volunteers and over time, optical purity and limits of quantification).

Analysis: Cmax, Tmax and half-life calculated, with at least three data points used for each calculation. AUCs (estimated with trapezoidal method), apparent oral clearance and renal clearance all calculated. Values for each enantiomer or its metabolite compared with paired t tests. (Utility of using drug or metabolite enantiomeric composition for forensic applications also assessed via regression).

Results: Plasma – Maximal plasma concentration reached for both S and R MDMA at 4 h post-drug, mean R(-)MDMA versus mean S(+)MDMA (33.7 + / - 14.9 Ug / L vs. 21.2 + / - 10.8 Ug / L); plasma concentrations of R and S isomers of MDMA significantly different, with more R than S isomer found. Tmax was between 4 and 8 h post-drug for MDMA. Fewer analyses conducted for MDA because later Tmax produced fewer data points. The enantiomeric ratio between R and S MDA (R: S) initially decreases, with low at 2 h post-drug (0.02 + / - .03), and then it steadily increases 1.29 + / - .15 at 24 h.

Urine – Most material recovered at 24 h post drug, <2% recovered in 24-72 h period. Mean R(-)MDMA recovered = 21.4%, mean S(+)MDMA = 9.3%, with significant differences in recovery of R versus S MDMA, with greater recovery for R isomer. Quantification of both enantiomers at 24 h only possible for 1 subject, and only the R enantiomers in 4 subjects, with only in one case could R(-)MDMA be detected in 48-72 h period. MDA also excreted within 24 h, recovering being < 1% for both enantiomers. Ratio of R to S MDMA (R: S) increased from 1:4 in 0-2 h period to 4.2 in 12 h sample. Mean ratio of R to S MDA (R:S) = .48 at the 2-4 h period to 1.2 at the 12-24 h post-drug sample.

Pharmacokinetic Variables - Authors provide evidence for enantioselective disposition of MDMA in humans, with shorter half-life, reduced AUC and increased clearance for S-isomer (the more active form), and more extensive distribution for S-isomer than for R-isomer.

Overall Effects: Human metabolism of S(+)MDMA (the more active form) was more rapid than that of the R isomer. S(+)MDMA was cleared more extensively in the bloodstream, as indicated by comparisons between levels of S(+)MDMA and R(-)MDMA in plasma, and the less-active R isomer was predominant in urine. In contrast, there was less difference between R and S isomers of MDA in urine.
**Adverse Effects:** None reported in this paper.

**Comments:** This paper is one of a few that examines the pharmacokinetics of two enantiomers of MDMA separately. Apparently, the S isomer seems to be more rapidly cleared from the body than the R isomer. More R(-)MDMA was excreted in urine unchanged, compared with S(+)MDMA. The S isomer seems to be more extensively transformed into MDA or HMMA, another metabolite not measured in this study. While sample size is still small in this paper, it is notably larger than the sample used in the Lanz paper, and this increases the chance that the findings in this paper accurately represent metabolic processes in the general population.

**Gamma et al. (2000).** 3,4-methylenedioxymethamphetamine (MDMA) modulates central and limbic brain activity as measured by [H215O]-PET in healthy humans.


**Purpose:** Neuropsychological, brain imaging; “…to elucidate changes in regional cerebral blood flow (rCBF) produced by a single oral dose of MDMA in MDMA-naïve human subjects.” (p. 389). Specific hypothesis tested – that MDMA-induced changes in CBF would be correlated with MDMA-induced changes in mood and state of consciousness as assessed through psychometric measures.

**Design:** Randomized double-blind placebo-controlled within-subjects study, with all volunteers taking part in 1 placebo session and 1 MDMA session, receiving 1.7 mg / kg MDMA. Volunteers received 4 PET scans per session (2 during control task / resting state, 2 during performance task).

**Subjects:** 16 MDMA-naïve volunteers (6 women, 10 men, mean age 26 + / - 2.5 years) recruited from university students and hospital staff.

Criteria for inclusion – Lack of major medical or psychiatric illness as assessed through medical history, psychiatric interview, physical exam, ECG and blood analysis. Lack of history of psychiatric illness for self and 1st-degree relatives, lack of any psychiatric, psychopharmacological or psychotherapeutic treatment, and no history of substance abuse.

**Measures:** PET – 4 60-second H2[15-O]-PET scans with PET set in 3D-acquisition mode. PET sessions conducted 75 min after drug administration (placebo or MDMA), at predicted time of peak drug effects.

Mood – Measured via AM, administered 4 h post-drug, after most drug effects have subsided, but with responses referring to subject’s experience during PET scan.

Alterations in Consciousness – Assessed via ASC, measured 4 h post-drug, after most drug effects have subsided, but with responses referring to subject’s experience during PET scan.

Adverse Effects – Measured via modified LC (“jaw clenching” added to scale), administered during session.

Task – Continuous Performance Task (CPT) used to standardize cognitive activity across volunteers and conditions. In this task, volunteers click a mouse button with right index finger whenever they view target sequence (“A” followed by “X”) on screen, with stimuli presented for 120 ms in center of screen. Control task = Volunteers directed to relax and watch screen, and target sequence removed from display. Control task replaced with simple “resting state” in 5 / 16 subjects.

Physiological (Cardiovascular) Effects – BP and HR measured throughout session.

**Analysis:** PET – Comparisons between drug (placebo or MDMA) and task (CPT or control) conditions made on a voxel by voxel basis using t-statistic and linear contrasts with opposite weights used for contrasting, when contrasting between conditions. Resulting maps transformed to unit normal distribution. Significance set at p = .05 and corrected for multiple comparisons.

Mood and Alterations of Consciousness – AM (mood) and ASC (alterations in consciousness) scores analyzed through a MANOVA, within-subjects design, with drug (placebo or MDMA) as within-subjects factor. Post-hoc comparisons made with Tukey’s test.
Cardiovascular Effects - A 2-way within-subjects ANOVA conducted on cardiovascular data, with drug (placebo or MDMA) as within-subjects factor. Post-hoc comparisons made with Tukey’s test.

Adverse Effects – Not reported; probably a two-way ANOVA, within-subjects design with drug (placebo or MDMA) as within-subjects factor, and with post-hoc comparisons made with Tukey’s test.

Task – Drug effects on CPT and control task measured through within-subjects MANOVA, with drug (placebo or MDMA) as within-subjects factor. Post-hoc comparisons made with Tukey’s test.

Psychological Effects with PET – Correlations between mood (AM) and altered state of consciousness (ASC) scores and PET scan made for MDMA condition only. An ANCOVA model was performed with psychometric scores as covariates and mean scan over all tasks (CPT / control or resting), with p set at .05, corrected for multiple comparisons (procedure not described).

Results: PET – Analysis found main effects for drug (MDMA vs. placebo) and task (CPT vs. control task / resting) but no task x drug interactions, indicating that task did not affect MDMA’s effects on rCBF.

MDMA Effects – Compared with placebo, MDMA increased rCBF in ventromedial prefrontal area (L, R), inferior temporal region, also referred to as fusiform gyrus (L, R), occipital lobe (L, R) and cerebellum (widespread activation throughout cerebellum). Compared with placebo, MDMA decreased rCBF in dorsal posterior and anterior cingulate (L, R), precentral, paracentral cortex (hemispheres not listed), superior temporal gyrus (L, R), insula (L, R) and dorsomedial thalamus (L, R). Decreases also seen in R uncus and R parahippocampus and L amygdala.

Task Effects – When compared with control task, the CPT produced an increase in rCBF in; R medial occipital cortex, L precentral gyrus, L superior temporal gyrus, L superior frontal gyrus and L anterior cingulate. Compared with the control task, the CPT produced decreased rCBF in; R medial temporal gyrus, L superior temporal gyrus, R precuneus, with trend for difference in R medial frontal cortex.

Mood – When compared with placebo, MDMA produced increases in well-being, heightened mood, self-confidence, extroversion and emotional excitability (emotionality, sensitivity) as assessed by AM.

Alterations in Consciousness – When compared with placebo, MDMA increased all three item-clusters of the ASC; OB, VR and AED. Increase in OB scores after MDMA largely due to increase in positive mood, derealization and depersonalization. Increase in VR due to increased ratings of change in meaning of percepts, visual illusions, facilitated recall, facilitated imagination, but no hallucinations reported. Volunteers also reported intensification of tactile awareness. Increase in AED chiefly due to increases in thought disorder and loss of body control.

Correlations between Psychometric Scores and PET – None of the correlations between drug-induced changes in rCBF and AM (mood) scores or ASC (alterations in consciousness) scores reached statistical significance. Significance value lowered for exploratory purposes. Correlations reaching significance under the lower p value are as follows; Heightened mood positively correlated with CBF in the R parietal region and heightened mood negatively correlated with CBF in the R caudate nucleus; Extroversion (on AM) correlated positively with CBF in L precuneus.

OB score (on ASC) positively correlated with CBF in the R lateral prefrontal cortex, R supramarginal gyrus and R fusiform / lingual gyrus; AED score (on ASC) correlated positively with CBF in L amygdala, L superior temporal gyrus and AED negatively correlated with CBF in the R inferior temporal / fusiform gyrus;

Continuous Performance Task (CPT) Performance – No significant differences between task performance under MDMA and performance under placebo. Trend for greater number of errors under MDMA compared with placebo (p. < .06), with errors increasing from .15% errors to .3% errors, and trend for decrease in correct responses under MDMA compared with placebo (p. <.09), with 99% correct responses under placebo and 97.9% correct under MDMA.

Cardiovascular Effects – MDMA produced significant increase in systolic and diastolic BP, both compared with placebo and compared with pre-drug levels, with peak increase between 75 and 150 min post-drug. Changes in HR data not reported.

Adverse Effects – Jaw clenching, lack of appetite, thirst, sweating, difficulty concentrating all reported by volunteers after MDMA (see details in Adverse Effects). Volunteers did not report any great discomfort from any of the adverse effects.
**Overall Effects**: MDMA consistently produces changes in regional cerebral blood flow, as compared with placebo, and these changes were not moderated by performing a task demanding attentional resources (the CPT). Increases in rCBF were seen in some brain areas related to emotion, such as the cingulate (CBF increase in ventral anterior cingulate and CBF decreases in dorsal anterior and posterior cingulate), left amygdala, perhaps pre-frontal regions (increase in CBF in ventromedial prefrontal cortex) and even the cerebellum. Performance on a task that requires visual attention and response to specific stimuli was slightly impaired on MDMA (compared with placebo). The authors’ hypothesis was not confirmed; a few relationships between CBF and psychometric scores were found, but correlations fell below the pre-set significance value. These include an association between the OB score (measuring positive mood and pleasant derealization) and CBF in the right lateral prefrontal cortex, the right supramarginal gyrus and the right lingual / fusiform gyrus, an association between AED (fear of ego dissolution and losing control) with CBF in the left amygdala, the left superior temporal lobe and a negative association between AED and CBF in the inferior temporal lobe / fusiform gyrus. MDMA was well tolerated in this sample of drug-naïve subjects, and they were not overly troubled by the minor discomforts of the experience (such as jaw clenching, lack of appetite).

**Adverse Effects**: Jaw clenching (64%), lack of appetite (63%), sweating (50%), sensitivity to cold (50%), dry mouth / thirst (50 %), palpitations (38%) and difficulty concentrating (50%), though difficulty concentrating also reported in 31% after placebo.

**Comments**: This was an ambitious paper packed with data. Not only did the authors attempt to compare rCBF under MDMA with rCBF under placebo, but they also attempted to find relationships between brain activity and scores on measures of mood and alterations in consciousness. They were not entirely successful in this ambitious goal, since the relationships they did report were only uncovered after using a more lenient test of significance (i.e. a higher probability value). Yet the authors report that some of their findings, such as an association between euphoria and decreased CBF in the left amygdala, have been replicated in investigations using other drugs (like amphetamine.) They also acknowledged that it is possible that MDMA-associated changes in CBF may not be related to psychological effects. Instead, it might be due to direct cerebrovascular effects that uncouple CBF from neuronal activity. Still, as an exploration of the connections between subjective experience and brain activity, this study stands out as a good preliminary effort. This paper also demonstrated that PET can be conducted on MDMA-naïve volunteers while they experience the peak effects of MDMA without severe psychological distress.

**Greer & Tolbert (1986). Subjective reports of the effects of MDMA in a clinical setting.**


**Purpose**: Summary of qualitative outcome data, preliminary psychotherapeutic outcome study; Authors present effects of MDMA-assisted psychotherapy immediately after 1 MDMA sessions and again 2 months to 2 years after sessions. “…summary report of data gathered from the first 29 people administered MDMA in a clinical setting.”

**Design**: Non-randomized, without blinds or placebo controls; used in context of MDMA-assisted psychotherapy; number of sessions undefined, all patients took part in at least 1 MDMA-assisted psychotherapy session, receiving 75-150 mg MDMA (1 used 200 mg)., with booster dose of 50-75 mg. offered as effects of initial dose subsided and 20-40 mg propanolol or 5 mg diazepam offered to unspecified number of patients to reduce sympathomimetic effects. L-tryptophan offered to unspecified number of patients to reduce discomfort later in session.

**Subjects**: 29 individuals receiving MDMA-assisted psychotherapy conducted in California or New Mexico from 1980 to 1983. Information on subjects’ age, gender or past experience with MDMA not provided, but examining paper indicates at least 2 women took part in study and eldest subject aged 78. Patients recruited through referrals from friends or therapists; none received therapy from author’s practice.
Criteria for Inclusion – No history of hypertension, heart disease, hyperthyroidism, diabetes, hypoglycemia, seizure disorder, glaucoma, or liver dysfunction. Not currently pregnant. No history of “vocationally disabling” psychological conditions. Willingness to deal with any disturbing experience they might have while on drug. Health Exceptions - 1 subject with “essential hypertension” controlled with medication, 1 had macular edema and ocular implant.

Measures: Questionnaire - Verbally conducted interview after session(s), written follow-up questionnaire administered 2 months – 2 years later. Questionnaire contained items concerning benefits during session, undesirable effects, realization of the session’s purpose, (following refer to post-session) change in psychiatric disorders, mood changes, attitudinal changes, belief changes, relationship changes, occupation changes, activity changes, spiritual and physical practice changes, substance use changes, changes in life goals, changes in experiences sought. Changes in experiences avoided, and changes in attitudes preventing self-actualization

Analysis: No formal analyses applied to data; descriptive information (number of patients experiencing a particular effect) presented. Data presented in narrative form.

Results: Session and Short-term Sequelae, Benefits during session – All patients in group or couple sessions (27 / 29) experienced increased closeness, intimacy. All patients (29 / 29) reported positive changes in their attitudes or feelings. 22 / 29 reported cognitive benefits during session. 5 / 29 reported “clear cognition.” Undesirable Effects – All (29) reported some undesirable effects during session. All (29) reported some undesirable physical effects, 16 / 29 reported undesirable emotional effects and 4 / 29 reported undesirable cognitive effects during session [See details in “adverse effects”]. Realization of Session’s Purpose – 28 / 29 had goal for session; 16 / 28 felt goal completely realized after session, 4 / 28 felt significant progress had been made toward goals post-session, 7 / 28 felt some goals realized while others were not realized post-session and 1 / 28 felt no goal beyond goal of satisfaction of curiosity realized after session.

Post-session Changes, Changes in Psychiatric Disorder - 9 / 29 had minor psychiatric disorders (5 with dysthymia / depression, 3 personality disorders, 1 anxiety disorder). 9 / 9 with disorders reported significant relief from problem. 2 / 9 reported “full and lasting remission” (follow-up after nine months), 7 / 9 reported improvement. 1 / 29 previously without diagnosis experienced anxiety attacks post-session and entered long-term therapy (but did not regret MDMA session). Mood Changes – 18 / 29 reported positive changes in mood post-session, mostly good feelings and mood elevation, duration, several hours – several weeks, average 1 week post-session. 2 / 29 reported increased alertness, and 1 / 29 more relaxation. Attitudinal Changes – 23 / 29 reported positive attitude changes and 7 / 29 reported negative attitude changes post-session. Belief Changes – 16 / 29 reported persisting belief changes post-session. Relationship Changes – 29 / 29 reported positive relationship changes post-session and 2 / 29 reported negative relationship changes post-session. Positive changes lasted a few days to two years (at follow up). 14 / 29 reported positive changes in relationships with people besides spouse. Occupation Change – 16 / 29 reported positive occupational changes and 2 / 29 reported negative occupational changes. 1 / 29 changed jobs post-session. Activity Changes – 6 / 29 reported changes in non-work activities (hobbies, spiritual activities) post-session, with all changes either positive or neutral. Spiritual and Physical Practice Changes – 14 / 29 reported positive changes in spiritual or physical practices (i.e. meditation, exercise). 2 / 29 experienced MDMA-like states during meditation. 3 / 29 started new exercise programs, 2 / 29 increased exercise, 1 / 29 changed diet (more “health food”). Substance Use Changes – 14 / 28 reported reduction in use of psychoactive substances and 3 / 28 reported increased use of psychoactive substances. 2 / 28 (the only cocaine users in sample) reported abstention from cocaine (1) or decrease in desire for it, but without indication of changed use (2). Changes in Life Goals – 15 / 29 changed life goals post-session, all patients implying positive changes. Changes in Experiences Sought Out – 9 / 29 reported positive changes in experiences sought in life (in relationships, life goals). Changes in Experiences Avoided – 9 / 29 reported positive changes in experiences avoided (avoiding negative goals or behaviors). Changes in Attitudes Preventing Self-Actualization – 13 / 29 reported positive changes in these attitudes (presumably a reduction in them), including increased insights into psychological problems
(7 / 29), reduced guilt (3 / 29), fewer beliefs about limited possibilities (2 / 29), less self-defeat and less defensiveness (1 / 29 each).

**Overall Effects:** MDMA-assisted psychotherapy did not produce any severe physical or psychological distress during the session. Most people experienced positive changes in emotion, self-awareness and (when applicable) increased closeness and intimacy with others during the session, and most also experienced some minor adverse effects as well. In all but one case, people experienced positive change or no change in psychiatric function after MDMA, and most reported improvements in previous psychiatric problems. One subject experienced anxiety attacks post-session, attributed them to the MDMA-assisted session, but did not regret having undertaken this session. Most patients reported positive changes in attitudes, beliefs and behaviors, with only a few negative changes (many related to state immediately post-session). Changes included greater commitment to goals, more open communication in relationships, improvement on the job (either feeling better on the job or actually improved conditions) and changed beliefs about the self, but with a few reports of post-session difficulty on the job and relationship break-up. Effects on substance use are mixed, with substance use sometimes increasing and sometimes decreasing post-session. Patients felt their changes in life goals were positive; often with reported changes toward more inner-directed or spiritual life goals. Follow-up questionnaires suggested that improvement may persist for months and up to 2 years. Overall, patients reported more gains than losses after MDMA-assisted therapy, but the treatment did cause some difficulties and problems.

**Adverse Effects:** During session – Lack of appetite (28 / 29) – none found it unpleasant, fatigue (4 / 29), jaw-clenching, teeth shaking (22 / 29), with jaw clenching relieved by diazepam for 2 / 22 and by propanolol in 2 / 22 cases (propanolol worsened jaw clenching for 1 subject), nausea (7 / 29), muscle tension / tightness (6 / 29), nervousness / anxiety (5 / 29), reported impaired gait (3 / 29), 2 sweating (2 / 29), feeling cold (2 / 29), brief sadness or fear (3 / 29). Dose x Age - Oldest subject, aged 78, received highest dose (200 mg, after no response at lower doses) and had highest number of undesirable effects; nausea, vomiting, jaw clenching, less taste for alcohol (immediately post-session?), strong body odor, urinary urgency, blurred vision, brief short-term memory loss, brief impairment of depth perception and hallucination, with effects continuing for evening and day after (lack of appetite, insomnia, jaw clench through sleep, fatigue, impaired gait for 2 days. All other effects listed by 1 subject only. Post-session – Fatigue (16 / 29), insomnia (11 / 29), jaw clenching (3 / 29), muscle tension (2 / 29), stomach upset (2 / 29), depression (2 / 29), All other effects listed by 1 subject only. Note: Post-session appearance or anxiety attacks for 1 subject.

**Comments:** This is the first published paper describing outcomes after MDMA-assisted psychotherapy, and the collected reports indicate that MDMA sessions did benefit most subjects, though it caused harm on one occasion. People had more positive attitudes about themselves and their life-goals post-session, and they reported strengthened relationships with others. However, it is difficult to draw conclusions about the utility of MDMA-assisted therapy on the basis of this paper. The study had no comparison group and neither patient nor therapists were blind to treatment. Furthermore, many of the patients were directly reporting responses to the therapists, and may have been motivated to suppress any report of lack of benefit or occurrence of harm after an MDMA session in order to please the therapist or to justify their own participation in MDMA-assisted therapy. However, despite these problems, the study suggests that, at least when conducted using Greer & Tolbert’s methods, MDMA-assisted psychotherapy produces little or no detected harm to most participants and does some good in many cases.

**Grob et al. (1996). Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations.**

**Purpose:** Exploratory neuropsychological, neurophysiological and neuroendocrine study. “…inquiry into MDMA’s effects into central nervous system function.” (p. 104). Investigates elements of subjective experience and physiological effects in MDMA-experienced humans.

**Design:** Randomized double-blind mixed within-subjects / between-subjects design. All volunteers participated in all 3 conditions (placebo, MDMA-dose 1, MDMA-dose 2). 2 of 4 different dosages assigned to each subject, with doses ranging from .25 mg / kg to 1 mg / kg. 1 dose volunteers received always .25 mg / kg away from the other. No information on scheduling; on the basis of knowledge of studies, probably approximately 2 weeks between each session.

**Subjects:** 6 MDMA-experienced subjects, gender and age range not reported here. Recruited through local advertisements.

**Criteria for Inclusion** – Lack of history of major medical or psychiatric illness, no history of substance abuse or seizure disorder. Volunteers abstained from psychoactive medication or illicit drugs 1 month prior to sessions.

**Measures:**

- **Mood** – STAI (state anxiety scale only) and the POMS, with measures taken at baseline and immediately after session.
- **Alteration in Consciousness** - The ASGP, administered at 15-minute intervals beginning 1 h pre-drug and continuing the duration of the session.
- **Physiological Effects** – BP, HR and oral BT measured at 30-min intervals, with 4 samples pre-drug administration and 12 samples taken post-drug.
- **Neuroendocrine measures** – ACTH and prolactin concentration in blood measured. Blood samples taken at 30-minute intervals beginning 2 h before drug administration (4 samples) and continuing for 6 h post-drug (12 samples drawn). ACTH was measured through a two-site IRMA procedure and prolactin was measured through a standard radioimmunassay.

**Analyses:** Tests of significance were not conducted in this paper. Change (delta) scores calculated by subtracting average pre-drug measures from each post-drug measure, with measures have been plotted out for each of the four dosages plus placebo.

**Results:**

- **Mood and Alteration in Consciousness** - Positive mood increases after MDMA, increasing in a dose-dependent manner in doses ranging from .25 mg / kg to 1 mg / kg.
- **Physiological Effects** – .25 to 1 mg / kg MDMA modestly increase HR and BP, no clear increase in BT. HR and BP increase in a dose-dependent manner, whereas body temperature does not appear to increase in a dose-dependent manner with these dosages (.25 mg / kg to 1 mg / kg).
- **Neuroendocrine measures** – Threshold dose for stimulating ACTH and prolactin is between .5 and .75 mg / kg of MDMA. Peak elevation of both hormones appears between three and four hours after drug administration, (examining time course plot).

**Overall Effects:** All volunteers tolerated MDMA at doses of .25 mg / kg to 1 mg / kg. They reported increases in arousal (alertness) and positive mood after MDMA. In doses of .25 mg / kg - 1 mg / kg, MDMA produces positive mood and a small increase in HR and blood pressure, without a great deal of state anxiety. Level of hormones thought to be related to serotonin function also increased with these low to moderate doses of MDMA.

**Adverse Effects:** Adverse effects are neither reported nor measured in this paper.

**Comments:** This paper describes the first double blind, placebo-controlled laboratory study of MDMA in humans. This paper represents preliminary findings, and the results are not subjected to formal analyses, though they are plotted out in time-course charts. However, it does offer information on the effects of a range of low to moderate doses of MDMA. Surprisingly, mood, physiological and neuroendocrine effects appear even at these relatively low doses. The sample size is small, making generalizations to general population difficult. The study this paper describes is part of a larger study that includes investigating the effects of the 4 doses of MDMA described and 6 doses above 1 mg / kg. This paper indicates that these doses of MDMA can be administered to MDMA-experienced volunteers without any severe psychological or physiological distress.
Grob et al. (In Preparation). Psychological, physiological and neuroendocrine effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") in healthy humans.


**Purpose:** Neuropsychological, neurophysiological, neuroendocrine: A dose-response study performed to investigate the safety and tolerability of a range of doses of MDMA, with examination of psychological, neuroendocrine, and physiological effects.

**Design:** Ascending-dose, randomized, placebo controlled, mixed-model design, with drug state (placebo versus MDMA) a within subject factor and drug dose (.25, .5, .75, 1, 1.25, 1.5, 1.75, 2, 2.25 or 2.5 mg / kg) as a between subjects factor. All subjects took part in 3 conditions (placebo, MDMA-dose 1, MDMA-dose 2), with second dose of MDMA .25 mg / kg higher than dose 1. Each session approximately 2 weeks after previous session. Subjects: 18 MDMA-experienced subjects, 13 men, 6 women aged 19-75. Subjects recruited through local advertisements. 10/18 subjects also represented in Chang et al, 2000, 6/18 represented in Grob et al, 1996 and 14/18 represented in Boone et al (unpublished) neuropsychological assessment study.

**Criteria for Inclusion**
- Good health as assessed through medical examination and psychiatric interview.
- Used MDMA at least 3 times, with duration of use lasting at least 1 year. No personal or family history of major psychiatric disorders (in 1st degree relatives). No history of substance abuse (except for MDMA, in the case of 2/18 subjects). Not on any psychoactive medication and not taking illicit drugs for approximately 1 month.

**Measures:**
- Mood Measured via POMS. Anxiety measured via STAI State anxiety scale. Both measures taken at baseline and immediately after session. Alteration in Consciousness ASGP, administered at 15 minute intervals beginning 1 h pre-drug and continuing until 6 h post-drug.
- Physiological Effects: Oral BT, systolic and diastolic BP and HR measured, with measures taken at 30-minute intervals, with 4 pre-drug measures (2 h, 1.5 h, 1 h and .5 h pre-drug) and 12 taken after drug administration from 0 h to 6 h post-drug. Neuroendocrine measures: Blood samples drawn at 30-minute intervals beginning 2 h pre-drug up to 6 h post-drug. Serum concentration of cortisol measured; details on process unavailable at present. Serum ACTH concentration was measured via two-site IRMA procedure and serum prolactin concentration measured through standard radioimmunassay.

**Analysis:**
- Psychological Effects: A 2-way mixed measures ANOVA performed on ASGP scores averaged over 0 to 6 h post-drug, with drug (placebo vs. MDMA) as a within-subjects factor and dosage (.25, .5, .75, 1, 1.25, 1.5, 1.75, 2, 2.25 or 2.5 mg / kg MDMA) as a between subjects factor. Peak change from baseline for all doses analyzed via one-way ANOVA with time of measure taken during MDMA, but not placebo, administration as within-subjects variable. Post-hoc comparisons made with Tukey's test.
- Physiological Effects: A 2-way mixed measure ANOVA conducted on measures of HR, BT, systolic and diastolic BP averaged from 0 to 6 h post-drug, with drug (placebo vs. MDMA) as a within-subjects factor and dosage (.25-2.5 mg / kg MDMA) as a between-subjects factor. A one-way repeated-measures ANOVA performed on measures over time taken during MDMA, but not placebo, administration, with time of sample as within-subjects factor. Post-hoc tests conducted with Tukey's test.
- Neuroendocrine Measures: A 2-way mixed measure ANOVA was conducted on serum prolactin, cortisol and ACTH across conditions (placebo and MDMA), using the average measure from ingestion to 6 h post-ingestion. Drug (placebo versus MDMA) was a within-subjects factor, with post-hoc comparisons made via Tukey's test. Effects over time for each hormone (ACTH, cortisol and prolactin) analyzed via one-way repeated measures ANOVA with time of sample as a within-subjects factor, and with post-hoc tests performed with Tukey's test.

**Results:**
- Psychological Effects: When compared with placebo, MDMA increased arousal (wakefulness, alertness). MDMA induced greater arousal in a dose dependent manner in doses of .5 mg / kg to 1.5 mg / kg, and arousal level remains the same or drops when higher doses (2.25 mg / kg and 2.5 mg / kg)
are two few people in the lowest and highest dose conditions (2/18 in the .25 mg / kg and 2 / 18 in the 2.5 mg / kg condition) to draw firm conclusions about the effects of MDMA at very low or moderately high doses. Compared with placebo, MDMA induced elevated hedonic state (positive mood, euphoria). MDMA increased hedonic state in dose-dependent manner, with higher doses of MDMA producing a greater increase in hedonic state than lower doses. Both arousal and hedonic state peaked at 1.25 h post-drug and began to decline 2.5 h post-drug.

**Physiological Effects** Compared with placebo, MDMA increased systolic and diastolic BP, HR and BT. Systolic BP differentially increased by different doses, but only at a level that approached significance. A greater increase in systolic BP occurred with higher doses, with systolic BP at .5 mg / kg differing from effects at 1 mg / kg and 2.25 mg / kg. MDMA also significantly increased diastolic BP. In contrast with other physiological measures, MDMA's effects on diastolic BP and HR were not dose-dependent.

Diastolic BP rose with each successive dose, with doses at 1 mg / kg 1.75 mg / kg, and with the 2.5 mg / kg producing a significantly lower rise in diastolic BP than the 1 mg / kg. HR increased with each successive dose, starting from .25 mg / kg MDMA to 1.25 mg / kg. HR then declined from levels reached at 1.25 mg / kg, with the decline more marked with each successive dose from 1.75 mg / kg to 2.5 mg / kg. MDMA (compared with placebo) induced a statistically significant rise in body temperature, with rise in body temperature higher with high doses than with low doses. However, MDMA did not increase BT in a dose-dependent manner; higher doses did not consistently produce higher BT. Systolic BP peaked at 2.5 h post-drug, and diastolic BP peaked at 2 h post-drug. Elevation in HR peaked at 1.5-2 h post-drug. Rise in BT peaked at 2 h post-drug.

**Neuroendocrine Effects** When compared with placebo, MDMA produced a significant increase in serum ACTH, cortisol and prolactin. MDMA induces a dose-dependent rise in serum ACTH and cortisol, with higher doses producing a greater increase in these hormones. Doses from .25 mg / kg to 1 mg / kg produce significantly less rise in ACTH compared with doses of 2.25 mg / kg, doses of .25-.75 mg /kg produce a significantly smaller rise in serum cortisol than doses of 2.25 or 2.5 mg / kg. While MDMA produced what seemed to be dose-dependent increases in serum prolactin, the dose-dependent relationship did not reach significance. ACTH peaked at 1 to 2 h post-drug after MDMA. Serum cortisol peaked 2.5 3.5 h post-MDMA, and when cortisol levels are plotted across time, decline in cortisol is slow and incomplete at 8 h post-drug. Serum prolactin rises rapidly from 5. H post-drug, peaks at 1.5 2 h post drug and rapidly declines thereafter.

**Overall Effects:** All doses of MDMA were well tolerated by this sample of MDMA-experienced subjects, with no severe psychological or physiological distress. MDMA reliably increases arousal, hedonic state, systolic and diastolic blood pressure and body temperature. This increase was dose-dependent for hedonic state, systolic BP and perhaps BT, but the relationship between dose and response for arousal, HR and diastolic BP may be more complex. Heart rate was increased with doses of MDMA up to 1.25 mg / kg, but then HR did not increase as much with higher doses of MDMA as might be expected (though heart rate remained elevated). While MDMA-induced euphoria increases in a dose-dependent manner, alertness increased with doses up to about 1.5 mg / kg and then increases no further, perhaps declining at highest doses. Psychological effects began to appear at doses of .5 mg / kg, with a significant increase in effects often produced between 1 mg / kg and 1.25 mg / kg. MDMA produced a rise in three hormones thought to be associated with serotonergic function; prolactin, cortisol and ACTH. MDMA's effects upon concentration of ACTH and cortisol were dose-dependent, but its effects upon prolactin were less clearly dose-dependent. Effects first appeared at doses between .5 mg / kg and .75 mg / kg.

**Adverse Effects:** Not reported in this study. While 2 / 18 met the criteria for hypertension, they did not require medical intervention; 1 case was possibly due to unreported use of medication to treat asthma prior to a session.

**Comments:** This paper compares the effects of MDMA in humans at a wide range of doses, from .25 mg / kg to 2.5 mg / kg. This paper's findings concerning neurohormone release are also comparable to findings in other papers indicating that MDMA induces release of two stress hormones (ACTH and cortisol) and prolactin. However, the sample is still small for making inter-dose comparisons, and there are two few people in the lowest and highest dose conditions (2/18 in the .25 mg / kg and 2 / 18 in the 2.5 mg / kg condition) to draw firm conclusions about the effects of MDMA at very low or moderately high
doses. However, this paper does allow for comparisons of MDMA effects at different doses, with the dosage range being fairly representative of typical recreational and therapeutic doses.


**Purpose**: Pharmacokinetic; “…it was the aim of this work to develop a selective, specific and sensitive analytical procedure using…HPLC-DAD.” (p.87). Study examines MDMA and MDA concentrations found in urine of humans given 1.7 mg / kg MDMA during psychotherapy. (Study also measures mescaline and other compounds found in cacti).

**Design**: Within-subjects study, comparing urine collected over time (pharmacological recovery study), with MDMA administered in course of psychotherapy (non-blind, uncontrolled design). Each subject received 1.7 mg / kg MDMA. Urine from volunteers also compared with prepared “blank” and “spiked” standards.

**Subjects**: 4 patients (gender, age and information concerning previous experience with MDMA not reported) treated by psychiatrists of the Swiss Association for Psycholytic Therapy. No information on subject recruitment provided.

**Criteria for Inclusion** – None reported. Willingness to participate in MDMA-assisted psychotherapy.

**Measures**: Concentration of MDMA and MDA in urine measured through high performance liquid chromatography with photodiode array detection (HPLC-DAD). Quantitation was performed by measuring peak areas of MDMA and MDA, using external standards. Recovery of MDMA and MDA in urine measured, with spiked samples used to determine precision of measurement.

**Analysis**: Urine samples analyzed and compared with external standards, as described above. Tests of significance inapplicable in this case.

**Results**: After oral administration, most of 1.7 mg / kg dose of MDMA is recoverable in urine. MDMA concentration found in urine ranged from 1.48 to 5.05 Ug/ml. MDA also excreted in urine as main detected metabolite, in amounts ranging from .07 to .9 Ug / ml.

**Overall Effects**: MDMA is recoverable in urine samples from humans who took 1.7 mg / kg orally in clinical (psychotherapy) setting. Some MDMA is metabolized into MDA, as MDA is also recoverable in urine samples. There was a greater concentration of MDMA in urine than MDA.

**Adverse Effects**: None reported in this study;

**Comments**: This paper is one of several papers that examine MDMA metabolism by seeking to detect MDMA and MDA in human urine. At least at this dosage and in this sample, most MDMA apparently travels through the body unaltered, while some (but not all) is transformed into MDA. The sample sized used (2) is exceedingly small, so the results should be accepted with caution. In addition, metabolism appears to be partially dose dependent, and higher or lower doses may be metabolized differently.

**Helmlin et al. (1996). Analysis of 3,4-methylenedioxyamphetamine (MDMA) and its metabolites in plasma and urine by HPLC-DAD and GC-MS.**


**Purpose**: Pharmacokinetic, chemical detection: Using HPLC-DAD to detect MDMA metabolites in blood and urine and confirming results with gas chromatography. “It was the aim of this study to
establish the analytical methodology for monitoring MDMA and its metabolites in body fluids and to investigate the pharmacokinetic behavior of MDMA in man under controlled conditions.” (p. 433).

**Design:** Within-subjects recovery study comparing metabolites in plasma and urine over time, using 2 detection methods; liquid chromatography and gas chromatography, with samples drawn from two people over 24 h after single dose of 1.5 mg / kg MDMA administered during psychotherapy.

**Subjects:** 2 subjects, 1 woman, aged 40 and 1 man, and aged 23. No information on subject recruitment provided. Presence or absence of previous experience with MDMA not indicated.

**Criteria for Inclusion** – None reported. Willingness to undertake MDMA-assisted psychotherapy.

**Measures:** HPLC-DAD and GC – Performed on plasma and urine, with blood samples collected at 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 170, 190, 220, 250, 310, 380 450 and 530 min (approximately 8.5 h) after MDMA administration and urine samples collected at 0, 1.5, 3.5, 5.5, 7.5, 10, 22 and 23.75 h for one subject and at 0, 1, 1.25, 1.5, 3.75, 4.2, 5, 5.5, 6.4, 8.4, 10.5, 12.5, 16 and 21.5 h after MDMA administration. Urine preparation included enzyme hydrolysis and acidic hydrolysis. Quantitation performed for MDMA, MDA, HMMA and HMA performed at 200 nm and measuring peak areas and using internal standard method.

**Analysis:** Sample size too small for tests of significance. Recovery assessed in plasma and urine through comparing to prepared spiked samples of each fluid. Results produced by HPLC-DAD compared with results with gas chromatography. Concentrations compared over course of time without reporting tests of significance.

**Results:**

**Method Comparison** – HPLC-DAD is a good method for pharmacokinetic profiling of MDMA and its conjugated and unconjugated metabolites in plasma or urine. HPLC-DAD with gas chromatography recommended as confirmation method.

**Recovery** – 98% of 1.5 mg / kg MDMA p.o. recovered from plasma, and 99% recovered in urine. Extraction of metabolites considered good to excellent. Recoveries for metabolites in urine: MDA at 100%, HMMA at 90% and HMA at 68%

**Pharmacokinetics** – Plasma peak level of MDMA 331 ng / ml, at 2 h post-drug. Plasma peak level of MDA 15 ng / ml, at 6 h post-drug. Inter-individual differences found in time when peak urine level recorded, with early peak in MDMA and MDA for Subject A (5 h) and late peak MDMA and MDA for Subject B (21.5 h). Peak urine concentrations of MDMA 18.12 (A), 28.1(B) Ug / ml after 5 or 21.5 h post-drug. Peak urine MDA concentrations .11-2.3 Ug / ml at 16-21.5 h post-drug. Peak HMMA at 24.6-35.1 Ug / ml and HMA at 2.1 Ug / ml (B only), measured between 16-21.5 h post-drug. HMMA could be detected between 1.5 h and 16 h post-drug. Peak values for MDA appear to match those of MDMA. Highest concentrations of HMA appeared between 5 h and 21.5 h as well. HMMA found to be the major metabolite of MDMA found in urine, with concentrations exceeding MDA and (sometimes exceeding parent drug (MDMA)).

**Overall Effects:** Both MDMA and MDA can be found in blood after MDMA administration. Assessing concentration of MDMA and three metabolites in urine after administering 1.5 mg / kg to 2 volunteers suggests that HMMA, and not MDA, is the major metabolite of MDMA. The authors conclude that the major metabolic pathways for orally administered MDMA in humans are cleavage of the methylenedioxy bridge, through demethylenation and conjugation.

**Adverse Effects:** None reported in this paper.

**Comments:** This paper is one of several examining the metabolic pathways for orally administered MDMA by collecting samples from humans given known quantities of MDMA under clinical circumstances. As was also the case with the earlier Helmlin paper, it is difficult (and unwise) to generalize findings from two volunteers to the general population. This is particularly true given the great variability between the volunteers in peak concentration and time of peak concentration for all compounds studied. However, it appears that roughly the same ratio of metabolites arises in all volunteers (that is, the proportion of each compound in relation to the others). Helmlin et al’s findings that HMMA, and not MDA, is the predominant metabolite match the findings of Lanz et al. and Fallon et al., and contrast with Helmlin et al’s earlier report of MDA as the predominant metabolite.


**Purpose**: Pharmacokinetic, neuroendocrine, exploratory: to investigate effects of MDMA on AVP secretion and “whether the hyponatraemic effect of MDMA is a direct effect of AVP secretion.” (p. 1784). **Specific hypothesis tested** – that MDMA-induced release in AVP would reduce plasma sodium count.

**Design**: Non-randomized controlled mixed between subjects-within subjects study design, with all volunteers taking part in 1 treatment session and 3 / 8 volunteers taking part in no-placebo control session. Baseline plasma values for AVP (antidiuretic hormone), cortisol and MDMA measured in all sessions.

**Subjects**: 8 normally hydrated healthy males, aged 22-32 years. Information on presence or absence of MDMA use and recruitment not provided. If same sample as Fallon et al., 1999, then all MDMA-naïve. **Criteria for Inclusion** – Not reported beyond “healthy.” Possibly used criteria described in Fallon et al., 1999. Criteria in Fallon et al. paper: good health as apparently assessed through physical examination. Normal HR, blood pressure and liver function as assessed through laboratory tests and not currently receiving any drugs for medical condition, also not participating in any study “similar in nature.”)

**Measures**: AVP – Plasma concentration of AVP measured with RIA (radioimmununassay), with blood sampled pre-drug ingestion, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h and 1 day (24 h) post-drug.

MDMA – Plasma concentration of MDMA measured through GC-MS (capillary gas chromatography) with MDMA concentration measured from blood drawn at pre-ingestion, 30 min, 1, 2, 4, 6, 8 and 24 h post-drug.

Cortisol, Sodium – Procedure not described for measuring plasma concentration of cortisol or sodium, measures taken from blood drawn at pre-ingestion, 30 min, 1, 2, 4, 6, 8 and 24 h post-drug).

**Analysis**: All data either analyzed via repeated measures ANOVA comparing baseline values to post-drug values, or paired t-tests were used. AVP and MDMA concentration correlated using Spearman’s correlation coefficient.

**Results**: AVP – Plasma AVP reached maximum at 1 to 2 h post-drug. AVP concentrations significantly increased at 2 h post-drug when compared with baseline values. Mean AVP concentration significantly higher after MDMA compared with control session.

Cortisol – Plasma concentration increased from baseline to post-drug, but the change in plasma cortisol concentration was not statistically significant.

Sodium – Plasma sodium concentration significantly changed from baseline to 2 h post-drug, with 7 / 8 showing a decrease in plasma sodium concentration and 1 / 8 showing an increase in plasma sodium.

MDMA – Plasma AVP values did not correlate with plasma MDMA values, author states probably due to differing half-lives (6 min for AVP and “hours” for MDMA.)

**Overall Effects**: A relatively small (40 mg) dose of MDMA increased AVP secretion and sodium decreases as AVP concentration increases. Authors concluded that AVP increase was not related to a “generalized stress response” because MDMA at this dose did not significantly increase cortisol. The authors’ hypothesis is supported (with qualifier), in that MDMA appears to stimulate AVP release, with AVP reducing (or associated with reduction in) blood sodium content. However, MDMA concentration was not correlated with AVP concentration in plasma.

**Adverse Effects**: None described or measured in this report.

**Comments**: This study is reported as a brief communication in the form of a letter to the Lancet. It is clearly an exploratory study, as the authors do not randomize control versus MDMA sessions and do not use all volunteers when comparing effects after MDMA with effects without MDMA. It is unclear as to whether a placebo was administered in the control condition. The authors fear that larger doses of MDMA could stimulate secretion of even more AVP, further lowering sodium concentration, and causing hyponatremia. Hyponatremia in association with illicit ecstasy use has occurred when people drank large
quantities of water after ecstasy ingestion. However, it appears that MDMA-related hyponatremia is not reported under conditions of normal (as opposed to excess) hydration, suggesting that MDMA-induced AVP release is insufficient to cause hyponatremia on its own. (In fact, dehydration after MDMA due to insufficient water consumption is more commonly reported). However, Henry et al’s findings suggest that AVP (or other hormones) could play a role in producing some of MDMA’s physiological or psychological effects.

Hensley & Cody (1999). Simultaneous determination of amphetamine, methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA) and methylenedioxyethylamphetamine (MDEA) enantiomers by GC-MS.


**Purpose:** Pharmacokinetic, describing and validating methods for detecting amphetamines and ring-substituted amphetamines in urine. “The methods were applied to control samples… and to a series of samples from a controlled study looking at the metabolism of MDMA.” (p. 519).

**Design:** Methods of detection developed by comparing author-prepared concentrations of substances in urine. Measures in human volunteers used within-subjects design, with all volunteers receiving a single dose of 1.5 mg / kg MDMA and with urine sampled over time, with comparisons of MDMA and metabolites made over time. Authors state volunteers participated in “controlled” study but do not specify conditions.

**Subjects:** 8 subjects, gender and age unspecified, recruitment method unspecified.

**Criteria for Inclusion** – None reported. Willingness to ingest MDMA as part of a controlled study.

**Measures:** Urine samples taken “over 24 h” in 2 volunteers and “over 72 h” in 6 volunteers were analyzed with GC-MS after liquid-liquid extraction and derivitization with L-TPC. Specific times not provided but extrapolating from charts, appears samples taken at 0 h post-drug and at 2 h intervals afterwards up until 10 or 12 h post-drug; then samples at 24, 48 and 72 h post-drug. **Analysis:** No formal tests of significance applied. Human samples compared with internal standards prepared by authors. Ratios of R(-) to S(+) isomers of MDMA and MDA calculated for each sample. (Study also compares author-prepared samples of amphetamine, methamphetamine, R(-) and S(+)-enantiomers of MDMA, MDA and MDEA. Used selected ion monitoring (SIM) to compare these samples).

**Results:** Substance detection with both columns (DB-17 and HP-1) was found to be accurate and reliable for detecting amphetamines, including ring-substituted amphetamines. Using the HP-1 column provided higher resolution of analyte peaks. There was some difficulty in HP-1 column for measuring and differentiating enantiomers of ring-substituted amphetamines. More S(+)-MDMA excreted in urine than R(-)-MDMA, with excreted S(+)MDMA increasing over time whereas R(-)-MDMA in urine decreased over time. This was true for all subjects, though charts suggest inter-subject differences in rate of clearance. More S(+)MDA is initially excreted than R(-)-MDA, with amount of R(-)-MDA gradually increasing until it exceeds amount of S(+)MDA in urine, with this reversal occurring within 36 h post-drug. All volunteers had the same pattern of S(+) to R(-)-MDA excretion, but with apparent inter-subject differences in rapidity of excretions and percentage excreted for each isomer. Authors caution that accurately measuring enantiomers may be affected by purity of derivatizing agent, noting that their measurements were affected by different lots of L-TPC.

**Overall Effects:** The pattern of stereoselective excretion of MDMA and MDA as measured in urine was similar across a sample of 8 subjects. More S(+)-MDMA was excreted as unchanged drug than R(-)-MDMA, with difference in percentage of S(+)-MDMA to R(-)-MDMA growing over time (with S(+)-MDMA always exceeding R(-)-MDMA). At first volunteers excreted more S(+)-MDA (metabolite of
MDMA), but the percentage of R(-)MDA gradually increased over 36 h post-drug, making R(-)MDA the predominant isomer in urine after 36 h post-drug.

**Adverse Effects:** None reported in this paper.

**Comments:** This is one of several papers investigating the pharmacokinetics of MDMA by examining samples drawn from studies performed in Switzerland. Hensley & Cody are notable for using the largest sample (comparable to those of Fallon et al). Hensley & Cody’s findings appear to support others’ findings of enantioselective metabolism of MDMA in humans, with one isomer metabolized more rapidly than the other. Though this paper employs a larger sample, it does not provide exact figures on recovery or clearance for each isomer of MDMA and MDA, and none of the other metabolites are measured.

**Lanz et al. (1997).** Enantioselective determination of 3,4-methylenedioxymethamphetamine and two of its metabolites in human urine by cyclodextrin-modified capillary zone electrophoresis.


**Purpose:** Pharmacokinetic; To prepare, describe a method for separating the enantiomers of MDMA and its metabolites (specifically MDA and HMMA) and to describe stereoselectivity of metabolite excretion in human urine.

**Design:** Within-subjects study, with urine samples collected over time. Volunteers reportedly part of “controlled study” in Switzerland but details not provided. Urine samples drawn after administering a single dose of 1.5 mg / kg MDMA.

**Subjects:** 2 subjects, 1 man (PH), aged 45, weight 95 kg, 1 woman (UW), aged 24, weight 62 kg.

**Criteria for Inclusion – Not reported; willingness to ingest MDMA as part of “controlled study.”**

**Measures:** Enantiomers of MDMA and metabolites separated via capillary electrophoresis with a chiral selector (for detecting enantiomers). Samples compared with internal standards (blank urine and spiked samples.) Recovery studies performed on MDMA, MDA and HMMA (HMA not measured due to lack of material, as HMA too minor a metabolite). Urine samples collected at 0, 120, 240, 365, 480, 605, 720, 1445, 1800, 2190, 2880 and 4320 min post-drug. (Study also describes methods of validating detection method and comparing intraday and interday reproducability).

**Analysis:** No formal tests of significance conducted. Recovery calculated via comparing relative area ratios in spiked urine and standard samples containing same amount of each compound. Ratios of recovery for the R and S forms of MDMA and for detectable enantiomers of MDA and HMMA calculated for each sample. Data compared for intersubject differences.

**Results:** Electrophoresis able to detect R(-)MDMA and S(+)MDMA. Procedures detected 2 isomers of MDA and HMMA but unable to identify the 2 isomers. They are referred to as “1st” and “2nd” detectable forms. Most MDMA excreted unchanged (as MDMA) in both subjects; over 72 h post-drug. Over half 1.5 mg / kg MDMA excreted as MDMA; 52.4 % for PH and 37.98% for UW). R(-)-MDMA predominant isomer in urine for both subjects. The S/R ratio after 2 h was close to 1 (.80 for PH , .86 for UW). 48 h post-drug, S/R ratios for MDMA were .032 for PH and .093 for UW. 72 h post-drug, only the R isomer of MDMA detectable in urine of PH, whereas S/R ratio in UW = .04. More MDMA excreted as (either isomer of) HMMA than (either isomer of) MDA (9.19 % HMMA vs. 4.25 % MDA for PH, and 12.88% HMMA vs. 1.53% MDA in UW). Enantioselective excretion of MDMA metabolites is time-dependent and varied across the 2 subjects. (PH showed higher excretion of “2nd detectable enantiomer” of MDA up to 30 h post-drug, then concentration of 2nd isomer in urine superceded by 1st enantiomer at 30-72 h post-drug. In UW, 2nd isomer of MDA was always greater than 1st form, but this difference decreased over time; at 72 h post-drug, nearly equal ratios of MDA enantiomers from UW samples. UW was slower in demethylating MDMA to MDA than PH. PH excreted more of 2nd isomer of HMMA whereas UW excreted more of 1st isomer of HMMA in urine. For both subjects, maximum peak of 2nd HMMA isomer to 1st HMMA isomer reached 4 h post-drug, 2.33 for PH and .933 for UW.
Overall Effects: MDMA is enantioselectively metabolized, with the S(+)form of MDMA more extensively metabolized than the R(-) isomer in both subjects, and with R isomer more likely to be excreted unchanged. The majority of 1.5 mg / kg MDMA is excreted as unmetabolized drug, followed by HMMA, then MDA. There are significant inter-subject differences in course of enantioselective metabolism of MDMA, as measured as ratios of 2 (unidentified) forms of MDA or as 2 (unidentified) forms of HMMA. It appears that one subject is slower at metabolizing MDMA into MDA.

Adverse Effects: None reported in this paper.

Comments: This investigation into the metabolism of the enantiomers of MDMA pre-dates that of Fallon et al. Unlike those researchers, Lanz et al. were unable to confirm the absolute enantiomeric identity of the MDA or HMMA they detected. Their sample size is also smaller than that of Fallon et al. (2 volunteers vs. 8 volunteers). Both papers support the existence of enantioselective metabolic pathways and preferential metabolism of S-MDMA vs. R-MDMA. The findings support the case for HMMA, but not MDA, as a major metabolite of MDMA. The findings also suggest that people may vary widely in how they metabolize MDMA over time, since both volunteers differ on several measures of metabolism.

Lester et al. (2000). The cardiovascular effects of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy).


Purpose: Physiological, neurophysiological: To compare cardiovascular effects of .5 and 1.5 mg MDMA and three doses of the beta agonist dobutamine “…to evaluate the acute cardiovascular effects of MDMA using transthoracic two-dimensional (2D) and Doppler echocardiography.” (p. 2).

Design: Placebo-controlled, ascending-dose double-blind within-subjects study, with 4 sessions; dobutamine (5, 20 and 40 Ug / kg /min in 1 session), placebo, .5 mg / kg MDMA and 1.5 mg / kg MDMA, with each session occurring at least 7 days after previous session.

Subjects: 8 MDMA-experienced volunteers (5 men, 3 women, aged 24-39, mean age = 29 + / - 5).

Criteria for Inclusion – Good health as measured through medical examination and laboratory screening. Lack of major medical or psychiatric illness, history of drug dependence (except caffeine and nicotine), no history of adverse reactions to study drugs or psychoactive drugs, and good P450 2D6 activity, as assessed through dextromethorphan phenotyping. No high risk of cardiovascular problems (cholesterol above 250 dL, smoking > 2.5 packs of cigarettes a day), and not pregnant.

Measures: Physiological (Cardiovascular) Measures – HR, systolic and diastolic BP measured at .25, .5, .75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h after drug (placebo, dobutamine , .5 mg / kg MDMA or 1.5 mg / kg MDMA. Measures in dobutamine condition taken after ascending doses dobutamine i. v., (5 Ug/kg/min, 20 Ug/ kg / min and 40 Ug / kg / min, with doses increased every 5 min until final dose reached. Echocardiography – Echocardiograms performed 1 h post-drug (MDMA or placebo) and during (5, 20 and 40 Ug / kg / min) dobutamine), using Doppler echocardiography. End-systolic and end-diastolic volumes calculated and used for calculating average stroke volume, ejection fraction, and cardiac output. Meridional systolic wall stress calculated from cardiographic measures.

Mood Ratings – Not described here, but briefly summarized; rated strength of drug effect for each dose of MDMA and mood on-drug.

Analysis: A repeated measures ANOVA comparing cardiovascular response and echocardiogram after 5, 20 or 40 Ug / kg/ min), with drug condition (dobutamine, 5, 20, 40 Ug / kg / min), placebo, .5 mg / kg MDMA and 1.5 mg / kg MDMA) as 1 within subjects factor and time as 1 within-subjects factor. Post-hoc comparisons done via pairwise comparisons.

Results: Cardiovascular Effects (hemodynamic effects) – 1.5 mg / kg MDMA, 20 Ug / kg / min and 40 Ug / kg / min dobutamine significantly increased HR, diastolic BP and diastolic rate pressure product. .5 mg / kg MDMA and 5 Ug / kg / min did not significantly increase HR, diastolic BP, or diastolic rate
pressure product. 1.5 mg / kg MDMA produced greater increase in peak HR, systolic BP and systolic rate pressure product when compared to 20 Ug / kg / min dobutamine, but increases were not as high as with 40 Ug / kg / min dobutamine,

Echocardiography – Cardiac output increased by 1.5 mg / kg MDMA and with both the 20 and the 40 Ug / kg / min doses of dobutamine. 1.5 mg / kg MDMA produced increase in cardiac output similar to that produced by 20 Ug / kg / min dobutamine, but less than increase produced by 40 Ug / kg / min dobutamine. All doses of dobutamine decreased left ventricular end-systolic volume and increased ejection fraction. MDMA (.5 or 1.5 mg / kg) did not decrease left ventricular end-systolic volume or ejection fraction. None of the drugs produced significant increase in meridional wall stress. Meridional wall stress / ejection fraction ratio decreased with increase in dobutamine dose, with wall stress / ejection fraction ratio significantly reduced at 40 Ug / kg / min dobutamine. However, there was no differences between wall stress / ejection fraction ratio between the lower dose of MDMA (.5 mg / kg) and the higher dose (1.5 mg / kg).

Subjective effects; – Volunteers reported feelings of relaxation, increased well-being and elevated mood lasting 3 to 3.5 h. 6 / 8 rated .5 mg / kg dose of MDMA as “very weak,” 2 / 8 rated it as “medium” in effect. Volunteers rated 1.5 mg / kg MDMA as “medium” to “somewhat strong” in effects. Overall Effects: Cardiac abnormalities not recorded with either .5 mg / kg or 1.5 mg / kg MDMA in this study. Higher doses of MDMA and dobutamine produced comparable increases in cardiovascular responses and cardiac output when compared to lower doses of either drug. 1.5 mg / kg MDMA increased peak HR, systolic BP and systolic rate pressure product, with values falling between effects produced by 20 Ug / kg / min dobutamine and 40 Ug / kg / min dobutamine. While neither drug produced an increase in left ventricular wall end-diastolic volume, dobutamine, but not MDMA, decreased left ventricular wall end-systolic volume. Based on echocardiograms recorded for each drug, dobutamine, but not MDMA, has positive ionotropic effects. If MDMA is not ionotropic, then it may produce more wall stress, a measure related to myocardial oxygen consumption.

Adverse Effects: None specifically reported in this study;

Comments: This is the first extensive investigation of cardiac activity after MDMA. Examining echocardiograms and comparing MDMA’s effects with those of a beta agonist (dobutamine) provides more information on MDMA’s cardiac effects than simple measures of heart rate and blood pressure. MDMA-induced increases in cardiac oxygen consumption may be greater than would be predicted on the basis of measured changes in heart rate and blood pressure alone. The findings in this paper suggest that recreational users of MDMA may be stressing their hearts more than might be expected when exercising vigorously (as when dancing at a rave), and this increase in cardiac stress might lead to increased risk for cardiac complications after MDMA.

Liechti et al. (2000). Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”) are attenuated by the serotonin uptake inhibitor citalopram.


Purpose: Neuropsychological, psychopharmacological; “...the present controlled study was undertaken to determine whether pretreatment with the highly specific 5HT uptake inhibitor citalopram would attenuate the psychoactive effects of MDMA, as measured by psychometric rating scales, in healthy human subjects.” (p. 514). Specific hypothesis tested; that a 40 mg infusion of citalopram would reduce the psychological effects of 1.5 mg / kg MDMA.

Design: Randomized double blind, placebo controlled 2(Pretreatment: placebo/ citalopram) x 2 (Treatment: placebo/MDMA) within subjects design. All volunteers participated in all 4 conditions (placebo / placebo, 40 mg citalopram / placebo, placebo / 1.5 mg / kg MDMA and 40 mg citalopram / 1.5 mg / kg MDMA). Each session was conducted at least 2 weeks after the session preceding it.
**Subjects:** 16 mostly MDMA-naïve subjects, 12 men, 4 women, aged 21-39 years old, mean age 27.4 + / - 4.4 years, recruited at the university hospital and medical school; 15 / 16 either university students or physicians. Not all volunteers MDMA-naïve; 3 / 16 reported trying ecstasy once.

**Criteria for inclusion** – Healthy according to physical examination, psychiatric interview, and blood analysis. No history of major psychiatric disorders in subject or first-degree relatives, no history of head injury and no history of substance abuse. Normal “neuroticism” scores on FPI (no more than 2 standard deviations above norm).

**Measures:** Mood – Assessed via AM, with measures given 75 min post-treatment (at predicted peak of MDMA effects).

**Analyses:** All data tested for normal distribution with Kolmogorov-Smirnov test. Scores on ASC scales were normally distributed, but scores for some AM scales were not normally distributed. Effects of MDMA on ASC assessed via MANOVA, with placebo and MDMA condition as within-subjects factors. A 2-way ANOVA was conducted on ASC scores, with pretreatment (placebo or citalopram) as one factor and treatment (placebo or MDMA) as another factor, with post-hoc comparisons made via Tukey's test. Due to non-normal distribution, Wilcoxon’s matched pair test conducted on the AM scores. Significance set at p = .05 for all tests.

**Results:** Duration, MDMA alone vs. Citalopram + MDMA – The effects of 1.5 mg / kg MDMA alone lasted approximately 3 h. After 40 mg citalopram pretreatment, the effects of MDMA were attenuated but lasted approximately 5 h.

**Alterations in Consciousness, MDMA alone** - MDMA alone increased scores on all 3 scales of the ASC, including OB, VR and AED. Greatest contributors to OB increase were “positive mood,” “derealization,” “alteration of sense of time,” “mania-like state” and “depersonalization.” Greatest contributors to increase in VR were “changed meaning of percepts,” “facilitated recollection,” and “facilitated imagination.” Greatest contributors to increase in AED were “thought disorder,” “loss of body control” and “loss of thought control.”

**Alterations in Consciousness, Citalopram + MDMA** – Significant pretreatment x treatment affects on all three item clusters of the ASC. Pretreatment with citalopram attenuated MDMA effects on OB, VR and AED scores. Specifically, citalopram pretreatment (when compared with MDMA alone) reduced ratings of “positive mood,” “mania-like experience,” “derealization,” “depersonalization,” “alteration of sense of time,” “changed meaning of percepts,” “facilitated imagination,” “thought disorder,” “loss of thought control,” and “loss of body control” (in AED). In all cases, citalopram pretreatment decreased the MDMA-associated increases in these scores.

**Mood, MDMA Alone** – MDMA increased self-ratings of “self-confidence,” “heightened mood,” “extraversion,” “introversion,” “emotional excitability,” “sensitivity,” and “thoughtfulness-contemplativeness.” While MDMA (compared with placebo) reduced “tiredness,” it increased “dazed state.”

**Mood, Citalopram + MDMA** – Citalopram pre-treatment reduced MDMA-induced increase in ratings of: “self-confidence,” “extraversion” and “efficiency-activation.” Citalopram pre-treatment reduced ratings of “heightened mood,” but effect only approached significance. Tendency for ratings increased by MDMA to be less increased with citalopram + MDMA. However, scores for “emotional excitability” and “sensitivity” remained high even after citalopram pre-treatment.

**Overall Effects:** Citalopram attenuated most of MDMA’s effects; under citalopram pre-treatment, people did not experience the heightened or positive mood, extraversion, self-confidence, activation, alterations in perception, derealization or loss of body control and thought disorder usually induced by MDMA. This suggests that a large part of MDMA’s effects are due to its capacity as a serotonin releaser and uptake inhibitor. However, citalopram did not reduce “emotional excitability,” or “sensitivity.” Also, 40 mg. citalopram only produced a 60% reduction in MDMA-induced effects rather than completely antagonizing all psychological and physiological effects. MDMA alone and with citalopram pre-treatment can be administered to a largely MDMA-naïve sample without causing severe psychological or physical distress.
Adverse Effects: Adverse effects not reported in this paper. See Liechti et al., 2000.

Comments: This paper is part of a series of papers investigating the neurochemical correlates of the psychological and physiological effects of MDMA by attempting to block or antagonize a particular pharmacological action of MDMA through pre-treatment with other drugs. The physiological effects of MDMA with citalopram pre-treatment are explored in another paper (in press as of 10 / 2000). Other pre-treatments studied include a 5HT2A receptor antagonist (ketanserin) and a D2 receptor antagonist (haloperidol). This study finds that serotonin release is a very important component in producing the effects that make MDMA “MDMA-like” or “entactogenic.” However, the paper also notes that some aspects of the subjective experience, such as “emotional excitability” remain even after pre-treatment with an SSRI (citalopram) indicating that at least one important correlate of MDMA’s psychological effects is not mediated by serotonin release. If replicated, these findings seem to indicate that serotonin release is responsible for most, but not all, of MDMA’s “entactogenic” effects.


Purpose: Neuropsychological, neurophysiological, psychopharmacological; “…the present study examined the effects of the 5HT2A/C antagonist ketanserin on psychological and physiological responses to MDMA (1.5 mg / kg p. o.) in healthy volunteers.” (p. 397). Specific Hypothesis Tested – that ketanserin would attenuate some of MDMA’s moderately hallucinogen-like effects.

Design: Randomized double blind placebo-controlled within-subjects study with a 2(Drug 1; placebo / 50 mg ketanserin) x 2(Drug 2: placebo / 1.5 mg / kg MDMA) design, where all volunteers took part in all 4 conditions (placebo / placebo, ketanserin / placebo, placebo / MDMA and ketanserin / MDMA). Sessions were separated by at least 10 days.

Subjects: 14 mostly MDMA-naïve volunteers (13 men, 1 woman, ages 21-41) recruited from Medical School and the University Hospital at Zurich. 12 / 14 volunteers MDMA-naïve; 2 volunteers had tried ecstasy once. 7 / 14 had smoked cannabis a few times and 4 / 14 had tried a hallucinogen once.

Criteria for Inclusion – No current or past medical or psychiatric illness as assessed through medical history, psychiatric interview, physical exam, ECG and blood analysis. No personal or family (1st degree relative) history of major psychiatric illness, and no history of substance abuse.

Measures: Mood – Measured via AM. Anxiety assessed through STAI. Measures administered 75 min pre-drug 2, 75 min post-drug (during predicted peak effects of MDMA) and 120 min post-drug 2.

Alterations in Consciousness – Measured with ASC-AV, a revised version of ASC with additional clusters for “auditory alterations” (AA) and “vigilance reduction” (VIR). Revised ASC administered 75 min pre-drug 2, and 75 min and 120 min post-drug 2.

Physiological Effects – BP (systolic and diastolic), HR and BT measured at 75 min pre-drug 2 and 0, 60, 90, 120 and 150 min post-drug 2.

Adverse Effects – Measured through the LC. Acute adverse effects measured during session, short term sequelae measured 1 and 3 days post-session.

Debriefing – Not described; probably subject’s free-response (oral or written) to requests for description of all 4 sessions and comparisons between them, apparently with request as to whether subject could identify substances used in each session.

Analysis: After confirming normal distribution of data with Kolmogorov-Smirnov test, a repeated measures ANOVA was performed on all data, with ketanserin (drug 1: placebo or 50 mg. Ketanserin), MDMA (drug 2; placebo or MDMA) and time (75 min pre-drug 2, 75 min and 120 min post-drug 2) as within-subjects factors. ASC-AV and LC scores analyzed with a repeated measures ANOVA with ketanserin (placebo or ketanserin) and MDMA (placebo or MDMA) as within-subjects factors, with
separate analyses conducted for each time of administration (75 min pre-drug 2, 75 min, 120 post-drug 2). If there were no MDMA x ketanserin x time effects, but significant interactions between each drug and time, then additional post-hoc repeated measures ANOVAs performed with drug (MDMA versus ketanserin-MDMA) and time as within-subjects factors. Post-hoc comparisons made with Tukey’s test. Significance was set at p = .05

**Results:**

**Duration:** MDMA vs. Ketanserin + MDMA – Effects of MDMA alone lasted, on average, 3.5 h. Effects of MDMA with ketanserin pretreatment lasted, on average, 3 h.

**Mood, MDMA Alone** – MDMA did not induce significant changes in STAI score. On AM scale, 1.5 mg / kg MDMA alone increased scores on “well-being,” “self-confidence,” “extroversion,” “thoughtfulness-contemplativeness,” and “emotional excitability,” (emotionality, sensitivity) also “inactivity” and “dazed state.”

**Mood, Ketanserin + MDMA** – Pretreatment with 50 mg ketanserin did not effect MDMA-generated increases in scores on positive mood (“self-confidence,” “heightened mood”) or “extroversion.” Ketanserin attenuated MDMA-induced “emotional excitability” and “thoughtfulness” (described by some volunteers as “dreamy state.”) Ketanserin pretreatment did not change time course of MDMA’s effects (no drug x time interaction). While ketanserin alone and MDMA alone both increased general inactivation and dazed state, ketanserin pre-treatment attenuated MDMA-induced scores on “inactivation” and “dazed state.”

**Alterations in Consciousness, MDMA Alone** – 1.5 mg / kg MDMA significantly increased scores in all five ASC-AV scales, OB, VR, AED, AA and VIR. Increase in OB owed due to increase in “positive mood,” “mania-like state,” “derealization,” “depersonalization” and “alterations in perception of time.” Increase in VR due to “changes in meaning of perception.” Volunteers reported an increased vividness of perception, including an intensification of colors and tactile awareness.) AED scores increased due to “thought disorder” and “fear of loss of body control.” AA (auditory alteration) slightly but significantly increased, indicating alterations in auditory perception, but no auditory hallucinations. VIR increased, indicating reduced vigilance under MDMA.

**Alterations in Consciousness, Ketanserin + MDMA** – Ketanserin pretreatment significantly reduced VR scores and VIR (vigilance reduction) scores, but did not reduce MDMA-induced increases in OB or AED.

**Physiological Effects, MDMA Alone** – MDMA significantly increased BP, HR and BT.

**Physiological Measures, Ketanserin + MDMA** – Ketanserin alone reduces BP, HR and BT. When examining ketanserin + MDMA, initial analysis showed no ketanserin X MDMA effect. However, post-hoc ANOVA found that ketanserin also reduced MDMA-induced increases in BT and diastolic (but not systolic) BP. Ketanserin pre-treatment did not significantly reduce MDMA-induced increases in HR.

**Adverse Effects, MDMA Alone** – As listed in “adverse effects,” MDMA alone produced difficulty in concentration (10 / 14), dry mouth / thirst (10 / 14), impaired gait (10 / 14), dizziness (8 / 14), jaw clenching (8 / 14), lack of appetite (7 / 14), restlessness (7 / 14) and other effects listed by less than 7 / 14 (or 50%) of the sample. (See “Adverse Effects” for more details).

**Adverse Effects, Ketanserin + MDMA** – Ketanserin pretreatment attenuated most adverse effects (difficulty concentrating and dizziness only in 8 / 14 in ketanserin-MDMA instead of 10 / 14, jaw clenching in 4 / 14 rather than 8 / 14, and reduction in feeling cold (3 / 14 with ketanserin vs 6 / 14 MDMA alone). Some effects unchanged (lack of appetite, palpitation – actually increased from 6 / 14 to 7 / 14), and weakness (also slight increase, 6 / 14 vs. 5 / 14 with MDMA alone). However, ketanserin had little effects on short term sequelae, measured 1 and 3 days post-MDMA, though jaw- clenching 24 h later eliminated with ketanserin + MDMA (3 / 14 with MDMA alone).

**Debriefing Interview** – Only 5 / 14 volunteers could distinguish ketanserin alone from placebo. 9 / 14 volunteers retrospectively reported that their MDMA experience less intense under ketanserin pretreatment, and 5 / 14 reported feeling little difference between MDMA alone and ketanserin pretreatment + MDMA.

**Overall Effects:** MDMA alone heightened mood, caused moderate alterations in perception and moderate thought disorder. It increased blood pressure, heart rate and body temperature, and produced some acute adverse effects, as listed above. Ketanserin antagonized perceptual alteration and emotional excitability,
and it reduced MDMA’s effects on diastolic BP and BT. (Ketanserin did not significantly reduce MDMA-induced increase in HR.) While both ketanserin and MDMA alone increased scores for “inactivity” or “dazed state,” and MDMA reduced “vigilance” combining the two produced a lesser increase in “inactivity” or “dazed state.” MDMA alone was well tolerated when administered alone and with ketanserin pre-treatment. Most of the volunteers noticed that MDMA after ketanserin pretreatment was less intense, but a significant minority did not notice much of a difference between the 2 conditions. The authors’ hypothesis is largely supported; ketanserin pretreatment specifically reduced MDMA-induced increases in diastolic BP, VR scores on the ASC, and some side effects common to hallucinogens (dizziness, difficulty concentrating). In addition, ketanserin pretreatment reduced MDMA-induced rise in BT, an effect not necessarily predicted from 5HT2A receptor antagonism, and it acutely reduced some side effects more commonly associated with amphetamines (jaw clenching).

**Adverse Effects: Acute** - Difficulty concentrating (10 / 14), dry mouth / thirst (10 / 14), impaired gait (8 / 14), dizziness (8 / 14), jaw clenching-trismus (8 / 14), lack of appetite (7 / 14), restlessness (7 / 14), drowsiness (6 / 14), palpitations (6 / 14), being cold (6 / 14), inner tension (6 / 14); Mentioned by 5/ 14 or less (less than half of the subjects), nausea, transpiration, weakness, lack of energy, brooding, tremor, anxiety.

24 h later – Dry mouth / thirst (5 / 14), lack of appetite (4 / 14), drowsiness (4 / 14), jaw clenching (3 / 14), brooding (3 / 14), weakness (3 / 14), lack of energy (3 / 14) and in less than 3 / 14 subjects, difficulty concentrating, restlessness, transpiration, insomnia, hypersomnia

3 days later – Drowsiness (2 / 14). Only reported by one subject (1/ 14): dry mouth, jaw clenching, restlessness, inner tension, lack of energy, brooding, anxiety, hypersomnia.

**Comments:** This paper is one is a series investigating the neurotransmitter systems involved in producing MDMA’s effects in humans. 5HT2A and / or 5HT2c receptors play a role in the stimulus properties of MDMA (subjective experience associated with the drug), and ketanserin reduced some (but not all) physiological effects and unwanted effects. It is interesting to note that citalopram did not alter MDMA-induced changes in emotional excitability whereas ketanserin did attenuate this effect. This study demonstrates that MDMA can be administered to MDMA-naïve subjects, with or without ketanserin pre-treatment, without producing severe psychological or physiological distress.


**Purpose:** Neuropsychological, neurophysiological, psychopharmacological: “…the present study examined the effects of the dopamine D2 antagonist haloperidol (1.4 mg i.v.) on the psychological and physiological responses to MDMA (1.5 mg / kg) in healthy human volunteers.” (p. 290). **Specific hypothesis tested** – that haloperidol would attenuate some of MDMA’s stimulant-like effects (not listed; assume referring to positive mood, activation, increase in BP and HR).

**Design:** Randomized double-blind placebo controlled 2(pretreatment: placebo or 1.4 mg haloperidol) x 2(treatment: placebo or 1.5 mg / kg MDMA) within-subjects design. All volunteers took part in all 4 conditions (placebo / placebo, haloperidol / placebo, placebo / MDMA and haloperidol / MDMA), with each session scheduled at least 10 days after a previous session.

**Subjects:** 14 mostly MDMA-naïve volunteers (9 men, 8 women, aged 21-38, average age 26, recruited from the University Hospital and the Medical School in Zurich; all but one were students or physicians. 13 / 14 volunteers were MDMA-naïve; 1 / 14 had tried ecstasy. 7 / 14 had smoked cannabis a few times, and 3 / 14 had tried a hallucinogen once. 2 / 14 current “light” smokers.

**Criteria for Inclusion** – Healthy as assessed through psychiatric interview, medical examination, ECG, blood analysis. No history of major medical illness and no history of personal or family (1st degree
relative) major psychiatric illness, and no history of substance abuse. “Neuroticism” scores on the FPI within normal range (could not be 2 standard deviations above norm).

**Alterations in Consciousness** – Measured via ASC, with measures administered shortly after drug 2 (MDMA or placebo), 75 and 120 min after drug 2 administration.

**Physiological Effects** – BP and HR measured with subject in sitting position, and BT measured with an auxiliary clinical thermometer. Blood pressure, HR and body temperature measured at 0, 75, 120 after drug 2 administration.

**Adverse Effects** – Measured with LC, with adverse effects and short-term sequelae assessed during session, 1 and 2 days after session.

**Debriefing Interview** – Open-ended retrospective report of each session and subject’s comparisons between sessions, and requests as to whether volunteers could identify substance administered in each condition.

**Analysis:** Mood and Alterations in Consciousness – AM and ASC scores analyzed in separate repeated measure ANOVAs, with haloperidol (placebo vs. haloperidol) as one factor and MDMA (placebo vs. MDMA) as another factor. STAI state anxiety scores analyzed via 3-way repeated-measures ANOVA, with haloperidol, MDMA and time (0, 75 and 120 min post-drug) as factors.

**Physiological Effects** – BP, HR and BT analyzed via 3-way ANOVA, with haloperidol, MDMA and time (0, 75 and 120 minutes post-drug) as factors.

**Adverse Effects & Short Term Sequelae** – LC scores for adverse effects compared at each time point (during session, 24 h post-drug, 3 days post-drug) with 2-way repeated measures ANOVAs with haloperidol and MDMA as 2 within-subjects factors.

**All Data** – Post-hoc comparisons were made using Tukey’s test or simple effect tests. Significance value set at p. = .05.

**Results:**

- **Duration, MDMA vs. Haloperidol + MDMA.** 1.5 mg / kg MDMA alone produced effects lasting (average) 3.5 – 4 h. No differences in duration reported with haloperidol + MDMA.

- **Mood, MDMA Alone** – MDMA increases ratings of well-being and emotional excitability (emotionality, sensitivity). MDMA had no effect on state anxiety scores at 75 min post-drug but (compared to placebo) significantly decreases state anxiety scores at 120 minutes post drug.

- **Mood, Haloperidol + MDMA** – Haloperidol alone increased scores in “inactivation.” No haloperidol x MDMA interaction, but haloperidol pretreatment decreased MDMA-induced increase in ratings of “well being.” Haloperidol did not reduce MDMA-induced “emotional excitability.” There was a significant MDMA x Haloperidol x Time interaction for STAI state anxiety score. While MDMA alone became anxiolytic over time and haloperidol alone increased state anxiety (compared with placebo) at both 75 min and 120 min post-drug, haloperidol + MDMA increased state anxiety at 75 min post-drug, with anxiety scores declining from 75 min post-drug at 120 min post drug. Haloperidol + MDMA produced anxiety scores that were higher than anxiety scores under haloperidol alone.

- **Alteration in Consciousness, MDMA Alone** – MDMA increased all 3 ASC clusters; OB, AED and VR, compared with placebo. OB scores increased due to increase in “positive mood,” “alteration in sense of time,” “mania-like state,” “derealization.” AED scores increase due to increased ratings of “thought disorder,” “loss of thought control,” “loss of body control.” VR scores increased due to increased ratings of “changes in meaning of percepts.”

- **Alteration in Consciousness, Haloperidol + MDMA** – Compared with MDMA alone, haloperidol + MDMA reduced OB, due to reduction in rated “positive mood” and “mania-like state,” and increased AED, due to increase in ratings of “anxious derealization.” No changes in VR reported.

- **Physiological Measures, MDMA Alone** – MDMA increased systolic BP, diastolic BP, and HR, but not BT.

- **Physiological Measures, Haloperidol + MDMA** – Haloperidol pretreatment did not reduce MDMA-induced increase in systolic or diastolic BP. Haloperidol alone decreased HR, but haloperidol pretreatment did not significantly reduce MDMA-induced increase in HR.

- **Adverse Effects, MDMA Alone** – MDMA produced a number of adverse effects (see “Adverse Effects” for details) including jaw clenching, dry mouth / thirst, loss of appetite, difficulty concentrating and
impaired gait, when compared with placebo. Short-term sequelae at 1 day and 3 days post-MDMA (see below for more details) included fatigue, lack of appetite, thirst/dry mouth, insomnia, difficulty concentrating and weakness, and lack of energy.

### Adverse Effects: Haloperidol + MDMA

- Haloperidol alone produced fatigue (11/14), and occasionally restlessness (3/14) and difficulty concentrating (3/14). Haloperidol pretreatment decreased some of MDMA’s adverse effects (jaw clenching, from 10/14 to 7/14), thirst/dry mouth (from 8/14 to 3/14) and lack of appetite (from 7/14 to 4/14). However, haloperidol increased other MDMA-induced adverse effects, including difficulty concentrating (from 7/14 to 12/14), fatigue (from 4/14 to 8/14), restlessness (from 4/14 to 8/14) and inner tension (from 2/14 to 7/14). Haloperidol either did not alter or moderately increased other adverse effects (impaired gait, palpitations, vertigo, tremor).

- Haloperidol produced no significant changes in MDMA’s short-term sequelae at 1 or 3 days post-drug.

#### Debriefing Interview

- Discomfort and anxiety not reported under either haloperidol or MDMA alone, but were reported for the haloperidol + MDMA condition. Volunteers reported noticeable reduction in MDMA-induced rise in positive mood. Volunteers reported anxiety at drug onset in haloperidol + MDMA condition that disappeared after 1 h post-drug. 8/14 could not distinguish haloperidol from placebo. 13/14 rated study as positive experience. 7/14 expressed interest in taking MDMA in controlled setting, 13/14 did not express interest in recreational use of MDMA.

### Overall Effects

- 1.5 mg/kg MDMA alone increased positive mood, emotional excitability, and well-being, with a decrease in state anxiety during peak drug effects (120 min post-drug) and alterations in consciousness such as altered perception of time, thought disorders, loss of thought and body control and change in meaning of percepts. MDMA alone also increased systolic and diastolic blood pressure, heart rate, and the adverse effects listed below. When MDMA was preceded by an intravenous infusion of 1.5 mg haloperidol, well-being and positive mood were no longer increased by MDMA, and state anxiety at 75 was greater than with either drug alone. Haloperidol pre-treatment did not reduce MDMA-induced increase in systolic or diastolic BP, and it did not significantly reduce MDMA-induced increase in heart rate. Haloperidol decreased some adverse effects (jaw clenching, dry mouth) while increasing other adverse effects (especially difficulty concentrating, inner tension and fatigue.) The authors hypothesis was partially confirmed; haloperidol reduced positive mood and euphoria, both believed to be induced through dopaminergic pathways, and it reduced adverse effects believed to be “stimulant-like,” such as jaw clenching, dry mouth, and lack of appetite. However, haloperidol did not reduce stimulant-like physiological effects, such as increased BP and HR.

#### Adverse Effects: During Session

- Jaw clenching (10/14), dry mouth/thirst (8/14), difficulty concentrating (7/14), impaired balance/gait (6/14), fatigue (5/14), restlessness (4/14). These experienced by less than 4/14; palpitations, vertigo, tremor, inner tension.

1 day post-drug—Fatigue (7/14), loss of appetite (7/14), thirst/dry mouth (5/14), insomnia (5/14), difficulty concentrating (4/14), weakness (4/14) and headache (4/14).

3 Days post-drug—Fatigue (4/14), lack of appetite (4/14), lack of energy (3/14).

#### Comments

This paper reports one of several investigating the neurotransmitter systems involved in producing MDMA’s effects in humans. As might be expected when considering other dopaminergic drugs, the findings in this paper suggest that dopamine plays a role in MDMA-induced positive mood and euphoria; D2 blockade with haloperidol reduced MDMA-induced positive mood and euphoria, and state anxiety is increased during drug onset. However, D2 receptors have far less influence over MDMA’s effects on blood pressure, heart rate and body temperature. Changes in state anxiety over time evident under haloperidol pretreatment with MDMA suggest a possible avenue for further research into temporal changes in MDMA’s effects. MDMA alone was well tolerated by volunteers, most of them MDMA-naive, without any signs of psychological distress. Combining MDMA with haloperidol produces some discomfort, anxiety and minor distress. Despite the discomfort generated by haloperidol pre-treatment, nearly all volunteers still viewed the study as a positive experience. On the basis of the findings reported here, it would appear that haloperidol is not a good choice for coadministration with MDMA and is probably a poor intervention in cases of MDMA-produced distress.


**Purpose:** Neurophysiological, psychopharmacological: “…the current study was undertaken to determine whether pretreatment with the highly specific serotonin uptake inhibitor citalopram (40 mg i. v.) would attenuate cardiovascular, hyperthermic and vegetative effects of MDMA (1.5 mg/kg p.o.) in healthy human volunteers…” (p. 3 in manuscript). Specific hypothesis tested – that citalopram would attenuate physiological and adverse effects of MDMA.

**Design:** Randomized, placebo controlled double-blind 2(Pretreatment; placebo or 40 mg. Citalopram) x 2(treatment; placebo or 1.5 mg / kg MDMA) within subjects design. All volunteers took part in all 4 conditions; placebo/placebo, citalopram / placebo, placebo, placebo/ MDMA, citalopram / MDMA. Female volunteers tested during perimenstrual phase to reduce any variations due to menstrual cycle.

**Subjects:** 16 mostly MDMA-naïve subjects, 12 men, 4 women aged 21-39, recruited from the University Hospital or the Medical School. All but one were students or physicians. 13 / 16 MDMA-naïve; 6 / 16 had minor recreational drug experience; 2 / 16 had tried ecstasy, 3/16 had tried a hallucinogen and 1/16 had tried both ecstasy and a hallucinogen. (Same sample featured in Liechti et al., 2000; Psychological effects of citalopram).

**Criteria for Inclusion** – Healthy as assessed via medical history, medical examination and psychiatric interview, ECG and blood analysis. No history of substance abuse, no personal or family history (in 1st degree relatives) of major psychiatric illness, and no history of head injury. Normal “neuroticism” scores on FPI, with scores no more than 2 standard deviations above norm.

**Measures:** Physiological Measures – BP and HR measured by automated device with subject in sitting position. Measures taken at 0, 60 and 120 min after MDMA or placebo ingestion. BT measured, with measures taken at 0, 60 and 120 min after drug 2 (MDMA or placebo) ingestion.

Adverse Effects and Short-Term Sequelae – Measured with LC, with volunteers responding to LC during the session, 24 h (1 day), 72 h (3 days) and 2 weeks post-session.

Debriefing Interview – Conducted after all 4 sessions completed; volunteers provided retrospective reports of each session, compared each session with the others and answered requests for information about whether they could identify substances used in each session, and their future interest in controlled and recreational use of MDMA.

**Analysis:** Physiological Effects – HR, BT and BP analyzed via 2-way repeated measures ANOVA, with drug (MDMA vs. placebo) and time (0, 60 and 120 min post-drug) as within-subjects measures. Post-hoc comparisons made with Tukey’s test. Specific inhibiting effect of citalopram on MDMA effects assessed with 2 separate 2-way repeated measures ANOVAs for 60 min and 120 min, with pretreatment (placebo or 40 mg. citalopram) and treatment (placebo or 1.5 mg / kg MDMA) as within-subjects factors.

Adverse Effects – Responses to LC analyzed with 1-way repeated measures ANOVAs, with all 4 conditions (placebo/placebo, citalopram/placebo, placebo/MDMA, citalopram/MDMA) as within-subjects factors. 4 separate analyses performed for LC at each time point (during session, 24 h later, 3 days later, 2 weeks later). Post-hoc comparisons performed via Tukey’s test.

**Results:** Physiological measures, MDMA Alone – MDMA increased systolic and diastolic BP (60 and 120 min) compared with placebo and with baseline values. MDMA also elevated HR, compared with placebo or pre-drug values at both time points, and slightly but significantly elevated BT at both time points.

Physiological Effects, Citalopram + MDMA – Citalopram pretreatment reduced MDMA-induced increases in systolic and diastolic BP at 120 min, and systolic (but not diastolic) BP at 60 min. Citalopram reduced MDMA-induced increase in HR at 60 min but not at 120 min. Citalopram pretreatment did not reduce MDMA-induced increase in BT.
Adverse Effects, MDMA Alone, Acute – (See details in “Adverse Effects). MDMA alone produced difficulty concentrating, dizziness, lack of appetite, impaired gait, restlessness, restless legs, and jaw-clenching. 1 and 3 days post-drug – Short-term sequelae included lack of appetite, headache, difficulty concentrating, fatigue, exhaustability (after 1 day) with lack of appetite, difficulty concentrating sometimes lasting up to 3 days, 1/3 (3/16-4/16) reported irritability, gloomy thoughts and brooding at 3 days.

Adverse effects, Citalopram Alone – Citalopram alone produced tiredness (11/16), nausea without vomiting (6/16) and headache (5/16).

Adverse Effects, Citalopram + MDMA, Acute – Citalopram reduced most reported acute adverse effects, but increased inner tension (from 3/16 to 8/16). Citalopram did not significantly reduce short-term sequelae at either 1 or 3 days post-session (citalopram pretreatment reduced some short-term sequelae, but reduction not statistically significant).

Adverse Effects, 2 weeks post-session – No sign of any reported adverse effects after 2 weeks for all conditions.

Debriefing Interview – All volunteers reported MDMA-induced effects reduced in citalopram + MDMA condition. 8/16 unable to distinguish citalopram from placebo and 1/16 unable to distinguish MDMA from placebo. 14/16 volunteers had a pleasant experience overall, 2/16 reacted with moderate anxiety 1 to MDMA alone, one to citalopram alone). 7/16 reported they would consider taking MDMA again in a controlled setting, but none expressed interest in recreational use of MDMA.

Overall Effects: MDMA increased HR, BP and BT; it also produced acute and sub-acute side effects. Citalopram, an SSRI, reduced some, but not all, components of the physiological response to MDMA; heart rate, systolic and diastolic BP are reduced, but citalopram did not reduce MDMA-induced increase in BT or MDMA-induced increase in diastolic BP at 60 min post-drug. Citalopram also reduced many acute adverse effects, though it increased inner tension. It did not significantly reduce short-term sequelae measured 1 and 3 days later. The authors’ hypothesis was partially confirmed; citalopram reduced MDMA-induced increase in BP and some adverse effects possibly related to serotonin release, (lack of appetite, dizziness / vertigo). However, citalopram did not reduce MDMA-induced increases in BT despite indications that BT is under serotonergic control, but citalopram did partially reduce MDMA-induced increase in HR, previously assumed to be largely controlled by dopaminergic or noradrenergic systems.

Adverse Effects: Acute – difficulty concentrating (10/16), dizziness / vertigo (8/16), impaired balance / gait (8/16), lack of appetite (8/16), thirst (7/16), jaw clenching (7/16), restless legs (7/16) and inner tension (3/16).


Comments: This paper is a companion to the Liechti, Baumann et al., 2000 paper investigating the effects of citalopram pretreatment upon MDMA’s psychological effects in humans. The findings in this paper suggest that serotonin release plays an important role in generating “MDMA-like” or entactogenic effects. However, the findings also confirm a role for other neurotransmitters or receptors in producing MDMA’s effects. Most (but not all) volunteers reported that participating in this study was pleasant, none of the volunteers experienced severe psychological or physical discomfort after MDMA, with or without citalopram pretreatment.
MDMA effects were most pronounced on the VR scale, with women experiencing much greater increases in perceptual changes compared to men. More women than men reported feeling “carefree,” “free of..."
worries and obligations,” “boundless joy” and “comprehensive love.” Women also reported greater increases in “wonderful other world,” “at one with surroundings,” “dream-like state of the perception of space and time,” “physical sensations more pleasurable” (OB). Women were more likely than men to report experiencing thought disorders (accelerated thinking, impaired decision-making, losing track of thoughts) and fear of loss of body control (AED). More women than men reported “objects had a new and unfamiliar meaning,” “minor things carried a particular meaning,” facilitated recall (“recalled long forgotten things”) and facilitated imagination (“extraordinarily vivid imagination”) (VR). Elementary hallucinations (flashes of light, simple patterns) reported in both genders, but women reported experiencing more of them, and more visual (pseudo)-hallucinations. No significant gender differences for the ASC were found in the placebo condition. As dosage increased, women, but not men, experienced an increase in VR scores. Neither OB nor AED scores increased with dosage.

**Physiological Effects** – While MDMA significantly increased systolic BP in both genders, the increase was significantly greater in men compared with women. While MDMA increased HR in both genders, the difference was only significantly different from placebo in men. MDMA also produced a significant increase in BT in men, while it did not produce a significant increase in BT in women. There were no correlations between MDMA dose and elevation of BP or BT.

**Adverse Effects** – A significantly greater percentage of women reported experiencing most of the acute adverse effects (side effects) measured, with the exception of nausea and sweating, more often experienced by men than by women. For example, gender differences exist for all the most commonly reported effects: difficulty concentrating (59% all, 75% women versus 54% men), jaw clenching (60% all; 65% women versus 56% men), loss of appetite (54% all; 75% women versus 46% men), dry mouth (53% all; 65% women versus 48% men). Compare sweating, sweaty palms (31% all; 20% women versus 35% men) and nausea (15% all; 10% women versus 17% men).

**Short Term Sequelae** – A greater percentage of women reported experiencing short-term sequelae 24 h after MDMA than did men. Gender differences were found in the frequency of commonly reported short term sequelae, such as fatigue (41% all; 55% women versus 35% men), lack of appetite (39% all, 50% women, 35% men), difficulty concentrating (28% all, 30% women, 28% men), dry mouth (34% all; 60% women versus 24% men), headache (27% all; 35% women versus 24% men), lack of energy (24% all; 40% women, 19% men), insomnia (24% all; 30% women, 22% men), and jaw clenching (20% all, 25% women, 19% men). Men reported more sweating (12% all; 5% women versus 15% men) and restless legs (11% all; 5% women versus 13% men).

**Overall Effects**: After pooling data from 3 separate studies, the authors detected gender differences in psychological and physiological effects of MDMA. The MDMA-induced increases in all three scales of the ASC were greater in women than in men, and this was particularly pronounced for the VR scale, a measure of changes in perception. Women were more likely to experience anxiety or dysphoric reactions acutely after MDMA, with anxiety related to feeling helpless. There was a relationship between MDMA dosage and increase in VR for women, but not for men (at a dose range of 1.35 – 1.8 mg / kg MDMA). The MDMA-induced increase in systolic blood pressure was greater for men than for women, and increases in heart rate and body temperature acutely after MDMA were only significantly higher in men. Acute side effects were more frequently reported by women than by men, with this being true for the most common side effects, such as loss of appetite, jaw clenching and difficulty concentrating. Sweating and nausea were the only acute side effects more frequently reported by men. More women than men also reported experiencing short term sequelae 24 hours after MDMA administration, such as fatigue, continued lack of appetite and continued jaw tension. Only sweating and restless legs were more frequently reported in men. The authors’ hypothesis is largely confirmed, in that women experienced greater alterations in consciousness, more anxiety and more acute adverse effects and short-term sequelae than men. However, finding higher elevation in systolic blood pressure acutely after MDMA in men, and finding a trend for the physiological effects to be greater in men than in women suggests that men may be more sensitive to the sympathomimetic actions of MDMA. In addition, women’s experience with
MDMA was qualitatively different from men's (rather than simply more intense) in that there were more “hallucinogen-like” alterations in perception and meaning, more thought disorder and less activation.

**Adverse Effects:** See above for most commonly listed effects. Acute – Impaired balance (49% all, 50% women, 48% men), restless legs (40% all, 40% women, 41% men), sensitivity to cold (41% all, 50% women, 37% men), dizziness (38% all, 40% women, 38% men), palpitations (35% all, 50% women, 30% men), restless (34% all, 35% women, 33% men), being cold (34% all, 45% women, 30% men), sweating (30% all, 20% women, 35% men), forgetfulness (28% all, 40% women, 24% men), heavy legs (21% all, 50% women, 19% men), fatigue (26% all, 35% women, 22% men), weakness (26% all, 35% women, 22% men). Listed by >25% of 74 subjects: hot flushes, parasthesia, tremor, inner tension, brooding, nausea, lack of energy, exhaustability, (listed by >15% of 74) frequent urge to urinate, headache, anxiety, irritability, increased appetite, muscle ache

**Short Term Sequelae** – See above for commonly reported sub-acute effects. Exhaustibility (19% all, 30% women, 15% men), brooding (18% all, 20% women, 16% men), hot flushes (15% all; 20% women, 13% men), sweating (12% all; 5% women, 15% men), restless legs (11% all, 5% women, 13% men), heavy legs (12% all, 20% women, 9% men), restlessness (12% all, 15% women, 11% men), sensitivity to cold (12% all, 10% women, 13% men), forgetfulness (11% all, 10% women, 11% men). Listed by >10% of 74: Being cold, tremor, inner tension, impaired balance, dizziness, palpitations, bad dreams, irritability. Listed 3% or less: muscle aches, increased appetite, anxiety, parasthesia, and nausea

**Comments:** While a couple of retrospective studies of ecstasy users have found gender differences the effects of MDMA, this is the first paper that has found gender differences in the effects of MDMA in controlled clinical studies. The higher frequency of acute adverse effects and short-term sequelae reported in women than men has been reported in retrospective studies. Other gender differences in this paper could not be predicted by examining past reports. Specifically, the differences in subjective effects reported by women were not simply greater than those reported by men, but possibly qualitatively different as well. While women were found to be more sensitive to the acute effects of MDMA on perception and thought, men seemed to be more sensitive to the sympathomimetic effects of MDMA. These findings are likely to stimulate further research into gender differences in the effects of MDMA and how these differences may influence the course of use in therapeutic and non-medical settings. One limitation of this report is the disparate number of men to women in this sample. By pooling and presenting data from three previously published studies, this paper is also notable as a clinical report with a large sample size.

**Liechti et al. (2001) Effects of MDMA (Ecstasy) on pre-pulse inhibition.**


**Purpose:** Neuropsychological, psychopharmacological; investigation undertaken to replicate an earlier study that found an MDMA-induced increase in pre-pulse inhibition (PPI) in humans and an investigation of the neurotransmitter systems responsible for this increase. Specific hypotheses tested – 1). That MDMA would produce an increase in PPI in humans 2). That the SSRI citalopram would attenuate the MDMA-induced increase in PPI in humans and 3). That psychological changes produced by MDMA would be associated with differences in percentage of PPI (%PPI) or habituation (% habituation).

**Design:** All 3 studies used experimental 2 x 2,within-subjects designs, with pretreatment (placebo versus pretreatment drug) and treatment (placebo versus 1.5 mg / kg MDMA) each serving as within-subject factors. All subjects participated in 4 treatment conditions (placebo / placebo, pretreatment / placebo, placebo / MDMA, and pretreatment / MDMA), with intervals of at least two weeks between each experimental session. Each study featured a different pretreatment: 16 / 44 received citalopram pretreatment (40 mg IV), 14 / 44 received haloperidol (D2 antagonist) pretreatment (1.4 mg IV) and 14 / 44 received ketanserin (5HT2A/C antagonist) pretreatment (50 mg PO). Data were pooled across all
studies and comparisons were made between MDMA and placebo when investigating the effects of
MDMA alone.
Subjects: 44 mostly MDMA-naïve subjects (34 men, 10 women, ages 21-41) recruited from the medical
school or from hospital staff, with 42 / 44 being either students or physicians. 5 of 44 volunteers had used
ecstasy once or twice in their lives. Startle was successfully measured in 38 / 44 subjects (31 men, 7
women, ages not provided). Data from 6 subjects was not included in PPI studies either due to
insufficient startle response or to artifacts in data. (Same samples featured in Liechti, Baumann et al,
Criteria for Inclusion - Healthy according to physical examination, psychiatric interview, ECG and blood
analysis. No history of major psychiatric disorders in subject or first-degree relatives, and no history of
alcohol or substance abuse. Normal “neuroticism” scores on FPI (no more than 2 standard deviations
above norm).
Measures: Pre-pulse Inhibition (PPI) – A measure of sensorimotor gating. Eyeblink component of
acoustic startle response to noise bursts measured through EMGs of the orbicularis orculi muscle. Startle
trials consisted of 1) 115 dB 40-ms noise alone (no pre-pulse), 2) the same stimulus followed by pre-pulse
stimulus of 20 ms duration or 3) no-stimulus trials, with trials presented in pseudorandom order. Pre-
pulses consisted of 16 dB pulses appearing 30, 60, 120, 240, or 2000 ms before the pulse. PPI measured
90 after drug administration (placebo or MDMA).
Mood – Mood was measured by the AM, administered at time of peak MDMA effects, at 120 min after
drug administration (either placebo or MDMA).
Alterations in Consciousness - Alterations in consciousness were measured via the ASC at the time of
peak MDMA effects, at 120 min after drug administration.
Physiological Measures – HR, systolic and diastolic BP, and BT continuously monitored throughout the
session.
Adverse Effects – Self-reported side effects and short-term sequelae were measured via LC, administered
while subjects experienced acute effects, 24 h and 72 h (3 days) after drug administration.
Analyses: PPI – After calculating % habituation and % PPI, with % PPI calculated for each pre-pulse
condition (30, 60, 120, 240 & 2000 ms before pulse) 2-way analyses of variance (ANOVA) were
performed to exclude treatment order effects, comparing MDMA versus placebo first and MDMA +
pretreatment versus pretreatment first. The effect of MDMA on startle reactivity was examined via 2-way
ANOVA with drug condition (placebo or MDMA) and block (first, middle and last block) as within-
subjects factors. A 2-way within-subjects ANOVA was performed with drug (placebo or MDMA) and
pre-pulse type (30, 60, 120, 240 or 2000 ms before pulse) on % PPI. Pretreatment effects on % PPI were
examined via 3-way within-subjects ANOVA, with pretreatment (placebo or pretreatment drug),
treatment (placebo or MDMA) and pre-pulse type (30, 60, 120, 240 or 2000 ms before pulse) all serving as
within-subjects factors. Separate analyses were conducted for each of the three drug pretreatment
studies. Post-hoc comparisons were performed via Tukey’s LSD test.
Mood – Data were pooled across drug treatment study to examine MDMA-induced changes in mood, via
1-way ANOVA, with drug treatment (MDMA or placebo) used as a within-subjects factor. Pretreatment
moderation of MDMA-induced changes in mood were examined via 3 separate 2-way ANOVAs, with
pretreatment (placebo or pretreatment) and treatment (placebo or MDMA) both serving as within-
subjects factors. Post-hoc comparisons were made via Tukey’s test.
Alterations in Consciousness – Data were pooled across studies and examined via 1-way ANOVA with
drug treatment (placebo or MDMA) serving as a within-subjects factor. 3 separate 2-way ANOVAs were
conducted to examine pretreatment effects on MDMA-induced alterations in consciousness, with
pretreatment (placebo or pretreatment) and treatment (placebo or MDMA) serving as within-subjects
factors. Post-hoc comparisons were made with Tukey’s test.
Adverse Effects (LC) – Data were pooled across studies and examined via 1-way ANOVA, with drug
treatment (placebo or MDMA) serving as a within-subjects factor. 3 separate 2-way ANOVAs were
conducted to examine pretreatment moderation of MDMA-induced side effects, with pretreatment
produce a significant increase in BT. Detailed accounts of MDMA-induced changes in physiological (placebo or pretreatment) and treatment (placebo or MDMA) serving as within-subjects factors. Post-hoc comparisons were made via Tukey’s test.

% Habituation, %PPI and MDMA-Induced Psychological Changes – Spearman’s rank-order correlations were performed on psychological peak changes (MDMA value – placebo value) and changes in %habituation and %PPI, with separate correlations performed for pre-pulses appearing 60, 120 and 240 ms before pulse, using data from 43 / 44 subjects and with p. set at .05.

Results: Effects, Duration – MDMA effects first appeared 45 – 60 minutes after drug administration and peaked 90 – 120 minutes after drug administration. On average, duration of effects was 3.5 h.

PPI, MDMA Alone - MDMA did not significantly alter %habituation, as indicated by a lack of difference in startle response between first and last blocks of trials, when compared with placebo. There were no gender differences in startle reactivity. There was a significant main effect for % PPI indicating importance of duration of interval before pulse. MDMA significantly increased %PPI when compared with placebo. MDMA increased %PPI for pre-pulses appearing 60, 120 and 240 ms before pulse, but not for pre-pulses appearing 30 ms before pulse. A pre-pulse presented 2000 ms before pulse facilitated startle, both in placebo and MDMA conditions. Data from pre-pulses appearing 60, 120 and 240 ms before pulse were collapsed into a mean %PPI score for further analyses.

PPI, MDMA + Citalopram – Citalopram pretreatment did not affect %habituation. Citalopram alone and MDMA alone increased startle magnitude, but they did not produce additive increases in startle magnitude (sign of startle reactivity). Citalopram alone did not alter % PPI, but citalopram pretreatment significantly reduced the MDMA-induced increase in %PPI. Reduction in MDMA-induced %PPI by citalopram was strongest for pre-pulses occurring 60 and 240 ms before pulse, and there was little reduction in %PPI with pre-pulses presented 120 ms before pulse.

PPI, MDMA + Haloperidol – Haloperidol pretreatment did not affect % habituation. Haloperidol did not alter startle magnitude or habituation when given alone, and it did not change the effects of MDMA on startle magnitude. Haloperidol did not reduce the MDMA-induced increase in %PPI.

PPI, MDMA + Ketanserin – Ketanserin alone reduced startle magnitude, but did not reduce startle magnitude when combined with MDMA. Ketanserin did not alter %habituation. Though there was a trend for both MDMA alone and ketanserin alone to increase %PPI when compared with placebo, the increase was not significant. MDMA + ketanserin increased %PPI more than MDMA alone, but this difference just failed to reach significance (p. = .06).

Mood – MDMA significantly elevated scores for “self-confidence,” “heightened mood,” “extroversion,” “introversion,” “sensitivity,” “emotional excitability,” and “thoughtfulness-contemplation.” MDMA significantly increased scores on “inactivation” and “dazed state,” but also produced a non-significant reduction in “tiredness.” More details on pre-treatment moderation of MDMA-induced changes in mood. Presented in previously published studies.

Alteration in Consciousness – MDMA increased scores on all 3 OAV scales, including OB, AED and VR. Increased OB scores were largely due to increases in reported positive mood, positively experienced derealization and “mania-like experience.” Increased AED scores were mainly due to increases in reported thought disorder, and slight fear of loss of body control and fear of loss of thought control. (Thought disorders moderate, including difficulty concentrating, accelerated thinking, thought blocking and impaired decision making). Increased VR were scores were mainly due to reported increases in “changes in the meaning of percepts,” “facilitated recollection” and “facilitated imagination.” Participants reported that colors were more vivid, sense of touch was altered and sounds seemed closer or farther away.

Alterations in Consciousness, MDMA + Pretreatment – Citalopram reduced MDMA-induced increases on all 3 ASC scales (OB, AED and VR). Haloperidol reduced OB scores only, and ketanserin reduced VR scores only. More details of pretreatment moderation of MDMA-induced alterations in consciousness found in previously published studies.

Physiological Effects – MDMA significantly elevated systolic and diastolic BP and HR. MDMA did not produce a significant increase in BT. Detailed accounts of MDMA-induced changes in physiological...
measures and pretreatment moderation of MDMA-induced changes can be found in previously published studies.

**Adverse Effects** – The most commonly reported acute side effects (reported in at least half of the subjects, 22 / 44) were “difficulty concentrating,” “dry mouth,” “impaired balance,” “dizziness,” “lack of appetite” and “jaw clenching.” More detailed account of pre-treatment moderation of side effects and side effects reported 24 h and 72 h post-drug found in previously published studies.

**Adverse Effects, Pretreatments** – Nausea was the most commonly reported side effect of citalopram pretreatment. Drowsiness was the most commonly reported side effect for haloperidol and for ketanserin pretreatment. More details in previously published studies.

**Psychological Ratings and %PPI** – MDMA-induced changes in all 3 scores of the ASC (OB, AED and VR) were positively associated with changes in %PPI. %PPI for pre-pulses 60 ms and 240 ms before pulse (conditions most effected by MDMA) produced strongest correlations. Increased OB and VR scores were correlated with MDMA-induced changes in %PPI with pre-pulses 60 and 240 ms before pulse. Increased AED score was correlated with changes in %PPI in the pre-pulse 60 ms before pulse. Correlations were significant for male subjects but they did not reach significance for females.

**Psychological Ratings and % Habituation** – MDMA-induced changes in the OB and VR scales of the ASC were negatively associated with MDMA-induced reductions in %habituation. MDMA-induced changes in AED were not significantly related to changes in % habituation. There were no gender differences in relationship between change scores for ASC scales and % habituation after MDMA.

**Overall Effects:** MDMA elevated mood and altered consciousness, as reported in previous studies by this team. Most of these subjective effects were reduced by citalopram pretreatment, and some of these effects were altered by haloperidol or ketanserin pretreatment. Haloperidol reduced the increase in positive mood reported after MDMA, and ketanserin reduced changes in perception produced by MDMA. MDMA increased systolic BP, diastolic BP and HR, and produced a number of acute side effects, such as difficulty concentrating, dry mouth and lack of appetite. MDMA increased startle reactivity (startle magnitude) when compared with placebo. While citalopram alone increased startle reactivity and ketanserin alone reduced it, neither drug altered the effects of MDMA on startle magnitude. Haloperidol alone did not affect startle magnitude and did not alter the MDMA-induced increase in startle magnitude. Habituation to acoustic startle trials did not differ between MDMA and placebo conditions, and none of the 3 pre-treatments (citalopram, haloperidol or ketanserin) affected habituation. When given alone, MDMA facilitated pre-pulse inhibition; pre-pulses are more effective at reducing startle with MDMA than with placebo. The results of this study replicate findings from an earlier study conducted by the same team. Only citalopram significantly reduced the effects of MDMA on PPI. Haloperidol did not alter the effects of MDMA on PPI. While ketanserin did moderately enhance the effects of MDMA on PPI, this effect was not significant. When correlated, changes produced by MDMA on all 3 scales of a measure of alterations in consciousness had a significant positive relationship with changes in %PPI produced by MDMA, indicating a relationship between the intensity of the subjective effects of MDMA and the degree to which it increased PPI. The MDMA-induced increase in %PPI was strongest in people experiencing the strongest psychological effects after MDMA. Correlations between peak changes ASC scores and %PPI was not significant for female participants, probably due to there being far fewer females than males in this study. While MDMA did not have any effects upon % habituation, there was a negative relationship between MDMA-induced changes in mood and perception and changes in % habituation. This findings suggest that people experiencing strong psychological effects from MDMA were also liable to experience some disruptions in % habituation. MDMA-induced changes in fear of ego dissolution were not associated (either negatively or positively) with MDMA-induced changes in %PPI, indicating that the intensity of this subjective effect of MDMA is not associated with changes in % habituation after MDMA. All 3 of the authors’ hypotheses are confirmed in this study. MDMA increased %PPI in humans, as was found in an earlier study. Citalopram attenuated the increase in %PPI produced by MDMA. The intensity of the MDMA-induced changes on scores measuring alterations in consciousness were associated with increased %PPI after MDMA, and the intensity of MDMA-induced
changes in positive mood and perception were both negatively associated with decreased %habituation after MDMA.

**Adverse Effects:** See above: details featured in 3 previous studies (Liechti, Saur et al, 2000, Liechti & Vollenweider, 2000a, Liechti & Vollenweider, 2000b).

**Comments:** This study replicates an earlier investigation of the effects of MDMA on PPI in humans, and its results replicate the findings of the first study. Both studies found that MDMA increased PPI rather than reducing it. This is surprising because in rodents, MDMA and other serotonin releasers apparently reduce PPI. The authors present evidence that serotonin release is largely responsible for the MDMA-induced increase in PPI, and not dopamine release (or at least activity at D2 receptors) or activation of 5HT2 receptors through comparing the effects of three relevant pretreatments on PPI. The reduction in MDMA-induced increase in %PPI produced by citalopram is in turn used as evidence that MDMA produces most of its effects by carrier-mediated release of serotonin (5HT). Since people who experience greater elevation in mood, fears of ego dissolution and alterations in perception also experience the greatest changes in %PPI, the two effects may be related to the same process or processes, such as serotonin release. Finding a negative relationship between the intensity of the subjective effects of MDMA and %habituation also suggests that as intensity in subjective effects are further increased (as they may be with higher doses), MDMA may reduce habituation to startle. The authors conclude that MDMA increases PPI in humans and decreases PPI in rodents due to indirect activation of 5HT1 receptors (various types) via serotonin release, with differences in the distribution of these receptors in humans and rodents responsible for differences in the effects of MDMA on PPI seen in the two species.

**Mas et al. (1999). Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans.**


**Purpose:** Pharmacokinetic, neuroendocrine, neurophysiological: “To determine cardiovascular and neuroendocrine effects and pharmacokinetics of MDMA in healthy volunteers…” (p. 137).

**Design:** Randomized double-blind crossover within-subjects design, with drug (40 mg amphetamine, 75 mg MDMA, 125 mg MDMA or placebo) as a within-subjects factor. Volunteers participated in all four sessions, (placebo, 40 mg amphetamine, 75 mg MDMA and 125 mg MDMA, all p. o. Sessions took place two weeks apart.

**Subjects:** 14 MDMA-experienced males, aged 21-30), recruited via “word of mouth” All had used cannabis, cocaine and methamphetamine at least once, and average alcohol consumption was (estimated at) 2 units of alcohol, or 16 g.

**Criteria for Inclusion –** Lack of major psychiatric or medical illness as assessed through interview and physical examination, routine laboratory tests, urinalysis and ECG. Lack of substance abuse (except for nicotine dependence). Past use of MDMA at least 5 times. Urinary drug screens for opioids, cocaine, amphetamines conducted before and after study; all were negative. Identified as extensive metabolizers (measure of CYP2D6) via dextromethorphan / dextorphan assay.

**Measures:**

**Physiological Effects: Vital signs –** HR, BP (systolic and diastolic) and BT measured 30 min pre-drug, immediately after drug administration and at 15, 30, 45, 60 and 90 minutes after drug administration, and after 2, 3, 4, 6, 8, 10, and 24 hours after drug administration. Cardiac activity monitored through ECG.

**Pupillary diameter –** Subjects’ pupillary diameter measured by pupil gauge, with measurements made at 0, 15, 30, 45, 60, 90 min, 2, 3, 4, 6, 8, 10 and 24 h after drug administration.
Chemical assays – Subjects’ blood assayed for MDMA (or amphetamine) and metabolites through gas chromatography. Blood samples drawn immediately after drug administration and 15, 30, 45, 60, 90 min and 2, 3, 5, 6, 8, 10, and 24 h post-drug.

Hormones – Plasma cortisol concentration was detected with fluorescence polarization immunoassay, with assay sensitivity reported at .45 Ug / dl. Prolactin concentration measured through microsphere enzyme immunoassay. Plasma growth hormone concentration measured through solid-phase two-site chemiluminescence enzyme immunoassay, with assay sensitivity reported at .003 ng / ml. Hormones measured in blood drawn before drug administration, immediately after drug administration, and at 15, 30, 45, 60 and 90 min and 2, 3, 4, 6, 8, 10 and 24 h after drug administration.

Pharmacokinetics – Peak concentration (Cmax), time to reach peak concentration (Tmax) and area under curve (AUC0-24) calculated for MDMA and MDA. Using pharmacokinetics software, absorption and elimination half-life computed for MDMA and MDA.

Analyses: Physiological measures (HR, BP, BT, pupillary diameter and hormone concentrations all transformed into differences from baseline. Peak effect until six hours (absolute value of maximum change until 6 h post-drug) and 6-hour AUC calculated by trapezoidal rule for each variable. The transformed data were analyzed via 1-way within-subjects ANOVA with drug condition (placebo, 40 mg amphetamine, 75 mg MDMA or 125 mg MDMA) as within-subjects factor, with p. set at .05. Post-hoc comparisons made with Tukey’s test.

Results: Physiological Effects – Both doses of MDMA (75 mg and 125 mg) and 40 mg amphetamine significantly increased BP and HR compared to placebo. Increase in BP greater for amphetamine and 125 mg MDMA than for 75 mg MDMA, but difference not statistically significant. Maximum peak for both systolic and diastolic BP appeared 90 minutes post-drug for all active drugs. Maximal increase in HR seen 60 minutes after MDMA administration and 8 hours after amphetamine administration. Criteria for hypertension met in 4 volunteers in each of the MDMA conditions and in amphetamine conditions. Three volunteers met criteria for sinus tachycardia, two after 125 mg MDMA and one after 75 mg MDMA. All drugs (amphetamine, 75 mg and 125 mg MDMA) slightly raised BT, but BT not significantly increased by any drug. Pupils more dilated after both doses of MDMA, compared with placebo or with amphetamine. MDMA induced maximal changes in pupil size between 1 and 2 h post-drug, whereas amphetamine produced maximal change in pupil size at 10 h post-drug.

Neuroendocrine Effects – Cortisol concentration significantly higher after both doses of MDMA when compared with placebo (both peak and AUC), and 125 mg MDMA produced increase in cortisol higher than 40 mg amphetamine. Cortisol concentration peaked 2 h after MDMA and 60 min after amphetamine. Prolactin concentration only significantly increased with 125 mg MDMA when compared with all other treatments (placebo, amphetamine or 75 mg MDMA) for both peak and AUC, with prolactin peaking 2 hours after 125 mg MDMA. Growth hormone concentration not influenced by any active treatment (amphetamine or either dose of MDMA).

Pharmacokinetics – Tmax was observed at 2 hours for both doses of MDMA, with plasma levels declining at a mono-exponential level. Average elimination half-life was 7.9 h for 75 mg MDMA and 8.7 h after 125 mg MDMA. MDA (in plasma) appeared slowly shortly after MDMA administration. Cmax of 7.8 ng /l for 75 mg MDMA and 13.7 ng /l for 125 mg MDMA, with peaks reached at 5 to 7 h after drug administration. Formation rate constant for MDA is .75 h(-1) and elimination half life of MDA at 16 to 28 h. Amphetamine Tmax was 2 h after administration, and Cmax was 65 ng / l. Amphetamine had a half-life of 15.3 h (range 9.5-22.5 h).

Overall Effects: While MDMA and amphetamine appeared to have very similar physiological and neuroendocrine effects (increase in heart rate and blood pressure, increase in cortisol) there were some significant qualitative and quantitative differences between amphetamine and MDMA. While both drugs produced an increase in cortisol, only 125 mg MDMA produced a significant increase in prolactin. MDMA at both doses caused more pupillary dilation than did amphetamine. Amphetamine had a longer half-life than MDMA. Systolic and diastolic BP peaked at 90 min post-drug for both doses of MDMA and amphetamine. Yet while HR peaked at 60 min post-drug for MDMA, it peaked at 8 h after drug for amphetamine. Authors note that plasma MDMA concentration with 125 mg MDMA was greater than
would be expected from observing plasma MDMA with 75 mg MDMA, leading them to suggest nonlinear functions in pharmacokinetics for MDMA. None of the drugs produced a significant increase in body temperature, and neither drug stimulated growth hormone secretion. MDA appeared to be a minor metabolite of MDMA, making up 8 to 9% of metabolized MDMA in plasma.

**Adverse Effects:** None measured or reported. However, diagnostic criteria for hypertension (4 / 14) or tachycardia (3 / 14) appeared after either dose of MDMA. No need for clinical intervention reported in any of these cases.

**Comments:** This paper is a companion paper to the Cami et al. (2000) paper comparing 2 doses of MDMA with amphetamine on psychological effects and effects on psychomotor performance. Both papers may assist in differentiating between entactogens (MDMA-like drugs) and stimulants. The authors explain drug-related differences in HR (earlier with MDMA than with amphetamine) as arising from "baroreceptive reflex bradycardia" produced by amphetamine, and state that MDEA (a congener of MDMA) and methylphenidate (Ritalin, a stimulant) have heart rate profiles similar to that of MDMA.

Mas et al. employ a larger sample size than previous pharmacokinetic studies of MDMA, and their findings are comparable to those of Helmlin et al. (1996) and Fallon et all (1999). On the basis of finding an unexpected increase in plasma MDMA with the 125 mg dose when compared with the loser dose, the authors hypothesize that there are non-linear dynamics in MDMA pharmacokinetics.

**Pacifici et al. (1999). Immunomodulating properties of MDMA alone and in combination with alcohol; A pilot study.**


**Purpose:** Immunological, neuroendocrine: “Total leukocyte counts, blood lymphocyte subsets, and lymphocyte proliferative response to mitogenic stimulation, as well as plasma drug and cortisol concentrations, were investigated after the administration of MDMA alone and in combination with alcohol.” (p. PL-310).

**Design:** Randomized, double blind, placebo-controlled cross-over (mixed, within subjects-between subjects) design, with four conditions: placebo, MDMA alone, .8 mg / kg alcohol alone, or MDMA + alcohol, with 1 week between sessions. All volunteers took part in all 4 conditions, but 2/4 volunteers received 75 mg MDMA and 2/4 received 100 mg MDMA in MDMA and in MDMA + alcohol conditions.

**Subjects:** 4 MDMA-experienced males. Age and recruitment method not reported. May have been recruited through “word of mouth” as were men in Mas et al., 1999.

**Criteria for Inclusion –** Not reported beyond “healthy.” Other studies performed by this group used these criteria; lack of major psychiatric or medical illness as assessed through psychiatric interview and physical examination, routine laboratory tests, urinalysis and ECG and lack of substance abuse (except for nicotine dependence).

**Measures:**

- **Immunological Function:** Complete blood profile and cell count conducted on blood drawn from each subject, with samples drawn 1, 2, 6 and 24 h post-drug. Subjects’ lymphocytes cultured in vitro, and lymphocyte proliferation in response to phytohaemoaglutinin A measured via radioimmunassay. Number of lymphocytes counted by cytometer. Dual-color immunophenotyping used to detect immune cell types; helper-inducer, cytotoxic-suppressor, natural killer, mature B and T lymphocytes).
- **Plasma MDMA** – MDMA concentration measured with gas chromatography from samples drawn at preadministration, 15, 30, 45, 60, 75, 90 min, 2, 3, 4, 6, 8, 10 and 24 h post-drug.
- **Plasma Cortisol** – Using same set of samples described above (Plasma MDMA), performed a fluorescence polarization immunoassay (FPIA), with assay sensitivity set at .45 Ug / dL.
**Analyses:** No formal tests of statistical significance reported. Cell counts and tests of immune function apparently compared with published norms available for these procedures.

**Results:** All volunteers had normal immunological parameters (measured pre-drug). All treatments produced changes in immune function, and immune function partially restored to normal 24 h post-drug after all 3 drug treatments.

**Immunological, MDMA Alone** - MDMA produced a time-dependent decrease in CD4 / CD3 cell ratio. Fewer mature T and B lymphocytes were found in samples drawn after MDMA administration, and MDMA reduced lymphocyte response to PHA stimulation. MDMA increased numbers of natural killer cells (NK) in plasma. Change in immune function parallels blood MDMA and blood cortisol levels (with cortisol concentration increased by MDMA), and all changes in immune parameters peaking 1 to 2 h post-drug. Volunteers given 100 mg MDMA had greater reductions in CD4 T-cell counts and lymphocyte stimulation than volunteers given 75 mg MDMA (no tests of significance applied; comparing percentages).

**Immunological, alcohol Alone** - Alcohol alone produced decreased T helper cells (CD4) and B-lymphocytes (CD19), and reduced lymphocyte response to PHA. Time of peak changes in immunological function not reported for alcohol, but extrapolating from charts and alcohol + MDMA, peak change appeared at 1 – 2 h post-drug.

**Immunological Function, Alcohol + MDMA** - Alcohol + MDMA produced greatest reduction in CD4 count and greatest reduction in PHA-stimulated lymphocyte proliferation compared to all other conditions. Time of peak changes in immunological function not reported, but appears to be between 1 h – 2 h post-drug.

**Cortisol, MDMA Alone** – Both doses of MDMA produced a mean rise in plasma cortisol concentration at 2 h post-drug.

**Cortisol, Alcohol Alone** – Alcohol alone did not alter plasma cortisol concentration.

**Cortisol, MDMA + Alcohol** – Alcohol appears to blunt MDMA-induced rise in plasma cortisol.

**Overall Effects:** Doses of MDMA comparable to doses used recreationally induced changes in immune function, including reduced CD4 count, fewer T lymphocytes, less proliferation in response to PHA stimulation and greater numbers of NK cells. Authors refer to this as “immune dysfunction,” since they are uncertain as to whether the net result of these changes will suppress or enhance immune response. MDMA-induced changes in immune function seemed to be time-dependent and dose-dependent and the course of effects ran parallel to MDMA and cortisol concentration in blood. A combination of MDMA and alcohol produced a more pronounced suppression of CD4 cells and a greater reduction in lymphocyte proliferation after stimulation via PHA for both doses. In all conditions, normal immune function was partially restored 24 h post-drug.

**Adverse Effects:** None described beyond reduction in amount of immune cells and responsiveness to mitogen stimulation (PHA stimulation).

**Comments:** This study is a preliminary investigation conducted by the same team that examined cardiovascular and psychological effects of MDMA in MDMA-experienced men. Findings have not yet been put to tests of significance and the small sample size will not allow for generalizing about immune response in the population. However, the results suggest that MDMA’s immunological effects should be pursued further, particularly if therapeutic use of MDMA is given to people with immunological problems (either immune hyperfunction or hypofunction). The findings for acute modulation of immune function is consistent with several studies using rodents (e.g. Connor, Kelly & Leonard, 2000). Authors state that MDMA-induced changes in immune function resemble those produced by (unspecified) psychological stressors, and suggest that MDMA may be viewed as a “chemical stressor.” MDMA did increase cortisol, but it should be noted that while alcohol blunted MDMA-induced rise in cortisol, immune function was most reduced in the alcohol + MDMA condition, suggesting that changes in immune function are not solely regulated via cortisol.
**Pacifici et al. (2000). Immunomodulating activity of MDMA.**


**Purpose:** Immunological: The paper summarizes three lines of research investigating the effects of MDMA on immune response, including in vivo studies performed with human volunteers. MDMA is also compared with the immunological effects produced by amphetamines and amphetamine derivatives.

**Design:** Pilot Study – Randomized, double blind cross-over study, with each subject receiving placebo in one session and MDMA in another session, with half of the subjects receiving 75 mg MDMA and half receiving 100 mg MDMA. (Data presented in Pacifici et al, 1999; half of the complete design, which crossed MDMA administration with ethanol administration). Definitive Clinical Trial – Randomized double blind cross-over design, wherein each subject took part in two experimental conditions, including placebo and 100 mg MDMA. (Data presented in Pacifici, 2001 but with 2 additional subjects included). A week was scheduled between each session for both the pilot and the definitive trials.

**Subjects:** Pilot – 4 MDMA-experienced men, ages not described. Method of recruitment not described, but previous publications indicate that authors recruited subjects through “word of mouth.” Definitive Trial – 8 MDMA-experienced men, ages not provided. 6 / 8 were aged 19-36, with a mean age of 23. Recruitment method not described here, but presumably through “word of mouth,” as was the case for Pacifici, 2001.

**Criteria for Inclusion** – Not described for either study beyond “healthy.” Previous papers (e.g. Mas, 1999) state health was assessed through medical examination and psychiatric interview. Having used ecstasy at least five times in the past and no history of substance abuse, save nicotine dependence. Subjects may also have been typed for CYP2D6 responses, with all subjects required to be extensive metabolizers.

**Measures:** Plasma MDMA and Cortisol – Plasma MDMA concentration was measured using gas chromatography coupled with a nitrogen-phosphorus detector. Plasma cortisol concentration was assessed through fluorescence polarization immunoassay (FPIA). Measures of plasma MDMA and cortisol were performed on blood samples drawn at 0, 15, 30, 45, 60, 75 and 90 min post-drug, and 1, 2, 3, 4, 6, 8, 10 and 24 h after drug administration. (Both studies).

Cell Counts - A complete blood profile and cell count was performed on samples from each subject. Lymphocytes typed by staining with monoclonal antibody reagent. Lymphocytes counted with a flow cytometer. (Both studies) Pilot Study – Cell counts were performed on blood samples drawn before drug administration and at 1, 2, 6 and 24 h after drug administration. Definitive Trial – Cell counts were performed on blood samples drawn before treatment and at 1, 1.5, 2, 6 and 24 h after drug administration.

**Lymphocyte Mitogen Stimulation** - Lymphocytes’ response to PHA tested with a [3H]thymidine test. Lymphocytes were gathered from series of samples described above (0, 1, 2, 6 and 24 h after drug administration for the pilot study and 0, 1, 1.5, 2, 6 and 23 h after drug administration for the definitive trial).

**Analyses:** Pilot Study – No formal tests of significance performed. Definitive Trial – Cell counts and degree of mitogen stimulation in lymphocytes analyzed via repeated-measures ANOVA, with drug condition (placebo or 100 mg MDMA) as one within-subjects factor and time of sample (0, 1, 1.5, 2, 6, and 24 h after drug administration) as the other within-subjects factor. Post-hoc comparisons were performed with Tukey’s HSD test.

**Results:** MDMA and Cortisol – Pilot Study - Immunological alteration paralleled MDMA pharmacokinetics. No information reported on cortisol production. Definitive Trial – Immunological changes paralleled plasma concentrations of MDMA and cortisol, with immunological dysfunction appearing 1 to 1.5 h after drug administration. Plasma MDMA values appeared to peak between 1 and 2 h post-drug, and cortisol values peaked at 2 h after drug administration.
Cell Counts and Percentage of Immune Cell Types – Pilot Study – Total leukocyte count did not differ between MDMA condition and placebo. There was a decrease in CD4 T-cell / CD8 T-cell ratio and a reduction in mature T lymphocytes. When compared with placebo, MDMA increased number of natural killer (NK) cells. Definitive Trial – Results similar to those reported in pilot study; when compared with placebo, MDMA reduced number of CD4 T-cells, reduced CD4/CD8 T-cell ratios and increased numbers of NK cells. In addition, MDMA appeared to decrease the number of CD3 cells when compared with placebo. MDMA did not appear to affect number of CD8 T-cells or B lymphocytes. These changes in cell count were time-dependent, with number of various immune cells partially returned to normal values by 24 h after drug administration.

Lymphocyte Mitogen Stimulation – Pilot Study - MDMA apparently produced a decrease in lymphocyte mitogen stimulation, with the decrease more apparent in people receiving 100 mg MDMA when compared with people receiving 75 mg MDMA. Reduction in lymphocyte mitogen stimulation appeared at 1 h after drug administration in 2 / 4 receiving 100 mg. MDMA. Definitive Trial – Either this test not conducted or data not provided in this publication.

Overall Effects: MDMA in doses of 75 and 100 mg produced time-dependent changes in immune function in otherwise healthy male humans. Specifically, number of CD4 cells, number of mature lymphocytes, and CD4 / CD8 T-cell ratios were all decreased while number of NK cells is increased. There is also a decrease in lymphocyte mitogen stimulation after MDMA administration. These changes appeared at 1 hour after drug administration and they seemed to be associated with the effects of MDMA on cortisol and CRF secretion. The MDMA-induced changes in immune function appeared to parallel plasma MDMA and cortisol values. Normal immune function was partially restored 24 hours after MDMA administration. Findings with human volunteers are comparable to similar findings from in vitro studies using mouse immune cells and in vivo studies with rats. The authors state that similar changes in immune function also appear after psychological stress. Currently, there is no clear indication as to the consequences of these changes in immune system function.

Adverse Effects: None specifically reported in this paper beyond alterations in immunological function.

Comments: A large part of this paper consists of a review of data that has already been presented in two separate papers. The other papers also addressed the immunological effects of coadministering ethanol with MDMA. This study also compares findings in humans with findings from in vitro studies using mouse cells and in vivo studies with non-human animals, mostly rats. In vitro and in vivo rat studies also found that MDMA selectively reduced some T—cells and increasing NK cells. The consequences of these changes in immunological function are currently unknown, but the authors remark that chronic consumption of MDMA may be a health hazard for individuals with compromised immune systems. After comparing the effects of MDMA with the effects produced after psychological stressors, the authors suggest that MDMA is a “chemical stressor.” This last finding may prove interesting to researchers investigating the effects of stress in humans, especially as MDMA may produce a dissociation between feelings of stress or anxiety (generally not present during acute MDMA intoxication) and the physiological stress response. Such a dissociation would allow researchers to examine the “psychological” and “physiological” aspects of stress separately. However, the sample size in the studies with human volunteers remains small, making it difficult to draw definitive conclusions about the effects of MDMA upon the immune system.

Pacifici et al. (2001). Acute effects of 3,4-methylenedioxymethamphetamine alone and in combination with ethanol on the immune system in humans.

Purpose: Immunological, pharmacological: “…to examine acute immunological changes after administration of MDMA alone and in combination with ethanol” in humans.

Design: Randomized, double blind, placebo controlled within-subjects with 2(ethanol: placebo, 0.8 mg / kg ethanol) x 2(MDMA; placebo / 100 mg MDMA) design. All subjects took part in each of the four conditions (placebo / placebo, ethanol / placebo, MDMA / placebo, ethanol / MDMA).

Subjects: 6 MDMA-experienced volunteers, ages 19-36, mean age 23, with average weight of 67 kg and average height of 175.4 cm., recruited via “word of mouth.”

Criteria for Inclusion – Being in good health, as assessed through psychiatric interview and physical examination, smoking no more than 20 cigarettes per day and no more than 60 g of ethanol a day, having used ecstasy / MDMA at least 5 times in the past, no history of substance abuse except nicotine dependence and typed as an extensive metabolizer for CYP2D6.

Measures: Plasma MDMA and Ethanol - Plasma levels of MDMA and ethanol were measured in blood samples taken before treatment and at 1, 2, 4, 6, 8, 10 and 24 h after drug administration, with MDMA and ethanol detected through gas chromatography.

Cortisol – Plasma cortisol concentrations were measured with fluorescent polarization immunoassay, with measures taken from blood samples drawn before treatment and at 1, 2, 4, 6, 8, 10 and 24 h after drug administration.

Peripheral Blood Mononuclear Cell Stimulation – Mononuclear cells were cultured, stimulated with PHA and centrifuged after 72 h incubation. Blood used in all blood cell preparations drawn before treatment and at 1, 1.5, 2, 6 and 24 h after drug administration.

Cytokines – IL-1Beta, IL-4, IL-6, IL-10, TNFAlpha and IFNGamma were analyzed via solid phase sandwich enzyme linked immunosorbent assay. IL-2 and TGFBeta analyzed via solid phase enzyme amplified sensitivity immunoassay. Cytokines measured in blood drawn before treatment and at 1, 1.5, 2, 6, and 24 h after drug administration.

Leukocyte Immunophenotyping – Forms of leukocyte counted with a fluorescence-activated cell sorting analysis. Cells analyzed were helper / inducer cells, suppressor cells, B cells, B lymphocytes and natural killer (NK) cells.

Analyses: Values for lymphocyte subsets, plasma cortisol concentrations and cytokines were transformed into differences from baseline, and maximum change from baseline was calculated for these variables. AUC was calculated for reach variable via trapezoidal rule. A repeated measures ANOVA was performed on these variables, with ethanol (present or absent) and MDMA (present or absent) as the two within-subjects factors. Post-hoc tests using Tukey’s HSD test were conducted on any statistically significant differences. Changes over time course were analyzed with a 2(Time, 0 h to 6 h after drug) x condition (conditions 1 through 4) within-subjects ANOVA was conducted, with post-hoc analyses conducted via Tukey’s HSD test.

Results: MDMA – Alterations in immune function peaked between 1 and 2 h post-drug and had returned to baseline or near-baseline 24 h post-drug. Total leukocyte count was unchanged, but there was a decrease in CD4 / CD8 T cell ratio indicating a decrease in helper cells. There were no differences in amount of suppressor cells or B lymphocytes. The number of NK cells increased. MDMA produced a decrease in the production of the cytokines IL-2 and IFNGamma, both Th1 type cytokines. MDMA increases production of IL-4 and IL-10, both Th2 cytokines. Alterations in immune function paralleled plasma MDMA concentration. MDMA produced a decrease in TNFAlpha and IL-6 and an increase in TFG Beta produced by stimulated mononuclear cells.

Ethanol – Alterations in immune function produced by ethanol also peak within 1 – 3 h post drug and return to baseline or near baseline at 24 h post-drug. Ethanol produced a decrease in number of helper cells and B lymphocytes. Ethanol did not alter amount of suppressor cells or NK cells. Ethanol produced a reduction in the Th1 cytokine IL-2 and an increase in the Th2 cytokine IL-10.

MDMA + Ethanol – When combined, MDMA and ethanol produced changes in immune function that peaked at about 1 h post-drug. This combination had an additive effect on amount of helper T cells, with the greatest decrease in helper T cells produced at this level. The effects of ethanol on B lymphocytes were attenuated by MDMA, with a lesser decrease in B lymphocytes experienced with the MDMA-
ethanol combination. MDMA + ethanol disrupted the balance between pro-inflammatory and anti-inflammatory cytokines. There was a general trend for an increase in anti-inflammatory cytokines and a decrease in pro-inflammatory cytokines. Alterations in immune function paralleled plasma MDMA concentration. Combining ethanol with MDMA had no further effects on stimulated mononuclear cells. Cortisol — Cortisol levels did not change in either the placebo/placebo or the ethanol conditions. A statistically significant rise in cortisol appeared in both the MDMA and MDMA + ethanol conditions, with the rise peaking at 2 h post-drug.

**Overall Effects:** Both MDMA and ethanol produced time-dependent changes in immune function in human subjects. Specifically, MDMA alone decreased the amount of CD4 cells and increased the amount of NK cells. Ethanol alone decreased the amount of CD4 cells and decreased B lymphocytes as well. Combined, MDMA and ethanol produced an even greater decrease in T helper cells while producing less of a change on B lymphocytes. At least in the case of MDMA, these changes paralleled plasma MDMA values, suggesting that MDMA produced these changes in immune function via actions on the CNS, such as monoamine release or increases in cortisol. MDMA shifted the balance of cytokines by decreasing the amount of proinflammatory cytokines in relation ot the amount of anti-inflammatory cytokines. The authors compare alterations in immune function after MDMA to the effects of a psychological stressor, and they refer to MDMA as a “chemical stressor.” It is also suggested that combining MDMA with alcohol amplified the immunological disruptions produced by MDMA alone.

**Adverse Effects:** None reported in this paper beyond alterations in immune function.

**Comments:** This is the third in a series of publications investigating the effects of MDMA, given alone and with alcohol (ethanol), on the immune system. So far, it appears that MDMA at various doses produces the same effects upon the immune system. The authors compare the effects of MDMA to that of psychological stressors, suggesting that MDMA may be a “chemical stressor.” Since MDMA appears to reduce the number of helper cells, it is possible that recreational users face an increased risk of infection from temporary but frequently reduced numbers of CD4 cells. However, the outcome of the immunological changes produced by MDMA are currently unclear, and the sample size used in this study remains very small (six individuals). This research may be relevant when examining the effects of MDMA in people with compromised immune systems or people with auto-immune diseases.

**Shulgin & Nichols (1978). Characterization of three new psychotomimetics.**


**Purpose:** Pharmacological, psychological; to describe the chemistry and the effects of MDMA (and two other compounds) in humans.

**Design:** Uncontrolled within-subjects design, wherein all volunteers received various unspecified doses of MDMA, including doses of 75 mg - 150 mg (effective dose range).

**Subjects:** An unspecified number of human volunteers, all experienced with the effects of psychedelic drugs, gender information and age range not provided. No information on subject recruitment provided. Criteria for Inclusion — Prior experience with psychedelic drugs.

**Measures:** The time course and effects of MDMA were measured through unspecified means, apparently including reports either written throughout the period of intoxication or immediately afterwards. Reports contained information on the duration of the drug’s effects and a narrative description of the drug’s subjective effects.

**Analyses:** No formal tests of significance were performed. Information on the time course of MDMA and its effects is apparently summarized across volunteers.

**Results:** The chemistry and synthesis of MDMA are described, as are the chemistry and effects of two other compounds, para-DOT and alpha-methyl-5-tryptamine. The authors report that MDMA had a higher threshold level (dose at which effects are apparent) than the related compound MDA, but potency...
was similar to that of MDA. The effective dosage range was 75-150 mg in humans when it was administered orally. Volunteers reported the first effects within a half-hour of drug administration, and most volunteers (unspecified number) reached a plateau at 1 h – 1.5 h post-drug. The effects dissipated 3 h after drug administration (2 h after plateau) except for residual “sympathomimetic arousal” lasting several hours (up to 5 or 6 h post-drug). Physical effects were not reported in this paper, and none of the volunteers reportedly experienced any sub-acute psychological effects. The state was described as an “easily controlled altered state of consciousness with emotional and sensual overtones,” and volunteers compared it with marijuana, psilocybin without its hallucinogenic effects or to low doses of MDA.

**Overall Effects**: Volunteers in this study reported the time course of MDMA to be 3 – 6 hours, with most drug effects dissipating at 3 h after drug administration. The first effects were felt .5 h after taking an oral dose of MDMA, and a plateau was reached between 1 h-1.5 h after drug administration. Volunteers reported that MDMA produced an “easily controlled” altered state of consciousness with emotional and sensual overtones, a description that compares well with more recent descriptions of MDMA’s subjective effects. Volunteers rated MDMA as being similar to hallucinogens but without the hallucinogenic effects. None of the volunteers reported unspecified psychological sequelae after drug administration.

**Adverse Effects**: None reported in this paper.

**Comments**: This is the first published report of the effects of MDMA in humans. It is also one of the least detailed. Absent from the paper are any details about the number of volunteers or their recruitment, the nature of the measure, the time or times at which volunteers completed the measure or the manner in which information was summarized across subjects. This paper provided future authors with an oft-quoted phrase describing subjective effects of MDMA in humans. Also contained in the paper is an argument for continued studies of psychedelic drugs using human volunteers.


**Purpose**: Psychological, exploratory; To describe and explore the acute subjective effects of 2 psychoactive phenethylamines by comparing the self-reported subjective effects of the 2 drugs with the self-reported subjective effects of the well-known compound MDMA.

**Design**: Uncontrolled prospective between-subjects (across groups) study design, with drug administered (MDMA, 2CT2 or 2CT7) serving as a between-subjects factor. All subjects completed questionnaires concerning the subjective effects of the specific drug received (MDMA, 2CT2 or 2CT7) and provided open-ended comments about their experiences. Each subject was assessed after receiving 1 drug; there was no placebo condition. MDMA subjects received 120 mg MDMA with 40 mg supplements in requested. 2CT2 subjects received 10-30 mg 2CT2, including supplement, with average dose = 15.7. 2CT7 received 20-25 mg 2CT7, including supplement, average dose 23.1 mg.

**Subjects**: 55 drug-naïve subjects (28 men, 19 women, 8 gender unknown, ages 18-67) where drug-naïve refers only to the substance assessed via questionnaire, depending upon condition); at least 50 / 55 were experienced users of psychedelic drugs. MDMA – Effects assessed in 7 subjects, 3 men, 3 women, 1 gender unknown, ages 32-63, median = 48. 2CT2 – Effects assessed in 40 subjects (21 men, 13 women, 6 gender unknown, ages 18-67, median = 40. 2CT7 – Effects assessed in 8 subjects, 4 men, 3 women, 1 gender unknown, ages 30-57, median = 42. No information on recruitment provided; at least some subjects may have been friends or acquaintances of the researchers or had heard about the study via word of mouth. Criteria for Inclusion – No experience with the specific drug assessed, and a stable personality. While familiarity with psychedelic drugs was not a requirement of study participation, a large majority of the subjects were experienced users of psychedelic drugs.

**Measures**: Author-devised questionnaire, with items addressing physical symptoms, level of intensity, subjective psychological effects concerning emotion, perception and cognitive processes, overall evaluation of drug, evaluation of dosage and desire to repeat the experience. Drug intensity rating scale
devised by Shulgin, Shulgin & Jacob. Subjects completed questionnaire several days after drug administration. Some subjects provided verbal responses rather than completing the questionnaire. **Analyses:** No formal analyses were performed to compare responses across groups or within groups. Means and percentages are calculated for each response for each of the 3 drugs separately, and non-statistical comparisons are made concerning physical symptoms, areas of functioning, preferred dosage and desire to repeat experience. **Results:** **Onset and Intensity** – No measure of onset and intensity is taken for MDMA. However, 3 subjects rated MDMA as very intense, 3 rated it as moderately intense and 1 rated it as not very intense. (2CT2 and 2CT7 tended to have longer onset than MDMA and tended to have a longer plateau, but they were no more nor less likely to be rated as intense as MDMA).  **Physical Symptoms** – MDMA, 2CT2 and 2CT7 were all rated as producing a similar amount of “distracting” symptoms, with low amounts of physical symptoms reported in all 3 cases. The most frequently cited physical effects were self-perceived increase in HR, BT, nausea and “other” (2/7, rating distracting, short duration). 2/7 rated muscle tension as “distracting and long-lasting,” and 1/7 rated muscle tension as noticeable. Vomiting, self-perceived increase in BP, perspiration, and eye darting were not listed. (2CT2 generated the most physical complaints and 2CT7 the least amount. MDMA produced the most “distracting” effects (11.3% short-term distracting, 7.6% long-term distracting after MDMA vs. 6.6% short term, 1.7% long-term 2CT2 and 4.8 short-term, 4.8 long-term distracting 2CT7. Both 2CT2 and 2CT7 differed from MDMA in producing more nausea and vomiting as noticeable, short-duration or long-duration effects.)  **Psychological Effects** – All subjects (7/7) rated MDMA as producing a positive feeling tone, improved clarity of thought and greater perception of higher order meaning. 5/7 reported improved flow of insight, and 6/7 rated MDMA as improving communication with others while 1/7 rated MDMA as producing deterioration in communication with others. 3/7 reported improvement in recall of past events and visual perception. 3/7 rated physical skills, energy level and sense of elapsed time as deteriorating after MDMA, but 1/7 felt physical skills improved after MDMA. 1/7 reported an improvement in general fear after MDMA and 1/7 reported an increase in general fear after MDMA. Closed-eyes visual imagery was largely absent, with 6/7 reporting no closed-eye imagery after MDMA, but it was present in 1/7 individual. No open-eyes visual imagery or hallucinations were present in any subject after MDMA (7/7 reported absence of both). (In comparison, 2CT2 was middling to good in producing insights, ability to perceive higher order meaning while it decreased ability to communicate with others and decreased energy level. 2CT7 was best at improving overall functioning, produced the most euphoria, was both best and worst at producing clarity of thought, was middling at facilitating communication with others and produced a reduction in flow of insights and perception of higher order meaning. Both 2CT2 and 2CT7 produced closed-eye imagery and open-eye visual imagery and hallucinations, but the presence of open-eye visual imagery was more common or prominent with 2CT7.)  **Evaluation and Desire to Repeat Experience** – All subjects expressed a wish to repeat the experience after MDMA. 2/7 wished to repeat the experience with the same dose, 3/7 wished to repeat the experience with a higher dose and 1/7 wished to repeat the experience with a lower dose. (Nearly all (84%) wanted to take 2CT2 again and most, but not all, wanted to take 2CT7 again (75%), with 2CT7 eliciting the largest number of people who did not wish to repeat the experience. A majority of the subjects taking 2CT2 and 2CT7 wished to use a higher dosage if they took it again, and only a few from each group wished to use lower dosages.)  **Overall Effects:** Subjects who had completed a questionnaire a few days after receiving MDMA in an informal setting reported that MDMA produced a number of “distracting” physical effects, including muscle tension, perception of increased heart rate, perceived changes in body temperature and nausea. General feeling tone, clarity of thought and perception of higher order meaning were facilitated by MDMA. While most individuals reported that MDMA improved communication with others, 1 (of 7) reported that MDMA reduced the ability to communicate with others, and 2 of 7 reported decrements in physical skills and energy level. None of the subjects reported increases in energy level, though 3 of 7 reported no change. A small number of subjects reported decreased general fear after MDMA and a small
number reported increased general fear after MDMA. Subjects did not report any visual imagery with open eyes or hallucinations with MDMA, and only 1 of 7 reported some closed-eye imagery. All subjects wished to repeat their MDMA experience, with 2 satisfied with the dose they took, 3 desiring a higher dose and 1 a lower dose. MDMA produced more positive general feeling tone and improved or left intact clarity of thought when compared with 2CT2 and 2CT7. However, MDMA also produced a comparably large number of physical symptoms in contrast to the other 2 drugs, and it did not allow for exploring as wide an array of emotions or feelings.

**Adverse Effects:** See above for self-reported acute physical symptoms and decrements some aspects of functioning. Authors also remark that some subjects experience discomfort after taking MDMA or other psychedelic drugs from confronting “repressed material” or uncomfortable thoughts and feelings.

**Comments:** This paper described a study intended to describe and compare the effects of the phenethylamine hallucinogens 2CT2 and 2CT7, with MDMA serving as a comparison drug. Hence more attention is devoted to elucidating the effects of 2CT2 and 2CT7 than is devoted to considering the responses made after MDMA. Sample sizes for this study are very uneven, with the greatest number of people assessed after first use of 2CT2 and the smallest number assessed after first use of MDMA. Since the vast majority of people participating in this study were familiar with psychedelic drugs, the subjective effects and physical symptoms they experienced may differ substantially from the effects experienced in the population at large during the first exposure to MDMA. Specifically, a greater number of distracting physical symptoms, alterations in perception and disruptive changes in cognitive processes acutely after MDMA might be reported in a sample with little or no experience with psychedelic drugs. It is also unclear whether all subjects completed the questionnaire shortly after receiving the specified drug, or whether there was a great deal of variability in the period of time elapsed between drug administration and completion of the questionnaire. It is possible that the presence or intensity of some subjective effects were forgotten over time or were recalled to conform to peer experiences with the drug or to preconceived ideas concerning its effects. However, the setting employed in this study probably bears a greater resemblance to settings where MDMA is used recreationally than settings employed in controlled laboratory studies.


**Purpose:** Pharmacokinetic: “…a controlled study of MDMA metabolism and disposition in a single patient…” (p. 1649).

**Design:** Single dose study with one subject; authors refer to it as “controlled,” but not enough information provided to confirm accuracy of statement; 50 mg. MDMA administered to subject, with blood samples collected over a 24 h period and urine samples collected over a 72 h period.

**Subjects:** 1 man, aged 40. No information on previous experience with MDMA or of subject recruitment provided.

**Criteria for Inclusion** – Healthy, information on assessment not provided, willing to ingest MDMA as part of controlled study.

**Measures:** MDMA and MDA measured in plasma and urine with gas chromatography/ mass spectrometry. Plasma MDMA and MDA measured in blood sampled at 1, 2, 4, 6, 8, 12, 18, 22 and 24 h post-drug and. Urine MDMA and MDA in fractional urine samples taken at 0-2 h, 2-4 h, 6-8 h, 8-12 h, 12-16 h, 16-24 h, 24-48 h and 48-72 h post-drug.

**Analysis:** No tests of significance over time course: only descriptives and comparison of peak concentration provided.

**Results:** Plasma – MDMA concentration peaked at 2 h post-drug, at 105.6 ng / mL, with values declining mono-exponentially to levels of 5.1 ng / mL. MDMA half-life calculated at 7.6 h. Peak plasma MDA
concentration at 3 h post-drug = 28.4 ng / mL, and declining to 2.4 ng / mL at 12 h post-drug, levels undetectable after 12 h post-drug.

Urine – Unchanged MDMA = major excretion in urine. Over 72 h, 36 mg / 50 mg (72%) MDMA recovered in urine (65% as MDMA, 7% as MDA), and 28% excreted as other (unmeasured) metabolites. 3.52 mg MDA excreted in urine. In urine, MDMA concentration peak at 2 h post-drug (10.77 ng / mL) and MDA concentration peak at 3 h post-drug, at .75 ng / mL. MDMA content declined but remained detectable at 24 h – 72 h post-drug (.026 ng / mL) and MDA still detectable 24 h – 72 h post-drug (.22 ng / mL).

**Overall Effects:** Peak concentrations of MDMA in plasma and urine occurred at approximately same time, 2 h post-drug, with peak concentrations of the metabolite MDA appearing in plasma and urine at 3 h post-drug. MDMA continued to appear in plasma 24 h post-drug, but MDA was no longer detectable in plasma after 16 h. Both MDMA and MDA were found in urine up to 72 h post-drug. In this single-subject study, MDA was the major detected metabolite of MDMA, but more unchanged MDMA was excreted in urine than MDA.

**Adverse Effects:** None reported in this study.

**Comments:** This appears to be a recounting of an early unpublished single-case, single-dose study of MDMA metabolism in humans, conducted in 1985 as part of a doctoral dissertation. The half-life reported here (7.6 h) compares well with the half-life reported by Mas et al. in 1999 for 75 mg MDMA (7.9 h), assessed in 14 male subjects. At this dose and in this subject, a large quantity of MDMA was not metabolized at all before excretion in urine, and only 7% was metabolized into MDA. The remaining 28% was excreted as other metabolites, and these were likely to have been metabolites mentioned in later papers, such as HMMA and HMA.

**Vollenweider (1998).** Recent advances and concepts in the search for biological correlates of hallucinogen-induced altered states of consciousness.

Vollenweider, F. X. (1998). Recent advances and concepts in the search for biological correlates of hallucinogen-induced altered states of consciousness. Heffter Review of Psychedelic Research, 1, 121-132. *(This is a review paper containing information on research performed by the author and his colleagues prior to and during 1998).*

**Purpose:** Neuropsychological; To investigate brain modules and neurotransmitter systems involved in producing drug-induced altered states of consciousness, specifically psychosis-like features produced by hallucinogens and related drugs and to present a model of brain activity during the altered states of consciousness present after use of hallucinogens, entactogens or dissociative anesthetics. *(Review paper).*

**Design:** Comparison across studies. Most studies used a double-blind, placebo controlled experimental design, with at least 2 conditions (placebo or treatment) and occasionally with 4 conditions (placebo / placebo, pretreatment / placebo, placebo / treatment and pretreatment / treatment). Studies that use different treatments and similar measures are compared across drug (ketamine, psilocybin, MDMA, d-amphetamine and placebo), and studies investigating the same drug across different measures are also compared. Nearly all studies reviewed were performed on human subjects, but some studies assess how drugs affect PPI (pre-pulse inhibition) in rats.

**Subjects:** All studies performed on “healthy human subjects.” Subjects in studies involving the measures of the effects of MDMA on PPI and the psychometric effects of MDMA were conducted on a sample of 13 MDMA-naïve subjects. 10 men, 3 women, aged 23-47, recruited from among university students and hospital staff. Imaging studies with MDMA appear to post-date this paper and are not addressed here. (One paragraph refers to an electroencephalographic investigation of the acute effects of MDMA, using LORETA, but little information is given about this study or the individuals participating in it).

**Measures:** Alterations in Consciousness – Via ASC, a self-report measure containing 3 scales, OB (“oceanic boundlessness”), VR, “visionary restructuring” and AED, “fear of ego dissolution.”
Overall Effects: MDMA produced measurable differences in responses to a psychometric measure of alterations in consciousness. Moreover, the acute effects of MDMA were distinguishable from those of a

Pre-Pulse Inhibition – Measured in humans via the eye-blink component of the human startle response to noise bursts presented binaurally, with eye-blink measured with EMGs of the obicularis oculi muscle.

Imaging – Performed via PET. This paper addresses PET studies of the acute effects of psilocybin and ketamine, and does not address imaging after MDMA.

EEG – Performed via low resolution electromagnetic tomography (LORETA), a form of EEG that can locate electrical activity in the brain. LORETA allows for locating differences in distribution of active neuronal populations with high time resolution.

Drug-Drug Interaction Studies – The effects of a test drug on specific neurotransmitter systems are measured by combining the test drug with pre-treatments hypothesized to alter the drug’s actions. Pretreatment drugs mentioned in this paper include 5HT2 antagonists (ketanserin, risperidone) and D2 antagonists (haloperidol, risperidone). This paper does not address the drug-drug interaction studies performed with MDMA as the test drug; studies with psilocybin and ketamine are addressed.

Analyses: NA. (Individual investigations with MDMA used either a 1-way or a 2-way repeated measures ANOVA with post-hoc comparisons made via Tukey’s test. Other studies also used correlations. One study used a factor analysis of PET brain activity and performed a multiple regressions, associating ASC scores with distinct factors of brain activity.)

Results: Alterations in Consciousness – MDMA was compared with other drugs with respect to changes produced in the 3 ASC scale scores (OB, VR and AED). Ratings on all 3 ASC scales were higher after MDMA than after placebo. Comparing across studies, ASC scores after MDMA were different from scores produced after a stimulant (d-amphetamine), a hallucinogen (psilocybin) and a dissociative (ketamine). Ratings of OB, or pleasant derealization and changes in sense of self were high after MDMA, but with only moderately increased scores on VR (changes in perception) or AED (fear of ego-dissolution or loss of control). Psilocybin and ketamine both produced similar OB scores to those produced after MDMA, but the hallucinogen and the dissociative produced higher ratings of VR and AED, indicating a greater degree of altered perceptions and more fear of losing control or of losing the “self.” Subjects who had received amphetamine had AED scores similar to subjects who had received MDMA, but their scores on the VR And OB scales were lower after amphetamine than after MDMA.

Pre-Pulse Inhibition – MDMA reduces PPI in rats, but in humans, MDMA increases PPI. Studies had not been performed on the effects of hallucinogens on PPI, though studies with non-human animals suggest that PPI is reduced by hallucinogens, with 5HT2 antagonists attenuating the reduction in PPI.

Imaging – No information directly relevant to studies involving MDMA. Review addresses studies that find similar patterns of hyperfrontality after the hallucinogen psilocybin and the dissociative ketamine. Using PET conducted with S-ketamine, R-ketamine, psilocybin and amphetamine, the authors found a five-factor model of brain activity, including these factors: “frontal parietal,” “temporal,” “occipital cortex,” “striatum” and thalamus. Overall cortical / sub-cortical organization did not differ between people receiving placebo and drug treatments (psilocybin, R-ketamine, S-ketamine or amphetamine). Yet subjects experiencing hallucinations had higher scores on the “frontal-parietal” and “striatal” networks and lower scores on the “occipital” network. Subjects experiencing hallucinations or changes in perception had alterations in the fronto-parietal, temporal, striatal and occipital network. Positive derealization (OB) was associated with changes in the fronto-parietal, temporal and occipital networks, and fear of ego dissolution (AED) was associated with changes in thalamic activity.

EEG – A study was recently conducted or is nearing completion that has or will investigate the relationships between the thalamus and cortical regions (especially fronto-parietal) acutely after MDMA administration and psilocybin administration. The results were not available or complete at the time of publication.

Drug-Drug Interactions – The author does not report on data gathered from drug-drug studies with MDMA (these were published in 2000). Most of the effects of psilocybin could be attenuated by pretreatment with ketanserin (5HT2 antagonist) or risperidone. Haloperidol pretreatment lowered ratings of OB after psilocybin pretreatment, but increased ratings of AED on the ASC.
stimulant, a hallucinogen and a dissociative. Specifically, the acute effects of MDMA were marked by high levels of “oceanic boundlessness” (pleasant derealization and loosening of ego boundaries) and low to moderate levels of “visionary restructuring” (alterations in perception) and “fear of ego dissolution.” By contrast, psilocybin and ketamine produced higher scores on alterations in perception and fear of ego dissolution and amphetamine produced lower scores on all 3 scales than MDMA. While MDMA reduced PPI in rats, it facilitated PPI in normal human subjects. While the author had not yet investigated the acute effects of MDMA with PET or other imaging methods, he reported an association between different ASC scale scores and brain activity in people given various drugs, including psilocybin and amphetamine. These models found that positive derealization and changes in the sense of self or ego and fear of ego control seemed to arise from different cortical networks. Oceanic boundlessness was associated with changes in the fronto-parietal, temporal and occipital areas, while fear of ego dissolution was associated with changes in the thalamus. Drug-drug interaction studies found that pre-treatment with 5HT2 antagonists, but not D2 antagonists, decreased most of the effects of psilocybin. In contrast, haloperidol increased fear of ego dissolution. Though the author reported that he had conducted or was in the process of conducting a study using LORETA as a means to map brain activity after MDMA, no data was presented concerning the acute effects of MDMA or psilocybin on brain electrical activity as measured through LORETA.

**Adverse Effects:** Hallucinogens, dissociatives and entactogens all produce an increase in fear of ego dissolution or fear of losing control. MDMA produces far less fear of ego dissolution when compared with a hallucinogen or a dissociative. For more details, see above.

**Comments:** This paper reviews a number of studies conducted by the author and his colleagues in an attempt to better understand the effects of hallucinogens and related drugs, including MDMA. The author describes the “cortico-striatal-thalamo-cortical circuit” and its hypothesized relevance to psychosis and the acute effects of hallucinogens. In this framework, MDMA is investigated and used as a comparison drug when examining the effects of other drugs. Because this paper was published in 1998, it does not contain information on more recent studies of the effects of MDMA. Recent studies that measured blood flow acutely after MDMA with PET found that the drug also activates some frontal and temporal areas, as well as the cingulate and the cerebellum. The author does not present a clear role for MDMA in the model of brain activity during altered states of consciousness in this paper, perhaps because many of the studies investigating the effects of MDMA had not been conducted at the time this paper was published.

**Vollenweider et al. (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA (“Ecstasy”) in MDMA-naïve healthy volunteers.**


**Purpose:** Neuropsychological, neurophysiological: “To determine the acute psychological and physical effects, as well as short-term sequelae of a typical recreational dose of MDMA in MDMA-naïve normals in a clinical setting.” (p. 242).

**Design:** Randomized double-blind within-subjects design. Each subject participated in 1 placebo and 1 MDMA session (receiving 1.7 mg / kg MDMA p.o.), with sessions scheduled approximately one month apart.

**Subjects:** 13 MDMA-naïve subjects. 10 men, 3 women, aged 23-47, recruited from university and from hospital staff.

**Criteria for inclusion** – Lack of personal or family history (in first-degree relatives) of psychiatric disorder, no history of substance abuse, healthy as assessed through physical exam, ECG, blood and urine analysis. Scoring in normal range for “openness” and “neuroticism” on personality survey (no more than 2 standard deviations above norm for “neuroticism” and no more than 2 standard deviations below norm for “openness.”
Measures: Mood – AM. Measures taken at baseline and 75 min. post-drug (placebo or MDMA), 75 min post-drug predicted peak for MDMA effects.

Alteration in Consciousness – ASC, measured at baseline and 75 min post-drug (MDMA or placebo).

Stroop Task – Measure of attentional processes. Color words either printed in same color as word (congruent) or in different color (incongruent). Subject names aloud the color the word is printed in. Time between word presentation and speaking aloud (response time or latency) measured for congruent, incongruent and other conditions and these compared. Facilitation = percentage of time reduction in congruent condition compared with control conditions. Interference = percentage of increase in time in incongruent condition compared with control word condition and with control “string” condition.

Adverse effects – The VL, throughout session and 24 h (1 day) post-session.

Physiological Effects – Measures of BP, pulse and BT taken at zero, 75, 150 and 300 minutes after drug ingestion.

Analysis: 2-way within-subjects ANOVA with drug state (placebo versus MDMA) and time (baseline versus measures after ingestion) as within-subjects factors. Post-hoc comparisons performed with Tukey’s test.

Results: Mood – MDMA produced an increase in extroversion, well being, emotional excitability (emotionality, sensitivity) and anxiety as measured by AM. Well-being high due to high ratings of “self-confident” and “heightened mood” and anxiety high due to increases in “thoughtfulness” component of scale.

Alterations in Consciousness – MDMA increased ratings on all 3 item-clusters of the ASC; OB, VR and AED. Increased OB was due to high scores on positive mood, derealization, depersonalization, change in perception of time and space and mania-like experience. Increased VR was due to increased ratings of changed meaning of percepts, illusions, facilitated recall and facilitated imagination, but without increase in hallucinations or synesthesias. Increased AED was due to increased ratings of thought disorder (thought blocking, accelerated thinking and impaired decision-making, but not delusions or paranoia) and loss of body control.

Physiological Effects – MDMA increased systolic and diastolic BP. For systolic BP, greatest changes were between zero minutes and 75 minutes and between 75 minutes and 150 minutes after drug administration. For diastolic BP, greatest changes were between 75 and 150 minutes and between 150 minutes and 300 minutes, with BP peaking at 2 h post-drug. 12 / 13 only mildly hypertensive after MDMA, but BP increased to 240 / 145 in 1 / 13 (age 49), without any signs of hypertensive crisis. Pulse rate was elevated in all subjects, A third (4-5/13) reported experiencing palpitations, but little discomfort. Increase in BT after MDMA was present but not statistically significant.

Adverse Effects – Volunteers experienced side effects acutely and a day later (24 hours post drug), with fewer sub-acute effects versus acute effects. Most of these classed as (acute) stimulant effects, bodily sensations and (24 hours later) lack of appetite, continued jaw clenching, fatigue. Not all volunteers experienced these effects. See below for more details.

Overall Effects: MDMA increased positive mood, extroversion and emotionality. MDMA produced moderate derealization and altered perception without hallucination or confusion. MDMA also increased BP, and pulse, and non-significantly increased BT. Jaw clenching and lack of appetite were the most commonly reported acute adverse effects, lack of appetite and energy were most commonly reported adverse effects 24 h post-drug.

Adverse Effects: Acute: Jaw clenching (8/13), lack of appetite (8/13), difficulty concentrating (8 / 13), impaired balance / gait (8/13), restless legs (6 / 13), perspiration (5 / 13), heavy legs (5 / 13), increased sensitivity to cold (5 / 13), thirst (5 / 13). Others lower than 5 / 13 include forgetfulness, palpitations, restlessness, insomnia, dizziness, and tremor. Less than a third of the volunteers experienced parasthesias, weakness, hot flashes, feeling cold or inner tension. As noted above, BP in 1 / 13 increased to hypertensive range but without signs of hypertensive crisis, and no intervention necessary to reduce BP.

24 h later – Lack of appetite (6 / 13), lack of energy (6 / 13), thirst (6 / 13), fatigue (5 / 13), feeling restless (5 / 13), heavy legs (5 / 13), insomnia (5 / 13), Below 5 / 13 of the volunteers experienced feeling...
weak, urge to urinate, difficulty concentrating, decreased libido. Less than a third of the volunteers experienced: jaw clenching, perspiration, increased sensitivity to cold, brooding or job-related worries. **Comments:** This study is the first to administer MDMA to MDMA-naïve subjects. The psychometric profile supports the existence of an “entactogen” classification for MDMA and like drugs that separates them from stimulants and classical hallucinogens, since MDMA’s effects on mood and consciousness were measurably different from changes produced by stimulants and hallucinogens (measured in other papers). This paper demonstrates that MDMA can be administered to healthy MDMA-naïve volunteers (if selected for normal neuroticism and openness scores) without severe acute adverse reactions or psychological distress.

**Vollenweider et al. (1999).** *Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans.*


**Purpose:** Neuropsychological, psychopharmacological: To compare “the effects of a 5HT releaser, MDMA on [pre-pulse inhibition, PPI] and habituation of acoustic startle in normal laboratory rats versus healthy human volunteers.”

**Design:** A randomized, double blind within-subjects design, wherein volunteers received either placebo or 1.7 mg / kg MDMA during each experimental session, with sessions taking place 2-4 weeks apart. All volunteers underwent PPI testing at baseline and at 75 min post-drug during each session. (Study with rats used similar design, but with different groups of rats receiving different doses of MDMA).

**Subjects:** 13 MDMA-naïve volunteers, 10 men, 3 women, aged 23-47, recruited from university and from hospital staff. (Same sample as used in Vollenweider et al., 1998).

**Criteria for inclusion** – Healthy, as assessed via physical examination, ECG, blood and urine analysis. Lack of personal or family history (in 1st –degree relatives) of psychiatric disorder and no history of substance abuse. Normal range for “openness” and “neuroticism” as scored on FPI.

**Measures:** Mood – AM administered at baseline and approximately 75 min post-drug, (placebo or MDMA), with 75 min post-drug predicted peak time of MDMA’s psychological effects.

**Alteration in Consciousness** – ASC, with measure administered at baseline and approximately 75 min post-drug.

**Pre-Pulse Inhibition (PPI)** – A measure of sensorimotor gating. Eyeblink component of acoustic startle response to noise bursts measured through EMGs of the obicularis orculi muscle. Startle trials consisted of 1) 115 dB 40-ms noise alone (no pre-pulse), 2) the same stimulus followed by pre-pulse stimulus of 20 ms duration or 3) no-stimulus trials, with trials presented in pseudorandom order. Pre-pulse stimuli appeared either 30 or 120 ms before the pulse and either 8 or 16 dB in volume; all pre-pulses lasted 20 ms. (Similar procedure used with rats except whole-body flinch startle response measured and noise presented through speakers placed above rats).

**Analyses:** PPI – % pre-pulse inhibition (PPI), % habituation calculated and compared with absolute scores for PPI and habitation, and both scores found to be similar. After confirming absence of order interactions and presence of treatment effects, % PPI and % habituation analyzed in 2-way ANOVA with drug condition (placebo versus MDMA) and block as within-subjects variables, with post-hoc comparisons made via Tukey’s test. (Rat data analyzed similarly, but with drug dose as a between-subjects factor).

**Mood and Alterations in Consciousness** – A 2-way ANOVA was conducted on measures of mood and alterations in consciousness, with treatment (MDMA versus placebo) and psychological dimension as within-subjects factors. Post-hoc comparisons were made with Tukey’s tests.

**Results:** PPI – MDMA increased startle reactivity and habituation in all 3 blocks, with strongest increase occurring in middle block of trials. MDMA increased % PPI, and this especially so for 16 dB pre-pulse
presented 120 ms before pulse. (In rats, MDMA decreased % PPI at higher doses and did not change % PPI at 1.7 mg / kg dose, same dose as increased PPI in humans.)

Mood – MDMA increased AM scores for extroversion, well-being, heightened mood, emotional excitability (emotionality, sensitivity) and thoughtfulness. Volunteers also reported experiencing enhanced insightfulness, self-confidence and closeness to others.

Alterations in Consciousness - MDMA increased all clusters of ASC (OB, VR and AED). Increase in OB due to increased ratings of “positive mood” (much higher than placebo), “derealization” and “depersonalization” (moderately higher) and “alteration in the sense of space and time.” VR scores increased due to increased ratings of “changed meanings of percepts,” “illusions” and “facilitated recall.” AED scores increased due to increased ratings of “loss of body control” and “thought disorder” (but not delusions).

Overall Effects: 1.7 mg / kg MDMA in humans increased startle reactivity, habituation and % PPI. While MDMA increased pre-pulse inhibition in humans, it either had no effect on PPI in rats (at 1.7 mg / kg) or reduced it (at 5.4 mg / kg and at 17 mg / kg). MDMA did not seem to impair normal sensorimotor gating in humans, and it may have increased sensorimotor gating in humans, at least at the dose examined. Humans who ingested 1.7 mg / kg MDMA experienced an increase in positive mood, extroversion, emotionality, thoughtfulness, some perceptual alterations, facilitated recall, derealization, depersonalization, thought disorder and loss of body control.

Adverse Effects: Adverse effects not reported in this paper. See Vollenweider et al., 1998 for report of adverse effects in this sample.

Comments: In contrast to psychotomimetic drugs such as ketamine, MDMA (at those dose used in this study) did not reduce PPI. This paper is also notable in finding interspecies differences in the effects of MDMA, since it is usually assumed that mammals will respond similarly upon receiving a drug. The paper’s findings indicate that while MDMA might disrupt sensory gating in rodents, it does not do so in humans. Alternately, another effect of MDMA in humans may have counteracted reduction in PPI, or differences between rats and humans might have been an artifact of measurement conditions. This paper is one of the first in an ongoing series of studies examining the neurochemical correlates of PPI in rodents and humans, particularly changes produced by serotonergic agents such as MDMA.
Appendix B: Structured Abstracts of Reports on Human Ecstasy Neurotoxicity Research

Lisa Jerome, Ph.D.

Contains: summaries of all 38 available studies published as of June 1, 2001 in the English-language literature that examined ecstasy users for evidence of neurotoxicity.


Purpose: Sleep study: to investigate whether ecstasy use affects sleep or specific aspects of sleep architecture. Specific Hypotheses Tested – that MDMA users would have decreased total sleep time (TST) and that reduction in TST would be related to reductions in NREM and REM sleep.

Design: Non-experimental (retrospective) 2-group between-subjects (across group) design, with sleep variables measured in ecstasy users and matched non-user controls. All subjects spent 2 nights in a sleep laboratory. Only data gathered from the 2nd night was used in this study.

Subjects: 23 regular ecstasy users and 22 non-users. Recruitment information is not provided in this study, but since ecstasy users came from different geographic locations, recruitment of ecstasy users was not restricted to one locality. Matching – Ecstasy users and non-user controls matched on gender and age. Criteria for Inclusion – Ecstasy Users – Having used ecstasy on more than 25 separate occasions. Controls – No prior history of ecstasy use. All Groups – Absence of any major medical or psychiatric illness, no personal history of major medical illness, absence of current depressive disorder, alcohol dependence or psychosis and no history of sleep disorders. All subjects required to abstain from any psychoactive substances for at least two weeks before the study days, with compliance verified through analysis of blood and urine performed on first study day.

Drug Use Parameters – Ecstasy users reported using ecstasy on an average of 79.4 occasions (25-300). No information is provided on duration of use, typical dose used or frequency of ecstasy use.

Group Demographics and Matched Variables – Ecstasy users matched with non-user controls on age and sex, but not on place of residence. Gender, as M / F ratio – Ecstasy users, 15/8: non-users, 17/5. Age. Ecstasy users, average age 26.7 ± 6, no range provided: non-users, 26.1 ± 4.5, no range provided. Other Variables - Place of Residence. 11 ecstasy users resided in locations in the Eastern and Central time zones, and 12 ecstasy users resided in locations in the Mountain and Pacific time zones. 17 non-users resided in locations in the Eastern and Central Time zones and 3 non-users resided in locations in the Mountain and Pacific Time zones. The study was performed in the Eastern time zone. 6 ecstasy users diagnosed with conditions that might affect sleep and 4 non-users diagnosed with conditions that might affect sleep.

Measures: Sleep EEG recordings, including 2 EEG channels, 2 channels for eye movements, and 1 submental EMG channel. Respiratory activity measured via oximetry, measures of airflow from mouth and nose and respiratory effort measured through abdominal and thoracic strain gauges. Sleep time was from 11:00 to spontaneous waking after 6:00 AM, with a maximum of 8 h sleep permitted. Polysomnograms taken on both nights, but only night 2 analyzed in this study. Sleep stages visually scored for sleep on night 2 by 2 independent raters.

Analyses: Analysis of variance (ANOVA) performed on TST (in minutes) and all stages of sleep save Stage 1 (Stages 2, 3, 4 and REM) sleep. Drug use (ecstasy user versus non-user), time zone of origin (from East to West), age and presence (versus absence) of diagnoses, like alcohol dependence, that might affect sleep all served as independent (subject) variables.
Results – Significant Differences: Ecstasy users had less TST, spent less time in non-REM sleep and had less Stage 2 sleep than non-users.

Results – No Differences Found: Total time spent in REM sleep did not differ between ecstasy users and non-users. There were no differences between ecstasy users and non-users in time spent in Stages 1, 3 or 4 sleep. Though Stage 2 sleep was reduced in ecstasy users, there were no differences in structural features of Stage 2 sleep between ecstasy users and non-users. No sleep abnormalities in sleep records of ecstasy users.

Results – Additional: Older subjects in both groups (ecstasy users and non-users) had less slow-wave sleep (SWS), measured as Stages 3 + 4. Analyses yielded the same differences between drug use groups when 11 / 45 subjects with possible psychiatric diagnoses associated with changes in sleep were removed from the sample. Conducting analyses on 28 / 45 subjects who resided in the Eastern and Central time zones (closest to study location) also yielded the same results.

Overall Effects: Ecstasy users were found to spend less time asleep, as measured via total sleep time (TST) when compared with non-user controls. Ecstasy users also spent less time in non-REM (NREM) sleep. When compared with non-users, ecstasy users spent less time in Stage 2 sleep. Despite these differences in sleep pattern, ecstasy users and non-users did not appear to differ in time spent in any other sleep stages, and no sleep abnormalities were recorded for any of the ecstasy-user participants. In order to account for differences between the two groups in time zone of origin, analyses took this variable into account. Both the differences in TST and Stage 2 sleep and the lack of significant differences in all other sleep variables remained when the analysis was restricted to individuals residing no farther than 1 time zone from the study location. The same results were yielded when age was used as a between-subjects factor. The authors’ hypotheses were partially confirmed: Ecstasy users did exhibit less TST and NREM sleep than did control subjects, but they did not exhibit less REM sleep or in any other facet of NREM sleep.

Comments: To date, this is the only study comparing sleep architecture in ecstasy users and non-users. Ecstasy users were matched with non-users on age and gender, but many more of the ecstasy users resided in an area three time zones away from the study location. However, an analysis that only considered individuals living in the same time zone still found differences in TST and Stage 2 sleep without finding any other differences in sleep pattern. The authors are unable to generate any explanations for the differences they found between ecstasy users and non-users. The results of the only follow-up to this study (presented as part of a review paper not summarized here) did not match these results; ecstasy users in the more recent study spent more time asleep, with increase due to more Stage 3 and 4 sleep, and had greater sleep efficiency than non-users.


Purpose: Cognitive function (memory); Investigation to determine whether regular ecstasy use is associated with memory deficits by comparing drug-free ecstasy users with non-user controls, with an examination of any possible relationships between levels of the serotonin metabolite 5HIAA in CSF and memory scores.

Design: Non-experimental (retrospective) 2-group between-subjects (across-group) design, with regular ecstasy users and matched controls compared on performance on memory tests. The relationship between ecstasy dose and performance on memory tests and between 5HIAA and memory score performance were also examined. Each subject underwent one series of neuropsychological assessments.

Subjects: 24 regular ecstasy users and 24 non-user controls, with ecstasy users recruited via word of mouth and non-users recruited via local advertisements (subjects a sub-set of people participating in McCann et al, 1994). Matching – Groups matched on gender, age, education, other drug use, and WAIS vocabulary score.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 25 separate occasions. Non-Users – No history of prior ecstasy use. All Groups – English as first language, below age 50, WAIS-Vocabulary raw score between 24 and 67, absence of past or present major medical illness, no current major psychiatric illness as determined by psychiatric interview, absence of current alcohol dependence and negative screens for psychoactive or prescribed medications. Abstinence from all recreational drugs for up to 2 weeks prior to the study day, with compliance verified through analysis of urine and blood.

Drug Use Parameters – Ecstasy users reported using approximately 1.6 tablets per occasion (.6-5), and they had used ecstasy an average of 60 times (25-300). Average frequency of use (per month) was 2 times per month (0-20 times), and average duration of use (in months) was 57 months (12-204 months). Average dose of ecstasy per month was approximately 4.4 tablets (.6 – 40 tablets per month). Average self-reported length of drug-free period before study day, in days, 30 days (14-252).

Use of Other Drugs – Ecstasy users reported using any of these substances at least once: alcohol (24 / 24), cannabis (22 / 24), cocaine (20 / 24), hallucinogens (19 / 24), nicotine (14 / 24), benzodiazepines (13 / 24), opiates (13 / 24), other amphetamines (10 / 24), sedatives (9 / 24), solvents (4 / 24) and PCP and related drugs (4 / 24). Non-users reported using any of these substances at least once: alcohol (23 / 24), cannabis (14 / 24), nicotine (9 / 24), hallucinogens (6 / 24), benzodiazepines (5 / 24), sedatives (5 / 24), cocaine (4 / 24), opiates (3 / 24), other amphetamines (2 / 24), solvents (2 / 24), and PCP and related drugs (1 / 24).


Use of Other Drugs – Ecstasy users, 24 / 24 had used alcohol or at least one other illicit drug: non-users, 24 / 24 had used alcohol or at least one other illicit drug (except ecstasy). However, a greater number of ecstasy users than non-users had used every drug listed except for alcohol.

Measures: Measures of Memory - Measured via WMS (13 subtests), RAVLT (verbal memory test), Rey-Osterrieth Complex Figure (RCT) (visual memory test). Individual memory tests reduced to 4 major factors: immediate verbal memory (RAVLT-Logical memory, Digit Span total and verbal paired associates), delayed verbal memory (RAVLT-Recall, RAVLT-Recognition, logical memory-recall and verbal paired associates-recall), immediate visual memory (RCF, visual reproduction, visual paired associates and figural memory) and delayed visual memory (RCF-Recall, visual paired associates-recall and visual reproduction-recall).

Vocabulary – Measured via WAIS-R Vocabulary sub-test, said to be insensitive to changes produced by neurotoxins.

5HIAA in Cerebrospinal Fluid – Concentrations of the 5HT metabolite 5HIAA measured via high-performance liquid chromatography coupled with electrochemical detection.

Analyses: Separate multiple linear regressions were performed on each of the 4 memory factors (immediate and delayed verbal memory, immediate and delayed visual memory). Exploratory analyses were also conducted to find possible relationships between gender, age, vocabulary score, ecstasy dose and performance on memory tests. Regression analyses performed with estimated ecstasy dose (in milligrams) used rather than discrete group membership (ecstasy user versus non-user), with 1 tablet or capsule estimated at 100 mg.

Results – Significant Differences: Tests of Memory – When the influence of gender and vocabulary score removed from analysis, estimated dose was found to be related to decreased performance on immediate paired verbal associates, delayed paired verbal associates and delayed visual paired associates, with performance decreasing as dose increased. When the influence of gender and vocabulary score removed from analysis, estimated dose was found to be related to decreased performance on immediate paired verbal associates, delayed paired verbal associates and delayed visual paired associates, with performance decreasing as dose increased. Significant differences between groups only found when average monthly estimated dose of ecstasy (estimated dose of ecstasy in mg x frequency of use per month) added into the model. (Model also included gender and vocabulary score). Ecstasy dose was
associated with performance on tests of immediate verbal memory and delayed visual memory, with dose associated with poorer scores on these tests. Interaction between vocabulary score and dose on performance on delayed verbal memory, with estimated ecstasy dose associated with poorer performance on delayed verbal memory for subjects with low vocabulary scores, but with no association between dose and poorer performance on delayed verbal memory test for subjects with high vocabulary scores. When the influence of gender and vocabulary score removed from analysis, estimated dose was found to be related to decreased performance on immediate paired verbal associates, delayed paired verbal associates and delayed visual paired associates, with performance decreasing as dose increased. A vocabulary x dose interaction was found for immediate paired visual associates, with decrement in test performance associated with increasing dose affecting those with low vocabulary scores more than those with higher vocabulary scores. There was an interaction between ecstasy dose and gender on performance on immediate verbal associates, immediate and delayed paired visual associates and delayed RAVLT-Recognition, with higher doses of ecstasy positively related to poorer performance for men, but relationship between dose and performance on these tests less strong for women.

Correlations between Performance on Memory Tests and CSF 5HIAA – Concentration of 5HIAA was lower in ecstasy users than in controls. As estimated average monthly dose increases, concentration of 5HIAA in CSF decreases. Lower concentrations of 5HIAA in CSF associated with lower performance on delayed visual memory when effects of gender and vocabulary score are removed from model. Lower concentrations of 5HIAA in CSF associated with lower performance on immediate figural memory and delayed visual reproduction.

Results – No Differences Found: Tests of Memory – First analysis found no differences between ecstasy users and non-using controls on performance on memory tests, as measured through all four factors (immediate and delayed verbal memory, immediate and delayed visual memory). In the analysis using average dose per month rather than group membership, a relationship between dose and poorer scores on delayed verbal memory approached but did not reach significance.

Correlations between Performance on Memory Tests and CSF 5HIAA – There was no relationship between 5HIAA concentration and performance on tests of memory when effects of gender and vocabulary score remained in model. When gender and vocabulary score were entered into model, concentration of 5HIAA was not related to performance on tests of immediate or delayed verbal memory or immediate visual memory.

Results, Other: There was no significant relationship between subject age and performance on any of the four memory factors. Gender and vocabulary score were significantly related to performance on tests of memory (relationships not specified here).

Overall Effects: No differences in performance on tests of memory were found between ecstasy users and matched non-user controls when comparisons were made across groups. There were also no differences in performance on tests of immediate verbal memory and delayed verbal memory when group membership was replaced with estimated monthly dose. There was a trend for a relationship between higher dose and poorer performance on tests of delayed verbal memory, without this reaching statistical significance. The relationship between dose and poor performance on tests of memory (delayed verbal memory) was stronger for people with lower vocabulary scores than for people with higher vocabulary scores. The relationship between increasing ecstasy dose and decreased performance on tests of delayed verbal and visual memory was stronger for men than for women. Ecstasy users were found to have lower concentrations of 5HIAA in their cerebrospinal fluid than non-user controls. While 5HIAA concentration was unrelated to vocabulary score, 5HIAA concentration was related to performance on tests of delayed visual memory, with lower 5HIAA associated with poorer performance on immediate and delayed visual memory.

Comments: Rather than presenting a simple comparison between memory performance in ecstasy users and in matched controls, this paper examines linear relationships between estimated monthly ecstasy dose and performance on tests of memory. While some non-user controls used alcohol and a number of other drugs, a larger number of ecstasy users had tried all drugs measured except for alcohol, indicating that the two groups are not matched with respect to general drug use. Hence it is possible that people who use a
greater number of drugs recreationally also tend to use higher doses of ecstasy, and that increased drug use, and not ecstasy dose, explains decrements in memory. The results from analyses that used gender and vocabulary score as main variables were not presented in this paper.

Boone et al. (In preparation). Neuropsychological Effects of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy).


Purpose: Cognitive function (general); to investigate the effects of regular ecstasy use on cognitive functions measured in a comprehensive neuropsychological test battery. (Also compares performance on a subset of neuropsychological tests before and after the administration of MDMA in a laboratory setting. See “Clinical Study Summaries” for more details).

Design: Non-experimental (retrospective) 1-group design, with performance of ecstasy users on tests of cognitive function compared with published norms, largely matched by age. (Paper also employs comparison between performance at baseline and performance after MDMA administration for a sub-set of the sample. See “Clinical Study Summaries” for details.)

Subjects: 24 regular ecstasy users recruited through local advertisements. Matching – None. There were no controls. However, test scores were mostly compared with age-matched published norms.

Criteria for Inclusion – Having used ecstasy at least three times and for at least 1 year. Good health as assessed through medical examination, psychiatric interview and neurological examination. Lack of personal or family history of major medical or psychiatric illness. No history of substance abuse (except for MDMA or nicotine) and no history of head trauma with loss of consciousness over 30 min. At least 1 month free of psychoactive medications or illicit drugs, with compliance verified on study day by urinary screen conducted before or on study day.

Drug Use Parameters – Subjects reported using ecstasy on an average of 203.8 ± 334 times over a lifetime (3-1500 times) over an average period of 96 ± 57.6 months (12- 204 months). No information on frequency of use is provided. Average dose used per occasion ranged from approximately .6 to 1.75 tablets (or 62.5 to 175 mg). The last reported use of ecstasy before the study, in days, was 193 ± 225.3 days (7.5 – 780 days). Other Drugs – Subjects reported using marijuana (83%), LSD (71%), magic mushrooms (46%) and other amphetamines (29%). 3 / 24 reported using cocaine on > 3 occasions, but were not dependent on it.

Group Demographics and Matched Variables – There were no controls participating in this study.

Gender, as M / F ratio – 16/8. Age. Average = 38 ± 12.6 years, no range provided. Education Level. Average education level was 15.8 ± 3.01 years of education.

Measures: MRI – Performed via clinical 1.5 Tesla scanner.

Neuropsychological Assessment – Tests of Intelligence – WAIS-R (Satz-Mogel format).

Tests of Attention – WAIS-Digit Span (recall and recite digits forwards and backwards). Speed of Information Processing – Stroop A (read color words in black ink) and B (speak aloud color of words printed in same or differently colored ink), WAIS-Digit Symbol (Learn and translate digits into symbols).

Tests of Language – Boston Naming Test. Tests of Constructional Ability – Rey-Osterrieth Complex Figure (Draw complex abstract figure immediately after viewing it). Verbal Memory – WMS-Logical Memory, Warrington Recognition Memory Test-Words (Select one target previously presented out of new list or array) and RAVLT. Non-verbal Visual Memory – WMS-Visual Reproduction, Warrington Recognition Memory Test-Faces (Select one target previously presented out of a new array), Rey-Osterrieth Complex Figure-3 Min Delayed Recall (Reproduce complex abstract figure after delay), Continuous Visual Memory Test (CVMT). Executive Function – Stroop C (color interference), Auditory Consonant Trigrams, Wisconsin Card Sort (WSC) (Derive rules about sorting cards through feedback.
from experimenter), and Verbal Fluency-Words (or Controlled Oral Word Association Test) (Generate as many words as possible in 60 s starting with selected consonant).

**Analysis:** Test Performance - Performance on each test scored for 24 subjects at baseline. (14 / 24 subjects re-tested and scored after MDMA administration). Performance scores on each test compared with published norms matched by age group, except for Copy and Recall scores for Rey-Osterrieth figure, which were matched for sample education. Performance below the 25th percentile or above the 75th percentile considered significantly different from published norms.

**Drug Use Parameters and Test Performance** – Spearman correlation coefficient was used to assess relationship between MDMA user parameters (duration, frequency and recency of use) and performance on each test. (Pre-drug performance compared with post-drug performance for 14 / 24 subjects on each test via paired t-test, see “Clinical Study Summaries.”)

**Results – Significant Differences:** Neuropsychological Tests: Tests of Intelligence – Ecstasy users scored higher than published norms on WAIS-R Full-scale and Verbal IQ scores (FIQ at 87th percentile and VIQ at the 87th Percentile). Tests of Executive Function – Ecstasy users performed below published norms on all trials of the WCS (categories, 11th Percentile, “pers. Response,” 25th Percentile, FTM, below 16th Percentile, errors, 32nd Percentile, %concept, 34th Percentile, Trials, 6th – 11th Percentile). Ecstasy users performed above published norms on Auditory Trigrams, at the 87th Percentile.

**Drug Use Parameters and Test Performance** – Frequency of MDMA use negatively correlated with scores on tests of visual memory and verbal recognition memory, and frequency of use positively correlated with speed in test of mental speed and cognitive inhibition. Length of abstinence prior to assessment positively correlated with performance on measures of divided attention / working memory and visual memory.

**Overall Effects:** When tested on a comprehensive test battery assessing cognitive function, a sample of ecstasy users performed in the range expected of their age group in the majority of tests. They performed above published norms on the WAIS-R, a test of general intelligence, and they performed somewhat below published norms (below 50th percentile). Tests of Non-Verbal Visual Memory – Ecstasy uses did not differ from published norms for WMS-Visual Reproduction, Immediate Recall and Retention (though performance on Immediate was > 75th percentile), CVMT (though “recognition” score at 41st percentile), Warrington Recognition Memory-Faces or Rey-Osterrieth-Delayed. Tests of Executive Function – Performance scores did not differ from published norms on Stroop C or Verbal Fluency-First Consonant (though performance was at 43rd and 47th percentile, respectively.

**Results – No Differences:** MRI – MRI scans normal for all subjects.

**Neuropsychological Assessment** – Tests of Intelligence – Ecstasy users did not differ from published norms for the WAIS-R Performance IQ (though they did perform above the 75th percentile). Tests of Attention – No difference from published norms for Digit Span. Speed of Information Processing – No difference from published norms for Digit Symbol, Stroop A or Stroop B (though performance on Stroop B at 48th percentile). Language – Ecstasy users did not differ from published norms for Boston Naming Test (though performance at 48th Percentile). Tests of Constructional Ability (Visual-Spatial) – Ecstasy users did not differ from published norms on Rey-Osterrieth Complex Figure-Immediate Recall. Verbal Memory – There were no differences from published norms for WMS-Logical Memory, Warrington Recognition Memory-Words or RAVLT scores (though scores on RAVLT over trials varied and fell below 50th percentile). Tests of Non-Verbal Visual Memory – Ecstasy uses did not differ from published norms for WMS-Visual Reproduction, Immediate Recall and Retention (though performance on Immediate was > 75th percentile), CVMT (though “recognition” score at 41st percentile), Warrington Recognition Memory-Faces or Rey-Osterrieth-Delayed. Tests of Executive Function – Performance scores did not differ from published norms on Stroop C or Verbal Fluency-First Consonant (though performance was at 43rd and 47th percentile, respectively.
speed. (Test performance measured 2 to 4 weeks after MDMA administration did not significantly differ from baseline performance).

**Comments:** This study makes a stronger contribution as the first prospective study of cognitive function measured acutely after MDMA administration, with comparisons made at baseline and after MDMA administration in 14 of the 24 subjects. Findings from the prospective study suggest that up to 2 doses of MDMA administered in a controlled setting have little effect on cognitive function, as post-MDMA performance does not differ greatly from baseline performance. Because it lacks a non-user control group and relies on comparisons with published norms, it is difficult to interpret findings concerning test performance in regular ecstasy users. It seems particularly surprising that a group of individuals who score at or above norms on general intelligence do so poorly on tests of executive function. Overall, the findings suggest that ecstasy use is associated with specific deficits in executive function, and that frequent and recent use may affect memory and attentional mechanisms.

**Brody et al. (1998). Cardiovascular autonomic dysregulation in users of MDMA.**


**Purpose:** Physiological, cardiology study; to investigate whether regular ecstasy use affects autonomic tone and function. **Specific Hypothesis Tested** – That ecstasy users would have less bradycardia after performing the Valsalva maneuver, and that they would also exhibit less resting heart rate variability (HRV), an index of parasympathetic tone.

**Design:** Non-experimental (retrospective) 2-group between subjects (across groups) design, with drug-free ecstasy users and matched non-user controls compared on HRV and performance on the Valsalva maneuver, with drug use serving as a between-subjects factor. All subjects underwent cardiovascular monitoring, performed the Valsalva maneuver and completed questionnaires.

**Subjects:** 12 regular ecstasy users and 12 non-user controls, with ecstasy users recruited by word of mouth and “snowball technique” from the local “techno scene.” Recruitment information on controls is not provided. Matching – Ecstasy users were matched with non-using controls on age, sex, weight, extent of cigarette smoking and on amount of exercise.

**Criteria for Inclusion, Ecstasy Users** – Not specified, but having used ecstasy on a regular basis (more often than once). **Non-Users** – Not specified beyond absence of any history of ecstasy use. **All Groups** – Abstinence from ecstasy for at least 6 days prior to study day, with compliance verified through self-report only.

**Drug Use Parameters** – No information is provided on average dose per use or number of days elapsed since last use. Average frequency of ecstasy use reported for the last 6 months was approximately 3.5 times a month (“a little less than once a week”) (approximately .125 – 20 times a month, reported as once in 8 mo – 20 times a month), and average duration of use in months was 48 months (18-84). All ecstasy users had also used marijuana, LSD, botanical hallucinogens and other amphetamines, and all but one had used cocaine. 8 / 12 had tried heroin and 6 / 12 had tried amyl nitrite.

**Group Demographics and Matched Variables** – Ecstasy users matched with non-users on gender, age, weight, cigarette smoking and amount of weekly exercise. Gender, as M / F ratio – Ecstasy users, 8/4: non-users, 8/4. **Age**. Not provided separately, but mean = 25.3 (22-38). **Weight** (not provided separately), in body mass index (kg/m² – 22.3. **Cigarette Use** – (not provided separately), 11 cigarette smokers. **Exercise** – Information for either group not provided.

**Measures:** **Cardiovascular Measures** – Resting blood pressure was measured 3 times, with median used in analysis. Heart rate measured via ECG. **Valsalva Maneuver** – A measure of autonomic tone. Subjects breathe continuously into a tube with a slight leak to produce pressure on a manometer for 20 seconds. **Valsalva ratio** = Maximum interval between R waves / minimum R-R interval during the blowing (strain) phase plus measure 20 seconds afterwards. Subjects performed 2 Valsalva maneuvers, with a 5-min rest period between each
performance. The greater value was used in analysis (ambiguous, but seems to refer to the greater pressure exerted by blowing).

**Personality** – German-language version of the Eysenck Personality Questionnaire (EPQ) was administered to ecstasy users and non-user controls.

**Drug Use** – Author-designed measure of drug use administered to ecstasy users, including items for the drugs listed in “Drug Use Parameters,” fluoxetine and a fictitious drug, KLZ, intended as a measure of self-report honesty. Ecstasy users also asked if they ever experienced any cardiovascular symptoms after ecstasy use. Non-user drug use survey only contained items on alcohol and cigarette use.

**Analyses:** Cardiovascular measures - Valsalva ratios for ecstasy users and non-users were compared via t-test, with further comparisons made via chi-square statistic. T-tests were also used to compare resting HRV, systolic and diastolic BP in ecstasy users and non-users. A correlational analysis (probably Pearson’s correlation coefficient) was performed on resting HRV and Valsalva ratio.

**Personality** – Not enough information provided; If the same procedures used as in other cases, then the EPQ scores of ecstasy users compared with non-users via t-test.

**Results – Significant Differences:** Cardiovascular Measures - Users differed from non-users on Valsalva ratio, with ecstasy users having decreased Valsalva ratio. 3 / 12 ecstasy users, but no controls, had Valsalva ratios below 1.5, the cut-off point for normal autonomic function (suggesting the Valsalva ratios for these users could be indicative of autonomic dysfunction). 5 / 12 ecstasy users but no controls had low Valsalva ratios. HRV differed between ecstasy users and non-users, with ecstasy users having smaller HRV values than non-users. This indicates a lack of bradycardia during the “release” (rest) of the Valsalva maneuver. 9 / 12 ecstasy users had low HRV values, whereas 3 / 12 non-user controls had low HRV values. Resting heart rate and systolic BP were higher in ecstasy users than in non-user controls.

**Results – No Differences Found:** Cardiovascular Measures – Resting diastolic BP did not differ between ecstasy users and non-user controls.

**Personality** – While there was a trend for ecstasy users to have higher extraversion and lower neuroticism scores than non-users, the difference did not reach statistical significance.

**Results, Other:** Correlations - A significant positive correlation was found between Valsalva ratio and HRV for both ecstasy users and non-user controls. Questionnaire – 8 of 12 ecstasy users reported experiencing tachycardia or circulatory problems acutely after taking ecstasy.

**Overall Effects:** Regular ecstasy users differed from a group of non-user controls matched on a number of variables, with ecstasy users demonstrating a lower Valsalva ratio and lower HRV. They also had higher values for resting HR and systolic BP. Since these measures are used as indicators of autonomic dysfunction, ecstasy users in this sample were considered more likely to have some form of autonomic dysfunction. Specifically, they showed less bradycardia during the rest phase after performing the Valsalva maneuver, which the authors interpret as a sign of decreased parasympathetic tone. The authors’ hypotheses were confirmed, with ecstasy users demonstrating less bradycardia after performing the Valsalva maneuver and having less heart rate variability than non-users.

**Comments**: Currently, this is the only paper examines cardiovascular function in regular ecstasy users. Other papers have either presented case reports of cardiovascular problems occurring acutely after ecstasy use or have investigated acute cardiovascular responses to MDMA in humans. This study suggests that ecstasy may alter autonomic function in otherwise healthy young humans, either through increased sympathetic tone or decreased parasympathetic tone. Sample size is small, with 12 subjects in each of the two conditions, making it more difficult to rely on the findings in this study to make predictions about the general population.

Chang et al. (2000). Effect of Ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow; A co-registered SPECT and MRI study.

**Purpose**: Brain imaging (SPECT) “This study evaluates the chronic and sub-acute effects of MDMA on brain function as measured by regional cerebral blood flow.” (p. 16). The study compared scans of MDMA users with scans from controls with no history of MDMA use, and also compared scans taken before MDMA administered in a clinical setting and scans taken after MDMA administration (See “Clinical Study Summaries.”)

**Design**: Non-experimental 2-group between-subjects design to compare scans of ecstasy users with scans of matched non-user controls, with drug use as between-subjects variable. (A randomized, double blind, placebo controlled within-subjects experimental design was used to compare pre-MDMA scans with scans performed after MDMA administration in sub-set of 10 ecstasy users). 

**Subjects**: 21 ecstasy users and 21 non-users recruited through local advertisements (in California area). **Matching** – Groups matched on gender, age and socioeconomic status. (Some individuals participating in this study also participated in studies reported in Chang et al., 1999 and Boone et al., in preparation). **Criteria for Inclusion, Ecstasy Users** – Reported using low doses of MDMA, with low doses defined as (< 3 mg / kg per occasion, with occasions occurring at least 6 times a year for at least one year. **Non-Users** – No prior history of ecstasy use. **All Groups** - Good health as assessed through medical examination, psychiatric interview and neurological examination, and not pregnant. Lack of personal or family history of major medical or psychiatric illness. No history of substance abuse (except for MDMA or nicotine) and no history of head trauma with loss of consciousness for more than 30 min, no metallic objects in body. Abstinent from psychoactive medications or illicit drugs for at least 1 month prior to study day, with compliance verified by urinary screen conducted before or on study day. 

**Drug Use Parameters** - Ecstasy users reported using ecstasy on a median of 75 occasions or 211 ± 340 times (6-1500), and they used an average of approximately 1.25 – 2.25 tablets per use. Average frequency of use was provided. Duration of use, in months, was an average of 103.2 ± 58.8 months, median 120 months, range 12 -204). Average lifetime exposure, in grams, estimated at 13.1 g (.5-263 g). Self-reported length of drug free period before study day, in days, was an average of approximately 198 ± 231 days (15-425, median of 120 days). **Use of Other Drugs** – 83% of ecstasy users had used marijuana at least once, 71% had used LSD at least once, 46% had used hallucinogenic mushrooms at least once and 29% used other amphetamines at least once. No one reported dependence on these other substances and use was minimal to moderate.

**Group Demographics and Matched Variables** – Ecstasy users matched with non-user controls on gender, age and socioeconomic status (as indicated through education). **Gender**, as M / F ratio – Ecstasy users, 17 / 4; non-users, 17 / 4. **Age** – Ecstasy users, 43.4 ± 12.5 years, range not provided: non-users, 43.7 ± 11.7 years, range not provided. **Education** – Ecstasy users had an average of 15.9 ± 2.2 years of education and non-users had an average of 16.2 ± 2.3 years education. **Other Variables** – All subjects were employed or attending school and none had a criminal record.

**Measures**: **Imaging** – Via [99mTc]-HMPAO SPECT scan co-registered with MRI scan. MRI performed with 1.5 T scanner. SPECT procedure relied on inhaled [133]xenon for absolute CBF and [99mTc]-HMPAO for higher resolution images. (A sub-set of 10 ecstasy users was scanned again after MDMA administration in a controlled clinical setting). 

**Analysis**: Regions of interest (ROIs) selected by investigator blinded to drug use condition. Scans from ecstasy users compared with controls via 3-way mixed model ANOVA, with drug use (ecstasy use or non-use) as a between-subjects factor and brain hemisphere (L or R) and brain region as within-subjects factors.

**Drug Use Parameters and Brain Image Variables** – Multiple linear regressions were used to assess the existence of any possible relationships between 3 drug use parameters (cumulative lifetime exposure, frequency of use and time since last use) and cerebral blood flow (global and regional CBF). Multiple regressions were performed to assess the relationship between cumulative lifetime exposure, frequency of use and time since last use global brain volume, global CSF and %CSF.
**Results – Significant Differences:** Imaging – None found. (Differences were found in rCBF in 8 ecstasy users scanned approximately 2 wks after MDMA administration, including decreased rCBF in visual cortex, caudate, superior parietal and dorsolateral frontal cortex, and increased global CBF found in 2 ecstasy users scanned a month after MDMA administration, see “Clinical Study Summaries”). Drug Use Parameters and Brain Imaging Variables - Multiple linear regressions found a negative correlation between brain volume and cumulative lifetime exposure to ecstasy (duration of use), with brain volume decreasing with increased duration of use. The association remained even when controlling for age.

**Results – No Significant Differences:** Imaging – No differences in MRI between ecstasy users and non-users, with all images normal. Global CBF lower in ecstasy users than in non-user controls (2.3% lower), but this difference was not significant. Global brain volume, global %CSF and %CSF were similar in ecstasy users and non-users. Drug Use Parameters and Brain Imaging Variables – Global and rCBF were not associated with duration of ecstasy use, frequency of use or recency of use.

**Overall Effects:** A comparison of SPECT scans of ecstasy users and age and gender-matched controls failed to find any significant differences in global CBF, rCBF, brain volume, global CSF or percentage of CSF. While global and rCBF were mildly decreased in ecstasy users, the decrease was small and did not reach statistical significance. Frequency and recency of ecstasy use were not associated with differences in CBF, brain volume or %CSF. Duration of ecstasy use (cumulative lifetime exposure) was associated with brain volume, with duration negatively correlated with brain volume. Regular ecstasy use did not produce changes in cerebral blood flow, and only duration of use affected one brain-related variable.

**Comments:** This paper reports findings from a SPECT study that did not employ radioligands. The lack of any significant differences in CBF between ecstasy users and non-user controls is more surprising given the fact that changes in CBF were found to occur 2 weeks and 1 month after MDMA administration. These findings are reported in the same paper and refer to a sub-set of ecstasy users given 2 doses of MDMA in controlled clinical settings. These findings suggest the possibility that ecstasy / MDMA produces change in CBF that are persistent but not permanent. However, the lack of an association between recency of ecstasy use (time since last use) and changes in CBF, reported in the same paper, does not support this conclusion. The consequences of reduced brain volume with increasing duration of use are unclear, but are consonant with other studies that find associations between duration of use or cumulative exposure and decrements in cognitive function.

Chang et al. (1999). Cerebral H-MRS alterations in recreational 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”) users.


**Purpose:** Brain imaging (MRS), to investigate neurochemical abnormalities in the brains of ecstasy users.

**Design:** Non-experimental (retrospective) 2-group between-subjects (across groups) design, with drug-free regular ecstasy users compared with matched non-user controls, with all subjects receiving MRI and 1H-MRS imaging.

**Subjects:** 22 regular ecstasy users and 37 non-user controls consecutively recruited from the local community (Southern California). Matching – Groups matched on age and sex. (A sub-set of this sample also participated in the studies reported in Chang et al, 2000 and Boone et al, in preparation).

**Criteria for Inclusion – Ecstasy Users** – Having used ecstasy at least 6 times a year for 1 year and abstinence from ecstasy for at least 2 weeks before study day, with compliance verified via drug screen (screen not described, but Chang et al, 2000 relied on urinary screen). Non-Users – No history of prior ecstasy use. All Groups – Healthy as assessed through medical and psychiatric examination, with no history of past or present medical or psychiatric illness, not taking prescribed medication for medical or psychiatric illness, no history of alcohol or substance abuse (other than ecstasy for ecstasy users), no history of head trauma with unconsciousness lasting over 30 min and no metallic objects in body.
Drug Use Parameters – Ecstasy users reported using ecstasy on a median of 75 occasions (6-1500), and they used an average of approximately 1.25 – 2.25 tablets per use. Average frequency of use not provided, but reported duration of use, in months, with a median value of 120 months, (12 -204).

Average lifetime exposure, in grams, estimated at 13.1 g (.5-263 g). Self-reported length of drug free period before study day, in days, was approximately 120 days (15-425 days). Use of Other Drugs – 83% of ecstasy users had used marijuana at least once, 71% had used LSD at least once, 46% had used hallucinogenic mushrooms at least once and 29% used other amphetamines at least once. No one reported dependence on these other substances and use was minimal to moderate.

Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender and age. Gender, as M / F ratio: Ecstasy users, 15 / 6, non-users, 22 / 15. Age. Ecstasy users, 19-75, median = 43 ± 14.6: non-users, 22-80, median = 38 ± 14.7. Other Demographic Variables – Median educational level reported by ecstasy users was 15.8 years (12-20 years). All ecstasy users were either employed or enrolled in school, and none reported having a criminal record.

Measures: Imaging – MRI – Performed via 1.5 T scanner. 1H-MRS – 1H-MRS performed in the mid-occipital gray matter, mid-frontal gray matter and R parietal white matter. Substances assessed in brain via MRS were N-acetyl-L-aspartate (NA), creatine (CR), choline compounds (CHO), myo-inositol (MI) and glutamate / glutamine ratios (GLX), with all substances converted from “institutional units” to millimolar concentrations using published norms for each brain area.

Analyses: Imaging - Two-tailed unpaired t-tests were performed on concentrations of all metabolites listed in each brain region, with comparisons made between ecstasy users and non-user controls. An analysis of covariance (ANCOVA) was also performed upon brain metabolite concentrations in ecstasy users and non-users, with age serving as covariate.

Metabolite-Ecstasy Use Parameter Relationships – Linear regressions were performed on brain metabolite concentrations in each selected brain region in ecstasy users only. Cumulative lifetime dose transformed into logarithm.

Results – Significant Differences: 1H-MRS – MI and MI / CR ratios in parietal white matter were elevated in ecstasy users. MI elevated in parietal white matter of ecstasy users when age was controlled for via ANCOVA with age as covariate. CHO / CR ratio in mid-occipital gray matter, elevated in ecstasy users, due to less CR found in ecstasy users.

Metabolite-Ecstasy Use Parameter Relationships – Positive relationship between concentration of MI in both parietal white matter and occipital gray matter and log of cumulative lifetime dose, with higher cumulative doses associated with greater MI in parietal white matter and mid-occipital cortex when compared with values in non-user controls. Duration of ecstasy use was positively correlated with MI concentration in parietal white matter and mid-frontal gray matter, with trend for significant relationship in occipital gray matter, with greater MI associated with longer duration of ecstasy use. Positive relationship between choline compounds (CHO) in parietal white matter and duration of ecstasy use, with elevated choline compounds associated with longer duration of ecstasy use.

Results – No Differences Found: MRI – No differences in brain structured between ecstasy users and non-users, with all images normal. 1H-MRS – Concentrations of NA, choline compounds, creatine compounds, glutamate / glutamine ratio in all three brain regions (mid-occipital gray matter, mid-frontal gray matter and R parietal white matter. No lactate or excess lipids found in brains of either group. (Amount of CR may be decreased in ecstasy users in mid-occipital gray matter only.)

Metabolite-Ecstasy Use Parameters – No relationship between log of cumulative lifetime ecstasy dose and concentration of NA, creatine-containing compounds, choline containing compounds or glutamate/glutamine ratio in all 3 selected areas (mid-occipital gray matter, mid-frontal gray matter and R parietal white matter). No relationship between log of cumulative lifetime ecstasy dose and MI concentration in mid-frontal gray matter. Figures not reported on relationships between duration of ecstasy use and other brain metabolites, indicating no significant relationships found between duration of use and NA, creatine compounds or glutamate / glutamine ratio in all three brain areas. No significant relationship between recency of ecstasy use and any of the brain metabolites (NA, MI, CHO, CR, GLX) in any of the three areas (mid-occipital gray matter, mid-frontal gray matter, R parietal white matter).
Overall Effects: When compared with non-using controls, ecstasy users had elevated concentrations of myo-inositol (MI), a tentative glial marker, in parietal white matter, and they also have elevated MI / creatine levels. Ecstasy users have elevated CHO / CR levels in mid-occipital gray matter when compared with non-user controls, with this difference chiefly due to lower levels of creatine compounds. However, there is no sign of increased N-acetyl-L-aspartate (NA), considered an indicator of cell death, in ecstasy users. For the most part, concentration of various markers within the brain were found to be similar in ecstasy users and non-user controls, and this remains true when controlling for age. However, some parameters of ecstasy use were associated with higher or lower levels of specific markers. Cumulative exposure to ecstasy was associated with higher levels of MI in parietal and occipital areas, and duration of ecstasy use was associated with higher levels of MI in parietal and mid-frontal areas, and perhaps with elevated MI in mid-frontal areas as well. Duration of ecstasy use was also associated with greater amounts of choline compounds in parietal white matter when compared to non-user controls. Recency of ecstasy use was not associated with amount of any marker measured in brain.

Comments: To date, this is the only paper that uses MRS Imaging to examine brain metabolites in ecstasy users and non-users. While lack of elevated NA values indicated lack of cell death arising from ecstasy use, an increase in MI in ecstasy users suggests that ecstasy use might still produce some form of harm to the brain. The findings in this paper suggest that regular ecstasy use may have an additive effect on specific markers of brain activity, with cumulative lifetime exposure and duration of use both associated with increased MI in selected brain areas. However, the authors did not conduct regressions using average dose per use, so it is possible that people who have used ecstasy for a longer time also tend to use higher doses. Because this is a new area of research, and the significance of elevated NA, MI or CR is not entirely clear, it is somewhat difficult to draw definite conclusions on the basis of these findings.

Croft et al. (2001). The relative contribution of Ecstasy and cannabis to cognitive impairment.


Purpose: Cognitive function (general), personality: to investigate the respective effects of ecstasy and cannabis on human cognitive function using measures comparable with those employed in previous investigations of the effects of regular ecstasy use on cognitive function.

Design: Non-experimental (retrospective) 3-group between subjects (across groups) design comparing drug-free ecstasy users with cannabis using and non-using controls, with drug use (ecstasy + cannabis, cannabis only or control) serving as a between-subjects factor. All subjects completed the same set of neuropsychological tests.

Subjects: 11 regular ecstasy users, 18 regular cannabis user controls and 31 non-user controls residing in the London (England) area, recruited via word of mouth, advertisements posted in the local area and in the London magazine “Time Out.” Matching – Authors did not appear to explicitly match subjects on any one variable. However, all 3 groups are matched for estimated full-scale IQ (via NART score), education and (approximately) on age. Non-user controls and ecstasy + cannabis groups were approximately matched in gender.

Criteria for Inclusion, Ecstasy Users – Having used ecstasy at least once and abstaining from ecstasy or cannabis use at least 48 h before study day, with abstinence confirmed by self-report only. Cannabis Users – Having used cannabis at least once, no prior history of ecstasy use, and abstinence from cannabis for at least 48 h prior to study day. Non-Users – Not currently using cannabis and little or no prior history of cannabis use or ecstasy use. All Groups – Absence of current or past neurological or psychiatric illness.

Drug Use Parameters – Ecstasy Use – Users reported taking an average of 41.9 ± 49.3 tablets over lifetime, range not provided. Information on duration or frequency of ecstasy use not provided. Information on average dose per use not provided. Cannabis users reported an average lifetime ecstasy
use of .6 ± 1.3 tablet. **Cannabis Use** – Ecstasy users reported an average lifetime use of 10,964.9 ± 13,235.5 joints. Cannabis users reported average lifetime use of 7762.4 ± 14,480.9 joints. Non-users reported an average lifetime use of .5 ± .8 joints. **Other Drugs** – Average lifetime use of cocaine was 6.4 ± 6.1 grams, 5.7 ± 13.3 grams for cannabis users and no exposures for non-user controls. Average lifetime exposure to speed was 20.4 ± 29.7 tablets for ecstasy + cannabis users, 12.1 ± 19 for cannabis users and no lifetime use for non-users. Ecstasy users had an average lifetime use of alcohol at 3484 ± 3254 “standard units” alcohol, cannabis users reported lifetime use of alcohol at 5309.8 ± 6517.5 “standard units” and non-users reported total lifetime alcohol use at 3875.3 ± 4407.8 “standard units.”

**Group Demographics and Matched Variables** – Authors did not report matching groups by any variable. However, ecstasy + cannabis, cannabis and non-user groups seem to be matched on the basis of estimated general IQ, education level and age, and the ecstasy + cannabis group is approximately matched with non-users on gender. **Estimated General IQ**, estimated via National Adult Reading Test score, a measure of vocabulary and verbal intelligence, with values presented as IQ: Ecstasy users, 116.2, cannabis users, 115.2, non-users, 115.2. **Age**. Ecstasy users, 25.7 ± 4.7, no range provided: cannabis users, 26.6 ± 8.1, no range provided: non-users, 23.5 ± 6.8, no range provided. **Education Level** – Coded as 1 = O levels (educational exam at 15 years old), 2 = A Level (examination at 17 years), 3 = university degree: Ecstasy + cannabis users had an education level of 2.5 ± .65 (approximately 15.5 years), cannabis users had an educational level of 2.43 ± .79 (approximately 14.8 years) and non-users had an educational level of 2.57 ± .63 (approximately 15.7 years). **Gender**, as M / F ratio, Ecstasy + cannabis users, 14 / 17: cannabis users, 5 / 6: non-users, 14 / 4.

**Measures**: Warrington Recognition Memory Tests, for Words and Faces (Select one target previously presented out of new list or array.) Grooved Pegboard (Rapidly place 25 pegs into non-uniform matching holes, performed with one hand, with test conducted with each hand. Authors distinguish performance by hemisphere presumably involved, not hand, so Left Pegboard performed by right hand). Spatial and Non-Spatial Associative Learning Test (Learns association between pairs, with subject first guessing and receiving feedback. Task complete when 18 associations reported and score = number of guesses). Digit Span (Forward and backward). Verbal Fluency (Generate words starting with consonant or belonging to category in 6 sec). Stroop A, Stroop B (Color words printed in black ink, read aloud in Stroop A; color words printed in same and different colored ink, name color ink (incongruent). Stroop A measures speed of reading, Stroop B measures cognitive interference. Coughlan List and Design Learning (Learn first list of 15 words through repetition of list and recall of all items (list 1to5), and interference measured with second list presented after first is learned (list B) and delayed recall measured on list (list6). Recall for design measured by redrawing design, also has interference and delayed recall.) National Adult Reading Test (NART) – Read 50 words aloud, where pronunciation cannot be derived from standard rules of pronunciation.

**Other Measures** – Several personality questionnaires, with results not reported in this paper. Half the subjects paid for participation to measure effects of motivation on performance. Authors reported that there were no differences between paid and unpaid subjects on any of the tests, nor any interaction between monetary incentive and drug use, indicating little or no effects of motivation.

**Analyses**: Across-Group Comparisons - Scores on several tests transformed before analyses. Scores from each test analyzed via between subjects ANCOVA (analysis of covariance), with drug use group (ecstasy + cannabis, cannabis or non-user) serving as between subjects factor and with age, gender or NART score serving as covariates if they were found to be significant in earlier analyses. Directional tests were used, with predicted outcome that ecstasy + cannabis group would perform worse than cannabis or non-user group.

**Drug Use Parameters and Test Performance** – 4 additional ANCOVAs were performed an all test scores where differences between drug user groups and control groups found. A separate ANCOVA performed, with one of the variables listed serving as the covariate: total lifetime ecstasy use, frequency of ecstasy use, total cannabis use and frequency of ecstasy use.

Drug Use Parameters and Test Scores, Ecstasy Use – Stroop A, total ecstasy use, correlated at .31, and frequency of ecstasy use, correlated at .24. Cannabis Use – Total cannabis use correlated with test scores on: Warrington-Faces (.21), spatial associative learning (.38), non-spatial associative learning (.29), and Digit Span-Backwards (.43). The following test scores are correlated with frequency of cannabis use: Stroop A (.21), Warrington Faces (.38), spatial associative learning (.23), Digit Span-Forward (.43), Digit Span-Backward (.32) and Verbal Fluency-Animals (.39).

Results – No Differences Found: Warrington Recognition Memory-Words, Spatial Associative Learning, Stroop B (interference), Verbal Fluency-First Consonant, Coughlan-List B (interference), Coughlan-List 6 (delayed recall), Coughlan-Design B (interference), Coughlan-Design 6 (delayed recall for design), Grooved Pegboard-Right (left-handed performance). No differences between performance of ecstasy + cannabis, cannabis or non-user groups.

Drug Use Parameters and Test Scores, Ecstasy Use – None of the following test scores correlated with either total ecstasy use or frequency of ecstasy use at values above .2: Warrington-Faces, Spatial-Associative Learning, Non-spatial Associative Learning, Digit Span-Forward, Digit Span-Backward, Verbal Fluency-Animals, Coughlan-List 1 to 5 or Pegboard-Left. Cannabis Use – The following test scores did not correlate with total cannabis use at values above .2: Stroop A, Digit Span-Forward, Verbal Fluency-Animals, Pegboard-Left. The following test scores did not correlate with frequency of cannabis use at values above .2: Non-spatial associative learning, Coughlan-List 1 to 5, Pegboard-Left.

Overall Effects: Both cannabis users and ecstasy + cannabis users performed less well than did non-user controls matched by age, education level and NART score on an array of neuropsychological tests measuring verbal and visual memory, verbal and visual learning, manual dexterity and executive function. Cannabis users did not perform as well as ecstasy + cannabis users on one test (Coughlan-Design 1 to 5), a test of immediate recall and learning. Analyses that employed lifetime exposure to ecstasy and frequency of ecstasy use as covariates found that only Stroop A performance, assessing reading speed, is related to ecstasy use variables. Analyses that employed total lifetime cannabis use and frequency of cannabis use as covariates found that both lifetime cannabis use and frequency of use affected performance on tests of immediate and delayed recall, cognitive interference, manual dexterity, learning and perhaps executive function. The authors conclude that cannabis use made a significant contribution to decrements in test performance, and that ecstasy use was generally less related to test performance than cannabis use.

Comments: This is one of a few investigations featuring both non-user controls and cannabis using controls to address the issue of cannabis use in ecstasy users. In this study, the authors found that ecstasy + cannabis users and cannabis users performed similarly on tests, with both groups scoring lower than non-users on many tests. While the authors note that Digit Span test performance (said to test working memory) was correlated with MDMA use, the correlation presented in the paper is below 0.2. The authors state that while cannabis is not neurotoxic, it is known to affect hippocampal neurons and that the residual drug effects of cannabis may produce reduction in memory and learning. However, the authors also suggest that ecstasy might produce decrements in performance on cognitive tests, but that concomitant cannabis use reduces the MDMA-induced deficits in performance. The findings in this study suggest that the relationships between ecstasy use, cannabis use and performance on tests of cognitive skills are complex, and that future studies should pursue the contribution made by cannabis use by employing a cannabis using control group in their design.
Dafters et al. (1999). Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence.


**Purpose:** Electroencephalography, cognitive function, mood: investigation performed to discover whether a correlation exists between extent of ecstasy use and quantitative EEG variables (spectral EEG power and coherence), and whether a correlation exists between quantitative EEG variables in ecstasy users and measures of mood and cognitive function. Specific Hypothesis Tested – That ecstasy use should produce reduced coherence, with coherence considered an indicator of synchronous activity in different locations.

**Design:** Non-experimental (retrospective) 1-group correlational design, with parameters of self-reported ecstasy use in past year serving as predictors and EEG power and coherence, mood scores, scores on tests of verbal intelligence, memory and executive function serving as dependent measures. Investigators conducting the EEG and neuropsychological tests were blind to subject drug history. All subjects underwent quantitative EEG and completed measures of mood and cognitive performance.

**Subjects:** 23 university students who were self-reported ecstasy users residing in the Glasgow (Scotland) area, recruited via snowball technique. Matching – No controls and correlational design, hence no matched variables.

**Criteria for Inclusion** – Having used ecstasy at least once, no history of neurological or medical disorder (such as cardiovascular disease or diabetes) that might affect EEG, no history of head injury, not currently taking prescribed medication and abstinence from ecstasy or other substances (except alcohol or nicotine) within 7 days of the study day, with compliance verified through self-report only.

**Drug Use Parameters** – No information provided on typical ecstasy dosage or frequency of usage. Subjects reported using, on average, 14.04 tablets in the year preceding the study (1-60 tablets). 12 subjects had taken less than 20 tablets across the lifetime (“low” users) and 11 used over 20 ecstasy tablets over a lifetime (“high” users). Other Drugs – 23 reported using alcohol (148.6 drinks in year), 21 used cannabis (154 joints in year), 20 used amphetamines (10.91 tablets in year) 16 used cigarettes (3173.8 in year), and 9 used LSD (2.82 “tablets” in a year).

**Group Demographics and Matched Variables** – This is a correlational study without controls, hence no matched variables. Gender – Information on gender not provided in this paper (personal communication from author indicates that gender was “approximately 50 / 50, but with more women than men). Age – Range 18-42 years, average = 24. Education – All subjects were either university students or their friends, hence estimated education between 12-16 years.

**Measures:** EEG – Measured on 128 channel electrode array with 125 samples taken per second. An artifact-free 60 s period located visually and analysis conducted on 1-second epochs. Spectral Power – Calculated for left frontal, right frontal, left posterior and right posterior quadrants and across each frequency band (alpha, beta, delta, theta). Coherence – Electrode pairs selected on the basis of connection via presumed white-matter fiber tracts (method of Leuchter et al, reduces chance for Type I error), Coherence was measured for fascicular tract, visual association pathways (visual tract) and trans-callosal interhemispheric tract (trans-callosal tract). Mood – Assessed via BDI and PANAS (Positive Affect Negative Affect Scale), two self-report measures of mood and affect, after EEG recordings were made. Cognitive Function – NART (Read aloud 50 words of decreasing frequency that do not follow standard rules of pronunciation), Rivermead Behavioral Memory Test (Immediate and delayed recall for story), Behavioral Assessment of Dysexecutive Syndrome (BADS) Card Sort Task (Similar to WCS, determine rule change in card sorting), and an author-derived test of working memory (recall for words presented between math problems used as distracters), with subject asked to recall words several times throughout task (delayed recall).
Analyses: Performed individual Pearson correlation coefficients calculated for all annual drug use measures, age and gender. EEG variables analyzed via multiple regression, with ecstasy use parameters and other drug use variables all included (with effects of other drugs controlled for in model by using partial correlations), with regressions performed for each EEG frequency band. Separate analyses performed on log 10 transformed EEG data as a means of reducing effects of skew and kurtosis in power data. (Results not reported, with findings not significantly different from findings arrived at with untransformed data). Regressions with the effects of other drugs removed (partialed out) performed on measures of mood and cognitive function, with ecstasy use as the predictor variable.

Results – Significant Differences: EEG – Extent of ecstasy use (number of tablets in year) was positively correlated with global increase in alpha rhythm power, with association weakest in right frontal quadrant, (just reaches significance). Extent of ecstasy use positively associated with increased beta rhythm power in the left posterior quadrant, and negatively associated with delta rhythm power averaged over whole scalp. Extent of ecstasy use (number of tablets used in a year) weakly but significantly negatively correlated with coherence in the visual tract.

Cognitive Function – Extent of ecstasy use associated with decrease in performance on BADS card sort.

Results – No Differences Found: EEG – Extent of ecstasy use was not correlated with theta rhythm power in any quadrant of the brain. Extent of ecstasy use not correlated with beta rhythm power in the left or right quadrants, or in the right posterior quadrant. Extent of ecstasy use not correlated with coherence in the fascicular or the trans-callosal tracts.

Mood – No significant correlations between extent of ecstasy use and scores on BDI, PA score of PANAS or NA score of PANAS (though NA correlation is .33).

Cognitive Function – Extent of ecstasy use not significantly associated with performance on NART, immediate or delayed scores for Rivermead Behavioral Memory Test or Word Memory test (though Word Memory correlates at .34).

Overall Effects: Degree of ecstasy use, measured here as number of tablets consumed in past year before study day (a combination of cumulative dose and frequency), is correlated with an increase in global alpha power in the left posterior quadrant, with alpha power usually considered an indicator of decreased mental activity. Delta activity is globally reduced. The authors state that there are some similarities with this spectral power profile and the profile seen in normal aging. Decreased coherence is seen in what the authors define as the visual tract, indicating there is less synchronized activity in this tract. However, while there are associations between extent of ecstasy use and changes in EEG measures, the authors did not find any significant associations between extent of ecstasy use and any of the measures of mood or cognition except for the card sort task, a measure of executive function. In this case, decreased performance on the card sort task was associated with greater extent of ecstasy use. These findings indirectly suggest that differences in spectral power and coherence are not associated with any changes in mood or cognitive function, with the possible exception of executive function.

Comments: This paper is the first to examine the effects of ecstasy use on electrical activity in the brain and how these effects relate to changes in mood and cognitive function, if present. Its weakness is that the authors do not employ a control group, but its strength is that the authors employ a correlational design rather than arbitrarily dividing up the sample into use categories. The paper is also notable for its attempt to control for the effects of other drugs through the use of partial correlations. The authors state that the spectral power profile associated with extent of ecstasy use bears some similarity to shifts in spectral power seen in normal aging. However, the reduction in coherence seen after regular ecstasy use differed from the pattern of reduced coherence seen in Alzheimer’s disease. Specifically, Alzheimer’s disease is associated with reduction in the fascicular tract while regular ecstasy use was associated with reduced coherence in the visual tract. This area of research is relatively new, and further research is needed to understand the significance of the changes in EEG activity and their relation to measurable changes in cognition or affect. Gamma et al. (2000) also measured EEG in ecstasy users.
Gamma et al. (2001). No difference in brain activation during cognitive performance between Ecstasy (MDMA) users and controls: A $[^{15}O]H_2$-PET study.


**Purpose:** Brain imaging (PET), cognitive function (visual search), mood: To investigate possible differences in mood and cerebral blood flow (CBF) between ecstasy users and controls, and to see whether differences in mood, if they are present, are related to differences in brain activity as measured by $[^{15}O]H_2$-PET. Specific Hypothesis Tested – That if ecstasy users are found to differ from non-user controls on measures of mood, that these differences in mood would correlate with differences in rCBF as measured through PET scan.

**Design:** Non-experimental (retrospective) 2-group between subjects (across groups) / within-subjects design, with ecstasy users compared with matched non-user controls on measures of mood and PET, and with resting PET scan compared with PET scan taken during task performance. All subjects completed measures of mood. 11 / 15 subjects underwent resting PET scans and all subjects underwent task-performance PET scans.

**Subjects:** 16 regular ecstasy users recruited from local raves (in the Zurich area) and from postings at the university and 17 non-user controls recruited from postings at the university. Matching – Groups matched on age, education and drug use, though non-user controls were slightly older and had attained slightly more education.

**Criteria for Inclusion, Ecstasy Users** – Having used ecstasy on at least 100 occasions (with the exception of 2 / 16 ecstasy users, with no information provided on drug use patterns in these subjects). Non-users – Never having used ecstasy, with use of other substances permitted. All Groups – Good health as assessed via physical examination, psychiatric interview, ECG and blood analyses. No past or current major medical or psychiatric illnesses, and no family history of psychiatric illness. Abstinence from all psychoactive substances save alcohol or nicotine for at least a week prior to study day, with compliance verified through self-report only.

**Drug Use Parameters** – Ecstasy Users - Ecstasy users reported an average lifetime use of 270 ± 397.2 tablets. No information is provided on duration (in years) of use, frequency of use, average dose consumed per occasion or time since last use (recency of use). According to personal communication with A. Gamma, frequency of ecstasy use reported over 2 years, per month, was 8 – 12 tablets per month (4 – 60). Average lifetime use of cannabis was reported at 332 ± 349.1 joints, and lifetime use of amphetamines was reported at an average overall use of 309 ± 757 mg. Average lifetime use of cocaine was reported at 615 ± 715 mg, average use of LSD over a lifetime was reported at 5 ± 7.5 “trips, and average lifetime use of magic mushrooms was reported at 3 ± 5.3 occasions. Non-Users – Non-users did not use ecstasy. Average lifetime use of cannabis was reported at 85 ± 173.2 “joints”, average lifetime use of amphetamines was reported at 0 mg, and average lifetime use of cocaine was reported at 161 ± 624 mg. Non-users reported an average lifetime use of LSD at 0 ± .3 “trips,” and an average lifetime use of magic mushrooms at 1 ± 1.9 occasions.

**Group Demographics and Matched Variables** – Ecstasy users matched with non-users on gender and approximately matched with non-users on age, education and drug use. Gender, as M / F ratio – Ecstasy users, 8 / 8: Non-users, 10 / 7. Age. Ecstasy users, average age = 22.6 ± 2.6, range not provided: non-users, average age = 26 ± 2.4. Education Level – Where 1 = junior high, 2 = high school, 3 = undergraduate, 4 = university: Ecstasy users had approximately 15 years (2.6 ± 1), non-users had approximately 17 years (3.8 ± .4). **Use of Other Drugs** – Both ecstasy users and non-users reported using cannabis, cocaine and magic mushrooms, with a few non-users reporting occasional experimentation with LSD. However, in all cases, ecstasy users had higher lifetime exposure to every drug measured than non-users, and this was particularly true for cannabis and amphetamine.
**Measures:** Mood and Depression – Mood was measured by the AM, administered immediately after PET scans were performed. Depressed mood and signs of depression were measured via HAM-D administered on a day previous to or after conducting PET scans.

CPT – A visual version of the Continuous Performance Task, a measure of vigilance in which subjects indicate the presence of target letters in an array of letters by pressing a button, with multiple trials presented. Control task presented arrays without target letters or requirement to attend or respond to arrays.

PET – 4 scans performed, 2 during performance of the CPT and 2 during the control task. Control task scans performed on a sub-set of subjects, with manuscript unclear on exact number. Either 22 / 33 received control task scans (11 from each group) or 11/ 33 received control task scans (11 overall, group membership distribution unknown).

**Analyses:** Mood – Psychological tests were examined via MANOVA, with drug use (ecstasy user versus non-user) as a between-subjects factor and scale scores as dependent factors. Post-hoc comparisons made via Tukey’s LSD test, with p. set at .05.

PET – Images were normalized and global counts were corrected via ANCOVA. Analyses performed on individual mean scans (2 task-equivalent scans averaged into 1 via t-test). CPT task scans were compared across groups (ecstasy users versus non-users) with a single-voxel statistic, and control task scans were compared with CPT scans within each group using single-voxel statistics, with p. at .05.

**Drug Use Parameters and PET scans** – Analysis of covariance (ANCOVA) was performed on rCBF and drug use and overall lifetime use of ecstasy and other drugs, with analyses only performed on ecstasy users.

**Results – Significant Differences:** Mood and Depression – Ecstasy users scored higher than non-users on the following AM scales: inactivation, emotional excitability (nervousness, vulnerability) and depressed mood. Ecstasy users had higher HAM-D scores than non-users, though no scores were within the range considered diagnostic of clinical depression. 5 / 16 ecstasy users reported experiencing pre-existing depression before ecstasy use and 2 of 5 reported that their symptoms of depression, including suicidality, were alleviated and eventually vanished after commencing ecstasy use.

PET – No significant differences found between two groups. CPT significantly different from control task for both groups, with increased rCBF in the R medial occipital area, the L precentral area, R postcentral area and R superior frontal lobe, and decreased rCBF in L and R superior and medial temporal lobe and R precuneus.

**Results – No Significant Differences:** Mood and Depression – Ecstasy users did not differ from non-users on the following AM scores: efficiency, extroversion / introversion, well-being and anxiety.

PET – CPT task performance produced similar pattern of brain activity in ecstasy users and non-users. No differences found when CPT scans directly compared between ecstasy users and non-users.

PET – No differences found in performance of ecstasy users and non-user controls on CPT, either in number of errors of omissions (missed targets) or errors of commission (false alarms).

**Drug Use Parameters and rCBF** – No relationships were found between total lifetime use of any other drug and patterns of rCBF.

**Overall Effects:** Ecstasy users reported a greater number of depression-related symptoms, as indicated in higher HAM-D scores, and they scored higher on measures of inactivation, emotional excitability and depressed mood. Yet there were no differences in rCBF recorded during performance of a vigilance task. Both groups showed increased activation in the same areas and less activation in other areas during task performance. Patterns of rCBF were unrelated to overall lifetime drug consumption for ecstasy, cannabis, amphetamines, cocaine, LSD or magic mushrooms, as measured in ecstasy users. The authors’ hypothesis was not confirmed; while ecstasy users had higher scores on measures of depressed mood and depression, there was no evidence of changes in rCBF in ecstasy users when compared with controls. Hence elevated scores on measures of depression could not be correlated with any changes in rCBF for ecstasy users.

**Comments:** This is one of several papers (e.g., Reneman et al., 2000a,b) seeking to compare cerebral blood flow in ecstasy users with that of non-user controls, with the findings being similar to that of Chang.
et al, 2000. The authors acknowledge that normalizing the imaging data may have reduced or eliminated evidence for global differences in CBF across groups. Since scans for ecstasy users and non-users were similar, it appears that the increased depressed mood and inactivation reported by ecstasy users is not correlated with any specific changes in brain activation. While there are no differences between the two groups on task performance, the authors acknowledge that the CPT may not be as complex as other tasks of sustained attention, and that it does not necessarily measure memory or other functions. The sample used in this study is nearly identical to that used in Gamma, 2000a.

**Gamma et al. (2000). Mood state and brain electric activity in Ecstasy users.**


**Purpose:** Electroencephalography, mood: To investigate whether regular ecstasy use is associated with changes in brain electrical activity and distribution of spectral band power, as measured through LORETA (low resolution brain electromagnetic tomography) and spectral analysis, respectively, and to investigate differences between ecstasy users and non-users in mood state during EEG. **Specific Hypothesis Tested** – That chronic (regular) ecstasy use would be related to changes in brain electric activity and spectral band distribution, and that differences in brain electric activity, if present, would parallel changes in mood state.

**Design:** Non-experimental (retrospective) 2-group between subjects (across groups) design where ecstasy users were compared with matched non-user controls, with drug use (ecstasy use versus no ecstasy use) serving as the between subjects factor. All subjects underwent quantitative EEG and completed measures of mood immediately after EEG was performed.

**Subjects:** 16 regular ecstasy users and 16 non-user controls (all university students), with ecstasy users recruited from local raves and postings at a university in Zurich, Switzerland and non-user controls recruited via word of mouth and by postings at the university. **Matching** – On gender and roughly matched on age and education

**Criteria for Inclusion, Ecstasy Users** – Having used ecstasy at least 100 times prior to study participation. **Non-users** – No prior history of ecstasy use (use of other drugs allowed). **All Groups** – Having no past or current major medical or psychiatric disorders, as assessed via physical examination, psychiatric interview, ECG and blood analysis. Abstinence from all psychoactive substances except alcohol and nicotine for the week prior study day, with no information provided on how abstinence would be verified.

**Drug Use Parameters** – (Information only presented for 15 ecstasy users and 14 controls with artifact-free EEG recordings) **Ecstasy Users** – Ecstasy users had taken an average of 222 ± 358.5 ecstasy tablets over a lifetime. No information is provided about duration (in years) of use, frequency of use, average dose consumed per occasion or time since last use (recency of use). Average lifetime use of other drugs by ecstasy users: cannabis, 320 ± 357.6 joints, amphetamines, 320 ± 782.3 mg, cocaine, 506 ± 586 mg, LSD, 6 ± 7.7 “trips”, magic mushrooms, 3 ± 5.4 occasions. **Non-Users** – Average lifetime use of other drugs reported by non-user controls: ecstasy, 0 tablets, cannabis, 46 ± 137 joints, amphetamine, 0 mg, cocaine, 198 ± 692 mg, LSD, 0 “trips,” magic mushrooms, 1 ± 2.2 occasions.

**Group Demographics and Matched Variables** – (Information reported only for 15 ecstasy users and 14 controls with artifact-free EEG recordings). Regular ecstasy users matched with non-user controls on age, and approximately matched on gender and educational level. **Gender**, As M / F ratio – Ecstasy users, 8/7: Non-user controls, 8/6. **Age**. Ecstasy users, 22.5 ± 2.7 years: Non-users, 26 ± 2.7 years. **Education Level**. Education rated from 1 (junior high) to 4 (graduate school). Ecstasy users, 2.5 ± 1 (approximately 14 years): Non-users, 3.7 ± .5 (approximately 16 years).

**Measures:** EEG and Spectral Band Power – Measured via 31 scalp electrodes placed according to the international 10 / 20 system. 3-min recordings made for all subjects under eyes-open and eyes-closed
Overall Effects: Ecstasy users did not differ from non-user controls in global EEG distribution as measured via LORETA, at least when analysis was performed with normalized data. (Artifact-free epochs could only be obtained from 15 ecstasy users and 14 controls).

LORETA – Intracerebral electric sources derived from computations performed by LORETA. Time-averaged LORETA images used in analysis, with each image representing 1-s (256 images produced per sec).

Mood – Measured by AM, completed immediately after subjects underwent EEG recording.

**Analyses:** EEG – Localized activity analyzed via voxel by voxel t-tests comparing ecstasy users with non-user controls, with one LORETA image used from each subject, each frequency band and each condition. Spectral Band Power – All data log transformed to address deviation from normal distribution. Each frequency band analyzed separately via mixed-model ANOVA, with condition (eyes open versus eyes closed) as a within-subject factor and drug use (ecstasy use versus no ecstasy use) as a between groups factor. Mood – Multivariate analysis of variance (MANOVA) was used to compare AM scores in ecstasy users and non-user controls, with drug use serving as a between-group factor and with each scale on the AM serving as a dependent measure, with post-hoc comparisons made via Tukey’s HSD test.

**Results – Significant Differences:** LORETA – Cluster analysis of non-normalized LORETA images found that ecstasy users had significant increases in theta, alpha1, beta2 and beta3, but only in the eyes-open condition.

EEG and Spectral Band Power – (Absolute power higher under eyes closed condition for both ecstasy users and non-users). Ecstasy users had higher beta2 power than non-users in the eyes-open condition, though both groups had similar beta2 power in eyes-closed condition. Trend for ecstasy users to have greater beta1 power than non-users in eyes open condition and lower beta1 power than non-users in eyes closed condition. Analyses of channel-wise EEG power found trend for globally higher power in ecstasy users in the theta, alpha1, beta2 and beta3 bands, with trend reflecting increases in these bands found with cluster statistics performed on non-normalized data. Beta1 – Higher in controls in eyes-closed condition, higher in ecstasy users in eyes-open condition. Beta2 – Higher beta1 power in ecstasy users, but only in eyes open condition. Ecstasy users had a trend for higher beta3 power than controls in both eyes-open and eyes-closed condition, but with difference between groups greatest in eyes-open condition. Alpha2 – Higher power in ecstasy users in right temporal-occipital region and left occipital region, with increased alpha2 in right temporal-occipital region associated with eyes open condition and increased alpha2 in left medial occipital region associated with eyes closed condition. Analyses with normalized data for alpha2 band used to clarify localization of this difference.

Mood – Ecstasy users different from non-users on the following AM scales: depression (ecstasy users > non-users), inactivation (ecstasy users > non-users) and emotional excitability, defined as nervousness or vulnerability (ecstasy users > non-users). Ecstasy users scored higher on anxiety scale than non-users, but at a level just short of statistical significance.

**Results – No Differences Found:** LORETA – No differences between ecstasy users and non-users in normalized images, whether analyzed by single-voxel statistics or cluster analyses, indicating similar distribution of brain electrical activity. No differences between ecstasy users and non-users found with non-normalized data in single-voxel statistics.

EEG and Spectral Band Power – No difference between ecstasy users and non-users in spectral power for any frequency band, though there was a tendency for ecstasy users to have higher overall power. Ecstasy users and non-users had similar beta2 power in the eyes-closed condition, but ecstasy users had higher beta2 power in eyes-open condition. No significant differences for any specific frequency band found in analysis of channel-wise EEG power. While ecstasy users had higher beta2 power in eyes-open condition, ecstasy users and non-users did not differ in beta2 power in eyes-closed condition. No difference in delta frequency band.

Mood – Ecstasy users did not differ from non-users on the following scales of the AM: Efficiency, extroversion / introversion and well-being.

**Overall Effects:** Ecstasy users did not differ from non-user controls in global EEG distribution as measured via LORETA, at least when analysis was performed with normalized data. While there was a
tendency for ecstasy users to have higher global EEG power than non-users, there were few differences in
global power in any frequency band. Yet ecstasy users were found to have increased power in the theta,
alpha1, beta2 and beta3 bands, but only in the eyes-open condition. Separate channel-wise analyses
found that ecstasy users had higher beta1, beta2 and beta3 power than non-users in the eyes-open
condition, but that band power was the same (beta2, beta3) or lower (beta1) in ecstasy users and controls
in the eyes-closed condition. There may be some differences in localization of the alpha2 band, with
ecstasy users showing greater alpha2 in the right temporal-occipital region in the eyes-open condition and
greater alpha2 in the left medial occipital region in the eyes-closed condition. Ecstasy users had higher
scores for depression, inactivation and emotional excitability than non-users on a measure of mood while
reporting similar values for efficiency, extroversion / introversion and well-being. It is not clear whether
differences in spectral power seen in the eyes-open condition is related to changes in mood state in
ecstasy users, since no analyses related the two sets of variables to each other. The authors’ hypothesis is
partially confirmed, as ecstasy users show some differences in EEG patterns and spectral band frequency
when compared with controls, but there is no indication that these changes in EEG pattern are related to
elevated scores on scales measuring depression, inactivation and emotional excitability.

Comments: Along with the work of Dafters, this is one of the few studies examining changes in EEG
variables in ecstasy users. Unlike Dafters et al, Gamma et al are comparing across groups of ecstasy users
and non-user controls rather than conducting correlational analyses within a sample of ecstasy users. It is
interesting to contrast the findings of Dafters et al with those of Gamma et al. While Dafters found that
total number of ecstasy tablets taken per year was not associated with changes in mood, Gamma et al
found that ecstasy users may be more depressed and less activated than non-users. The two papers report
related findings; Dafters found that greater lifetime ecstasy use was associated with increased beta power,
and Gamma found that ecstasy users had greater beta power in three statistically independent bands,
specifically when eyes were open. The authors interpret increases in spectral power during the eyes open
condition as evidence of disturbances of arousal or attention, and associate this with increased
depressiveness and inactivation in ecstasy users. Currently, there have been few quantitative EEG studies
conducted with ecstasy users, and interpreting the results is difficult without understanding the full
context of each variable measured.

Gerra et al. (2000). Long-lasting effects of 3,4-methylenedioxymethamphetamine (Ecstasy) on
serotonin system function in humans.

Gerra, G., Zaimovic, A., Ferri, M., Zambelli, U., Timpano, M., Neri, E., Marzocchi, G. F.,
(Ecstasy) on serotonin system function in humans. Biological Psychiatry, 47, 127-136.

Purpose: Personality, neuroendocrine challenge: to investigate possible long-term changes seen in
recreational ecstasy users after 3 weeks and after 12 months of abstinence from ecstasy, with changes in
personality and response to d-fenfluramine used as measures of serotonin system function.

Design: Non-experimental (retrospective) 2-group mixed (between subjects / within-subjects) design,
with comparisons made between drug-free ecstasy users and matched non-user controls 3 weeks after
ecstasy users stopped using ecstasy and again 12 months after ecstasy users had stopped using ecstasy.
Each subject underwent d-fenfluramine challenge and completed measures of personality and affect.

Subjects: 15 abstinent regular ecstasy users and 15 non-user controls residing in the Parma (Italy) area,
with ecstasy users recruited from individuals who had contacted the Drug Addiction Service, and controls
recruited from a local high school and from the hospital. Matching – Ecstasy users matched with non-
user controls on gender, age, height and possibly socioeconomic status.

Criteria for Inclusion, Ecstasy Users – Having used ecstasy at least 25 times, remaining abstinent from
ecstasy for the period between both tests (12 months) with abstinence verified through twice-weekly
urinary analyses, little or no use of other drugs besides ecstasy, and having contacted Drug Addiction
Services. Non-users – Having never used ecstasy or any other psychoactive drug, absence of alcohol
Drug Use Parameters – Ecstasy users reported using ecstasy on an average of 69.3 ± 38 occasions (25-95), with usual dose per use reported as being approximately 1 ± .9 tablets per use (approximately .25 – 2.5 tablets). Average frequency of use was reported at 4.7 ± 2.7 times a month (2.5 – 8.2 times monthly), and average duration of use was reported to be 15 ± 9 months (8-25 months). The length of drug-free period before the study times ranged from 21 days to 365 days.

Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender, age, height and possibly socioeconomic status. Gender, as M / F ratio – Ecstasy users, 15 / 0: non-users, 15 / 0. Age – Ecstasy users, 18-26, average = 21.8, non-users, 19-24, average = 21.5. Height, in cm. Ecstasy users, average = 175 ± 12.9 cm, non-users, average = 175 ± 9.9 cm. Socioeconomic Status – Ecstasy users, “middle or high” socioeconomic status. Information not provided for non-users, but authors assert non-users matched for socioeconomic status. Other variables – No information provided about education, but 10 ecstasy users were “students,” 3 were “workers,” and 2 were unemployed.

Measures: Mood and Personality – Personality measured via MMPI 2 and TPQ (Tridimensional Personality Questionnaire). Aggression and hostility measured via Italian-language version of BDHI (Buss-Durkee Hostility Inventory). Subjects monitored for depression through the HAM-D. All measures were administered at 3 weeks after abstinence from ecstasy (Time 1) and again 12 months after abstinence (Time 2).

Plasma Cortisol and Prolactin after d-Fenfluramine Challenge – Measures of plasma cortisol and prolactin after d-fenfluramine challenge, with samples drawn at –15, 0, 30, 60, 90, 120 and 180 min after d-fenfluramine administration. Challenge performed once at 3 weeks after abstinence from ecstasy (Time 1) and again 12 months after abstinence from ecstasy (Time 2). Prolactin – Plasma prolactin measured via specific radioimmunoassay. Cortisol – Plasma cortisol measured via specific radioimmunonoassay.

Analyses: Mood and Personality – Psychometric measures analyzed via 2-way between subjects / within subjects ANOVA, with ecstasy users versus non-users as a between-group factor and value at Time 1 (3 weeks) and value at Time 2 (12 months) as within-group factors. Psychometric measures were correlated with cortisol and prolactin AUC (area under curve) at Time 1 (3 weeks) and Time 2 (12 months).

Plasma Cortisol and Prolactin after d-Fenfluramine – Cortisol and prolactin release after d-fenfluramine were both analyzed via MANOVA, with drug use (ecstasy user versus non user) as a between group factor, time of measurement (Time 1 versus Time 2) as a within-subjects factor and with plasma cortisol and prolactin at each time point as dependent variables. Duration of ecstasy use and number of lifetime occasions of ecstasy use (total lifetime exposure) correlated with prolactin and cortisol values after d-fenfluramine challenge, presumably via Pearson correlation coefficients (method not described).

Results – Significant Differences: Mood and personality – Ecstasy users scored higher than controls on the MMPI D scale, both at 3 weeks and 12 months of abstinence from ecstasy. Ecstasy users scored higher than non-users on the BDHI Direct Aggression and Guilt scales at 3 weeks of abstinence from ecstasy, but not at 12 months of abstinence. Ecstasy users scored higher than controls on the HAM-D at 3 weeks and at 12 months of abstinence from ecstasy use. Ecstasy users scored higher than controls on the Novelty Seeking sub-scale of the TPQ at 3 weeks and at 12 months of abstinence from ecstasy. 8 ecstasy users reported dysphoric mood after 3 weeks of abstinence from ecstasy, and 4 ecstasy users reported tiredness and fatigue at the 3 week point. 4 reported subtle, unspecified cognitive impairment or confusional episodes.

Plasma Prolactin and Cortisol after d-Fenfluramine – Increase in plasma prolactin in ecstasy users was not as great as in controls after d-fenfluramine (blunted response) both at 3 weeks and at 12 weeks of abstinence from ecstasy. Increase in plasma cortisol after d-fenfluramine was lower in ecstasy users than non-user controls at 3 weeks of abstinence from ecstasy (blunted cortisol response) but not at 12 months.
of abstinence. Strength of prolactin response to d-fenfluramine (prolactin AUC) in ecstasy users was negatively associated with Direct Aggressiveness scores on the BDHI and Novelty Seeking scores on the TPQ at 3 weeks of abstinence from ecstasy. (Negative association implies that less prolactin release after d-fenfluramine associated with higher direct aggression and novelty seeking scores.) After 12 months of abstinence from ecstasy, there was only a negative association between prolactin after d-fenfluramine and direct aggression; novelty seeking and prolactin response to fenfluramine challenge was no longer associated. Duration of ecstasy use was inversely related (negatively correlated) with strength of prolactin response to d-fenfluramine at 12 months of abstinence from ecstasy, but apparently not at 3 weeks of abstinence from ecstasy.

**Results – No Differences Found:** Mood and Personality – Ecstasy users did not differ from controls on any other MMPI scale at either the 3 week or 12 month point after abstinence from ecstasy. Ecstasy users no longer had higher Direct Aggression and Guilt scores than controls on the BDHI at 12 months of abstinence from ecstasy, though scores were elevated at 3 weeks abstinence. Ecstasy users did not score differently from non-user on Reward Dependence and Harm Avoidance scales of TPQ at either 3 weeks or 12 months of abstinence from ecstasy.

**Plasma Prolactin and Cortisol after d-Fenfluramine** – Ecstasy users did not differ from controls on basic prolactin levels (before fenfluramine) either at 3 or 12 months of abstinence from ecstasy. Ecstasy users did not differ from non-user controls in basal cortisol levels at 3 weeks of abstinence from ecstasy. Cortisol was non-significantly higher in ecstasy users than controls at 12 months of abstinence. Scores on the HRS-D, Reward Dependence and Harm Avoidance scores on the TPQ and other BDHI and MMPI scores not correlated with strength of prolactin response (prolactin AUC) to d-fenfluramine in ecstasy users. Strength of cortisol response (cortisol AUC) to d-fenfluramine in ecstasy users was not significantly associated with any score on any of the psychometric measures employed (MMPI, BDHI, TPQ or HRS-D), either at 3 weeks of abstinence from ecstasy or at 12 months of abstinence from ecstasy. Strength of prolactin response after d-fenfluramine was not significantly correlated with either total occasions of ecstasy use or duration of use at 3 weeks of abstinence from ecstasy.

**Overall Effects:** Some differences between ecstasy users and non-user controls persisted after 12 months of abstaining from further ecstasy use, while other differences were only present recently after discontinuing ecstasy use. Ecstasy users scored higher on measures of depression and novelty seeking even after discontinuing ecstasy use for a year. Blunted prolactin response to d-fenfluramine challenge was also present in ecstasy users a year after abstinence from ecstasy. On the other hand, ecstasy users had higher scores on sub-scales for direct aggression and guilt from the BDHI only after 3 weeks of discontinuing ecstasy. After a year of abstinence from ecstasy, ecstasy users and non-users did not differ on direct aggression or guilt scores. Blunted cortisol response after d-fenfluramine challenge in ecstasy users was only seen after 3 weeks of abstinence from ecstasy. Ecstasy users and non-users no longer differed on cortisol response to d-fenfluramine after a year of abstinence from ecstasy use. (Basal cortisol levels were somewhat higher in ecstasy users at the 12-month point, but the difference was not significant). Duration of use was inversely related to prolactin response to d-fenfluramine, but only after 12 months of abstinence from ecstasy, and lifetime use (total number of doses) was not related to either neuroendocrine response to d-fenfluramine challenge. Novelty seeking was consistently and negatively related to strength of prolactin response to d-fenfluramine, both after 3 week and after 12 months of discontinuation of ecstasy use. There was a negative association between strength of prolactin response at the 3-week point and direct aggressiveness score, but this relationship was no longer present at the 12-month point.

**Comments:** This paper is notable for employing frequent drug-screening, hence reducing the likelihood of recent ecstasy use. Findings are relatively consistent with other papers that have measured plasma cortisol and prolactin after challenge with various serotonergic drugs. However, it should be noted that no differences were found in prolactin release after tryptophan challenge in one paper (McCann et al, 1994). The findings of persistent effects can either be interpreted as arising from regular ecstasy use or as pre-existing differences leading to ecstasy use (as may be true for novelty seeking). On the other hand, transient changes on measures of aggression and guilt and blunted cortisol response may either be signs of
reversible change, drug withdrawal effects, or residual drug effects. Since the authors only use male participants in their study, caution should be used in generalizing study findings to females. All ecstasy users in this sample contacted local addiction-related social services, so that it is possible that some of the effects seen in this sample may be more specifically associated with people who contact social services about their drug use. However, the paper is notable in its attempt to select ecstasy users with little or no exposure to drugs other than ecstasy. Five of the subjects in this study also participated in an earlier study performed by Gerra and colleagues in 1998. The fenfluramine challenge was not placebo-controlled, though comparisons were made between baseline and post-drug values.

Gerra et al. (1998). Serotonin function after (+ / -) 3,4-methylenedioxymethamphetamine (“Ecstasy”) in humans.


Purpose: Personality, pharmacological challenge: to investigate possible short-term changes seen in recreational ecstasy users who have abstained from ecstasy use for 3 weeks, with changes in personality and response to d-fenfluramine used as measures of serotonin system.

Design: Non-experimental (retrospective) 2-group between-subjects (across groups) design, with drug-free ecstasy users compared with matched non-user controls, and with drug use (ecstasy use versus non-use) serving as a between-subjects factor. All subjects completed psychometric measures of mood and personality and underwent d-fenfluramine challenge.

Subjects: 15 abstinent regular ecstasy users and 15 non-user controls residing in the Parma (Italy) area, with ecstasy users recruited from individuals who had contacted local Drug Addiction Service, and controls recruited from a local high school and from the hospital. Matching – On gender, age, height and possibly socioeconomic status.

Criteria for Inclusion - Ecstasy Users – Having used ecstasy at least 25 times, remaining abstinent from ecstasy for 3 weeks prior to study day, with abstinence verified through twice-weekly urinary analyses, little or no use of other drugs besides ecstasy, and having contacted Drug Addiction Services. Non-users – No past or current use of ecstasy or any other psychoactive drug, absence of alcohol abuse, and being similar to ecstasy users on matched variables. All Groups – Male, current or past major medical disorders, including severe liver and renal disorders, significant weight loss, obesity, endocrinopathies or immune dysfunction. No history of major (Axis 1) psychiatric disorders as detected through psychiatric interview: 2 ecstasy users diagnosed with personality disorders were included in study.

Drug Use Parameters – Ecstasy users used ecstasy on an average of 62.7 ± 34.2 occasions over a lifetime (25-90), with usual dose per use reported as being approximately 1 ± .9 tablets per use (approximately .25 – 2.5 tablets). Average frequency of use was reported at 4.7 ± 2.7 times a month (2.5 – 8.2 times monthly), and average duration of use was reported to be 14 ± 8 months (8-24 months). Length of drug-free period before study day was 21 days.

Group Demographics and Matched Variables - Ecstasy users matched with non-users on gender, age, height and possibly socioeconomic status. Gender, as M / F ratio – Ecstasy users, 15 / 0, non-users, 15 / 0. Age. – Ecstasy users, average age = 20.6 ± 2.9 years (18-24): non-users, average = 21.5 ± 2.9 (20-25). Height, in cm. Ecstasy users, average = 177 ± 10.4 cm, non-users, average = 175 ± 9.9 cm.

Socioeconomic Status – Ecstasy users, “middle or high” socioeconomic status. Information not provided for non-users, but authors assert non-users matched for socioeconomic status. Other variables – No information provided about educational levels, but 11 ecstasy users were “students,” 3 were “workers” and 1 was unemployed.

Measures: Mood and Personality – Personality measured via MMPI 2, the PDQ-R (Personality Diagnostic Questionnaire) and TPQ (Tridimensional Personality Questionnaire). Aggression and hostility
compared with controls. Blunted prolactin response to d-fenfluramine was associated with increased Direct Aggression scores. There were no significant relationships between duration of use or lifetime measured via Italian-language version of BDHI (Buss-Durkee Hostility Inventory). Subjects monitored for depression through the HAM-D. All measures were administered at 3 weeks after abstinence from ecstasy.

**Plasma Cortisol and Prolactin after d-Fenfluramine Challenge** – Measures of plasma cortisol and prolactin after d-fenfluramine challenge, with samples drawn at –15, 0, 30, 60, 90, 120, 180 and 240 min after d-fenfluramine administration, with challenge performed at 3 weeks after abstinence from ecstasy.

**Prolactin** – Plasma prolactin measured via specific radioimmunoassay. 

**Cortisol** – Plasma cortisol measured via specific radioimmunoassay.

**Analyses: Mood and Personality** – Analyzed via 1-way between-subjects ANOVA, with drug use (ecstasy use versus non-use) serving as between-group factor. Pearson correlation coefficients performed between psychometric measures and strength of neuroendocrine response to d-fenfluramine, with strength of response measured as prolactin and cortisol AUC.

**Plasma Prolactin and Cortisol after d-Fenfluramine** – A 2-way repeated measures ANOVA was used to analyze plasma prolactin and cortisol levels after d-fenfluramine, with drug use (ecstasy use versus non-use) as a between group factor and time of blood sample as a within-group factor.

**Results – Significant Differences:** 

**Mood and Personality** - Ecstasy users scored significantly higher than controls did on the MMPI-2 D scale. Ecstasy users had higher Direct Aggression and Guilt scores on the BDHI than controls, and ecstasy users had a higher score on the Novelty Seeking sub-scale of the TPQ than did non-users. When compared with non-users, ecstasy users obtained significantly higher HAM-D scores. 7 ecstasy users reported dysphoric mood, 5 reported tiredness or fatigue and 2 reported subtle, unspecified cognitive impairment and confusional episodes.

**Results – No Differences Found:** 

**Mood and Personality** – There were no differences between ecstasy users and non-users on all other MMPI-2 scale scores except for the D scale. Overall BDHI scores were higher in ecstasy users than in controls, but this difference was non-significant. While ecstasy users had higher overall PDQ-R scores than controls, the difference was not significant. Ecstasy users did not differ from controls on the Harm Avoidance and the Reward Dependents sub-scales of the TPQ.

**Overall Effects:** When compared after 3 weeks of abstinence from ecstasy, ecstasy users had higher MMPI D (Depression) scores than controls, and they had higher scores on the Hamilton depression scale (the HRS-D). When compared on a measure of aggression and hostility (the BDHI), ecstasy users obtained higher scores for direct aggression and guilt than did non-user controls. Ecstasy users had higher Novelty Seeking scores on the TPQ when compared with controls, but their scores, while obtaining scores similar to those of controls on harm avoidance and reward dependence. Prolactin and cortisol release were both blunted after d-fenfluramine challenge in abstinent ecstasy users when compared with controls. Blunted prolactin response to d-fenfluramine was associated with increased Direct Aggression scores. There were no significant relationships between duration of use or lifetime.
number of doses and either prolactin or cortisol response to d-fenfluramine, though there was a weak inverse correlation between duration of ecstasy use and degree to which prolactin release was blunted after d-fenfluramine.

Comments: Like the study performed subsequent to this one, this study is notable for the authors’ frequent drug-screening. Since the two papers only share 5 subjects in common, the later paper confirms findings in this paper for the 3-week time period. Findings of increased hostility in ecstasy users stand in contrast to other studies that either found lower scores on some BDHI scores in ecstasy users (McCann et al, 1994) or no differences between ecstasy users and non-users on measures of anger and hostility (Morgan et al, 1998). As was noted for the later study, all subjects in this study were male, and all ecstasy users had contacted the local drug addiction services. Hence caution should be used in generalizing study findings across gender or to other groups of ecstasy users who do not contact social services. Data from 5 subjects in this study are included in the second study. The fenfluramine challenge did not employ a placebo control.

Gouzoulis-Mayfrank et al. (2000). Impaired cognitive performance in drug free users of recreational Ecstasy (MDMA)


Purpose: Cognitive function, general: comparative study assessing various cognitive abilities in abstinent moderate ecstasy users, cannabis users and non-users.
Design: Non-experimental (retrospective) 3-group between subjects (across group) design, with ecstasy users compared with matched cannabis-user and non-user controls, with drug use as a between subjects factor.
Subjects: 28 ecstasy users, 28 cannabis users and 28 non-users in the Aachen (Germany) area, with subjects recruited directly by students participating in the dance scene or through word of mouth.
Matching – On gender, age and education. Ecstasy users and cannabis users matched on extent of cannabis use.
Criteria for Inclusion – Ecstasy Users – Regular ecstasy use for 6 months or longer, minimum frequency of use; twice a month or 25 instances in 2 years. No regular use of other legal or illegal drugs except cannabis, with regular use defined as at least once a month in past 6 months, and no heavy use of alcohol, defined as severe drunkenness 2 or more times a month. Cannabis Users – No use of ecstasy, all other criteria above concerning drug and alcohol use. Non-Users – No past or current use of cannabis, ecstasy or any other illicit substance, and lack of heavy alcohol use. All Groups – Absence of any major medical or psychiatric disorder (excepting substance abuse for drug user groups), ascertainment through medical and psychiatric interview, and abstinence from ecstasy or cannabis for at least 7 days before study day, with compliance verified through urinary analysis on the study day.
Drug Use Parameters – Ecstasy users took ecstasy, on average, 93.4±119.9 times over a lifetime (20-500), using an average dose of 1.4±.9 tablets per use (.5 – 3.5 tablets per occasion). Average frequency of use was 2.4 ± 1.6 times per month (.75 – 8 times), and average duration of use in months was 27 ± 18 months (6-60). Self-reported length of drug-free period before study day, in days was 41 ± 71 days (7-356 days). 26 / 28 were regular ecstasy users and 2 / 28 were sporadic users. The average age when ecstasy was first used = 19.4 ± 3.3 years (14-27 years). Cannabis use – 22 ecstasy users were regular cannabis users, 1 used cannabis sporadically and 5 did not use cannabis. In matched cannabis user group, 23 were regular cannabis users, 2 were sporadic cannabis users and 3 did not use cannabis. Cannabis was used on 20.7 ± 11.5) days a month by ecstasy users and 20.9 ± 10.2 days per month by cannabis users. Duration of cannabis use extends for 66.6 ± 37 months for ecstasy users and for 35.1 ±24 months for cannabis users. Ecstasy users had last used cannabis 4.3 ± 5.3 days before the study day and cannabis
users last used cannabis 4 ± 15.5 days before the study day. 17 ecstasy users and 20 cannabis users tested positive for presence of THC in urine on study day, and 11 ecstasy users and 8 cannabis users tested negative for THC in urinary analysis. Average age of first cannabis use for ecstasy users = 16.6 ± 2.9 years, and the average age of first cannabis use for cannabis users = 17.1 ± 2.4 years.

**Group Demographics and Matched Variables** – Ecstasy users matched with both cannabis user and non-user controls on gender, age and education level. **Gender**, as M / F ratio – ecstasy users, 16/12: cannabis users, 15/13: non-users, 17 / 11. **Age**. Ecstasy users, 18-29, mean = 23.25, cannabis users, 18-31, mean = 22.9, non-users, 18-30, mean = 23.5. **Education level**. Little / no secondary school – 1 ecstasy user, 0 cannabis users, 0 non-users: “Basic” school-leaving exam – 2 ecstasy users, 2 cannabis users, 0 non-users: “intermediate” school-leaving exam – 8 ecstasy users, 5 cannabis users, 8 non-users: “highest” school-leaving exam – 16 ecstasy users, 20 cannabis users, 20 non-users: university degree – 1 ecstasy user, 1 cannabis user, 0 non-users. Average education, ecstasy users = 3.5 (approx. 11 years), cannabis users = 3.7 (approx. 12 years), non-users = 3.7 (approx. 12 years).

**Cannabis Use** – Ecstasy users matched with cannabis using controls on cannabis use. Regular cannabis use – 22 ecstasy users, 23 cannabis users: sporadic cannabis use – 1 ecstasy user, 2 cannabis users: No cannabis use – 5 ecstasy users, 3 cannabis users: No cannabis use – 5 ecstasy users, 3 cannabis users.

**Measures**: **Tests of Attention** – TAP Subtest 1 (Simple RT), TAP Subtest 6 (Selective visual attention, matching to sample), TAP Subtest 5 (RT, simultaneous visual and auditory stimuli), TAP Subtest 8 (Intermodal integration RT; matched visual and auditory stimuli), TAP Subtest 12 (Visual scanning; Locate target in array), Stroop test (cognitive interference). **Tests of Memory** – Corsi block tapping test (Reproduce sequences of taps on blocks performed by experimenter), Digit Span, WAIS-R, German language (Verbal memory, working memory). **Tests of Memory and Learning** – VMLT (Immediate and delayed recall, recognition, similar format to RAVLT), VIG Visuospatial Memory (Immediate and delayed recall for geometric figures). **Prefrontal and General Intelligence** – Word fluency (Word generation; executive function), LPS-4-Abstract Logical Thinking (Discover rule for series of letters, digits and indicate “wrong” element, test of fluid intelligence), Mosaic Test, WAIS-R, German language (Subjects reproduce patterns with cubes, test of fluid intelligence, visuomotor performance, problem solving), General Knowledge, WAIS-R, German language (Crystallized intelligence). **Self Report Questionnaire** – Asked to report any difficulties in concentration or memory experienced in everyday life.

**Analyses**: Performance scores analyzed via 1-way between subjects ANOVA, with user group (ecstasy user, cannabis user, non-user) as between-group factor, post-hoc comparisons made with Scheffe test. A canonical discriminant analysis performed on entire data set. Relationship between ecstasy and cannabis use and performance scores on assessments made via Pearson correlation coefficient. Performance scores analyzed via ANCOVA, with general knowledge score serving as covariate. If findings were significant in tests of attention and memory, the relevant scores were correlated with 3 intelligence scores via Pearson correlation.

**Results – Significant Differences**: **Tests of Attention** – Increased RT on TAP6 (Selective Visual Attention), with ecstasy users > non-users, cannabis users. TAP5 (Divided Attention), with ecstasy users > cannabis users. TAP8 (Intermodal Integration) – ecstasy users > cannabis users. **Tests of Memory** – Digit Span-Backwards, poorer performers, with non-users > ecstasy users. **Tests of Memory and Learning** – VLMIT-Immediate recall, poorer recall, with non-users > ecstasy users, VLMT Interference, with non-users > ecstasy users, VLMT-Recall after 30 min, with non-users > ecstasy users. **VIG**-Immediate recall, with cannabis users, non-users > ecstasy users. **Executive Function and General Intelligence** – LPS-4, with cannabis users, non-users > ecstasy users. Mosaic test, with cannabis users, non-users > ecstasy users, General Knowledge, with cannabis users, non-users > ecstasy users.

**Results – No Differences Found**: **Tests of Attention** – TAP1 (Simple RT, Alertness), TAP2 (Visual Scanning), Stroop Test, Digit Span-Forward **Tests of Memory** – VLMT-Learning, Corsi Block Tapping, VIG-Learning and Number of Repetitions. Tests of **Executive Function, General Intelligence** – Word fluency. **Self-Report** – None of the 3 groups reported experiencing greater difficulty in concentrating or with memory.
**Results – Correlations, Significant:** Longer RTs on divided attention task associated with longer duration of ecstasy use. Poor digit span performance associated with larger cumulative ecstasy doses and with younger age of first cannabis use. Poor performance on VLMT associated with heavier ecstasy use (immediate recall associated with emulative dose, interference of second list associated with frequency of use and number of repetitions associated with estimated usual dose per use). Poor VLMT performance also associated with heavy cannabis use (number of repetitions associated with frequency of cannabis use).

**Results – Correlations, Not Significant:** All other test scores (Selective attention, intermodal integration, VIG-Immediate recall, LPS-4, Mosaic Test, General knowledge).

**Results – ANCOVA With General Knowledge as Covariate:** All significant findings remained the same except VLMT-Interference, with differences between non-users and ecstasy users only approaching significance. With ANCOVA, all 3 intelligence measures slightly to moderately associated with each other, but not with performance on other assessments.

**Results – Canonical Analysis:** Canonical analysis successfully classified 90.36% of all participants on the basis of performance scores, with 92.9% of ecstasy users successfully classified, 85.7% of the cannabis users successfully classified and 92.6% of the non-users successfully classified.

**Overall Effects:** Ecstasy users performed less well than either cannabis users or non-users on measures of fluid and crystallized intelligence, and they did not attain as high scores as non-users on various tests of working memory. However, members of all three groups did equally well with simple RT tasks, and findings are inconclusive on tasks of executive function, with differences appearing between groups on some assessments and not on others. Long reaction time and poor performance on measures of divided attention, working memory and memory and learning were related with longer duration of ecstasy use and higher cumulative ecstasy dose. However, a specific assessment of working memory and the “number of repetitions” score in another assessment of memory and learning were also associated with age of onset of cannabis use and frequency of cannabis use, respectively. The authors appear to favor an explanation for their findings via ecstasy-related deficits in working memory, with deficits in working memory affecting performance on other tests besides those directly measuring working memory. The authors hypothesize that the decline is related to serotonergic neurotoxicity, possibly in combination with or in addition to the effects of regular cannabis use.

**Comments:** This paper is one of several that employ cannabis-user control as well as non-user control, perhaps sampled from the same “dance scene” population, though information in text makes this uncertain. This paper is also notable in its attempt to select a sample of ecstasy users who were not polydrug users. Study findings indicate that cannabis use and ecstasy use may both affect cognitive function. While they found that ecstasy users performed less well on a greater number of measures than did cannabis users, the authors also found that cannabis use might be due in part to poor performance on some tests of learning and memory. Authors describe ecstasy use as “moderate,” though parameters indicate that their ecstasy use is heavier than ecstasy use in other studies. It is interesting that different drug use parameters appear to be associated with poorer performance on measures of different cognitive functions. Other studies have not found such distinct associations between specific drug use parameters (like duration of use or dose per use) and specific cognitive functions, but it is also true that not all researchers measure the same drug use parameters.

**Klugman et al. (1999). Toxic effects of MDMA on brain neurons (Letter).**


**Purpose:** Mood, cognitive function, general: To investigate whether long-term consumption of ecstasy affects cognitive function, with cognitive function measured via neuropsychological test.

**Design:** Non-experimental (retrospective) 2-group between-subjects (across group) design where ecstasy users were compared with an unequal number of matched non-user controls, and with drug use (ecstasy
use versus non-user) serving as a between-subjects factor. All subjects underwent assessments of cognitive function.

**Subjects:** 36 ecstasy users and 19 controls recruited through advertisements in popular magazines and through the internet. **Matching** – Groups matched on age.

**Criteria for Inclusion, Ecstasy Users** – Regular and “predominant” ecstasy user, with specifications not reported here, and no use of ecstasy or other psychoactive drugs less than 2 days prior to the study day; no information on verification of drug-free status. **Non-user** – No past or current use of used ecstasy or other psychoactive drugs. All Groups – Further requirements for inclusion not specified. Subjects were screened for psychiatric disorders via psychiatric interview, but those found to have “neurotic depression” were not excluded from study.

**Drug Use Parameters** – Ecstasy users reported an taking an average of 235 doses of ecstasy over a lifetime (12-2600 doses), with no information provided concerning average dose per use. Ecstasy users reported that they had used ecstasy for an average duration of 48 ± 31.2 months, with information not provided concerning frequency of use. Average time elapsed between last use of ecstasy and study day was 79 days (2-400 days).

**Group Demographics and Matched Variables** – Ecstasy users were matched with non-user controls on age. **Age** – Ecstasy users = 24.1 ± 4.9 years, range not provided; non-users = 22.7 ± 2.3 years, range not provided. **Gender** – No information provided about gender composition of either group (ecstasy users or non-users). **Other Variables** – No information is provided concerning education level, socioeconomic status or use of other drugs for ecstasy users or for non-user controls.

**Measures:**
- **Mood** – Depressed mood or signs of depression measured via BDI.
- **Tests of Cognitive Function** – No information is provided concerning identity of any test employed in this study. Measures listed included tests of learning, recognition, and recall, and tests of executive function. Tests of learning included test of list learning and possibly the Digit Span test, and tests of spatial and perhaps non-spatial learning and memory. Tests of recognition and recall employed at least a test for recall of faces and perhaps words, possibly the Warrington Recognition Memory test. Tests of executive function included tests of verbal fluency and tests of verbal and non-verbal working memory.

**Analyses:** Performance on tests of cognitive function analyzed via multiple analysis of variance (MANOVA). No further details given; presumably drug use (ecstasy user versus non-user) served as a between-subjects variable and each test score served as a dependent variable. Unspecified form of correlation performed on use of other drugs (with other drugs unspecified, but including cannabis) and scores on test of performance.

**Results – Significant Differences:**
- **Tests of Cognitive Function** – Ecstasy users had lower scores than non-users on tests of learning, recognition and recall. Ecstasy users had lower immediate recall of words from list. Ecstasy users recognized fewer target faces on a test of face recognition. Ecstasy users performed less well than non-users on learning a repeatedly administered list of words or a list of digits. Ecstasy users did less well learning spatial information than did non-users. 3 ecstasy users scored 2 standard deviations below presumed published norm for 2 tests, and 8 users scored 2 standard deviations below presumed published norms on 1 test, whereas only one non-user control scored more than 1 standard deviation below presumed published norms, with nature of test unspecified. There was a positive correlation between cannabis use and performance on unspecified tests of cognitive function, where more cannabis use was associated with poorer test performance.

**Results – No Differences Found:**
- **Mood** – No differences between BDI scores of ecstasy users and BDI scores of non-user controls.
- **Tests of Cognitive Function** – There were no difference between the scores of ecstasy users and non-users on unspecified tests of executive function (described as tests of verbal fluency and verbal and non-verbal working memory). Extent of using unspecified other drugs were not associated (either positively or negatively) with performance on most tests of cognitive function.

**Overall Effects:** When compared on tests of learning, recognition and recall, ecstasy users did not perform as well as a group of non-user controls matched on age. Performance lower than published norms was more likely for ecstasy users than for non-users, though the authors did not specify the tests
for which this is the case. However, performance on tests of verbal and non-verbal working memory and tests of verbal fluency were similar in ecstasy users and non-users. The authors describe the tests listed above as tests of executive function. Cannabis use may be correlated with a decrement in performance on an unspecified number of tests of executive function, but use of all other drugs did not correlate with performance on any test of cognitive function.

**Comments**: The findings reported by Klugman et al. are contained in a letter to the medical journal, The Lancet. As such, the information provided in this report was sparse. Attempts to contact the authors have thus far been unsuccessful. The identities of the tests used were unspecified, and information on the gender composition and on other demographics beyond subject’s age was not provided. In contrast with other studies, this study did not find that ecstasy users differed from controls in their performance on tests of working memory or verbal fluency. Instead, they differed on tests of learning and both verbal and non-verbal recall. This report has not been through the process of peer review, and it lacks information in a number of important areas, so caution should be used in interpreting the findings.

**Krystal et al. (1992). Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: Effects on mood and neuropsychological function?**


**Purpose**: Mood, cognitive function, general: To investigate the long-term consequences of ecstasy use by assessing mood and examining performance on tests of cognitive function in a group of ecstasy users.

**Design**: Non-experimental (retrospective) 1-group design without controls. Performance of ecstasy users on tests of cognitive function compared with published age-matched norms. All subjects completed test battery and measures of depressed mood.

**Subjects**: 9 regular ecstasy users recruited nationally, with recruitment criteria unspecified except “current or recent history of substantial” ecstasy use, with substantial use undefined. **Matching** – No matched groups: 1-group design.

**Criteria for Inclusion** – None explicitly specified beyond “substantial” use of ecstasy, with ecstasy being main drug of choice, and abstention from psychoactive drugs for at least 3 weeks prior to study day, with compliance verified through self-report. (3 / 9 reported infrequent marijuana use during 3-week period). However, all subjects underwent a psychiatric interview, including a personal and family history of major psychiatric disorders. However, it is not reported whether only subjects without a personal or family history of psychiatric illness were accepted into the study.

**Drug Use Parameters** – Subjects reported an average total lifetime use of approximately 130 tablets (estimated from cumulative exposure, 13.3 g) (range 120 – 440 tablets, 12 – 44 g), and an average frequency of use of 1.9 ± 1.7 times a month (.3 – 5 times a month). Average duration of use, in months, is 61 ± 27.6 months (24 – 84 months), and subjects reported using, on average, approximately 1.35 tablets (135 mg) (.5 – 2.5 tablets, 50 – 250 mg). “Many” subjects (unspecified) reported using much higher doses on occasion, reporting doses up to 500 mg (approximately 5 tablets) per occasion. The average last reported use prior to study day was 66 ± 50 days (20-180 days). **Use of Other Drugs** – Data collected on 8 / 9 subjects. 6 / 8 reported previous experimentation or use of alcohol, amphetamines, cocaine and marijuana. 5 / 8 reported using LSD, and 2 / 8 reported using DMT, PCP or psilocybin. 1 / 8 reported using additional hallucinogens and dissociatives (harmaline, mescaleine, 5-MeO-DMT, ibogaine and ketamine).

**Group Demographics and Matched Variables** – Only 1-group design, so no matching occurred. Performance on tests of cognitive function compared with age-matched norms.

**Gender**, as M / F ratio: 7 / 2. **Age**. Average age = 34 ± 7 (22-47 years). **Education Level** – Information on subjects’ level of education not provided. **Psychiatric Diagnosis** – No current reports of major

**Measures**: Tests of Cognitive Function – WAIS-R (general intelligence), Paragraph and Figural Recall sections of WMS (memory, immediate and delayed recall), Boston Naming Test (unspecified, others indicate a test of language), multiple choice version of Benton Visual Retention Test (visual memory), the Token test (language and transformational grammar, not described in paper) and Trail Making Test. Tactual Performance test, Finger Oscillation Test, the Lafayette Pegboard Test, and Grip Strength test (manual grip). “Mild” impairment defined as scoring 1 SD below age-matched norm and “moderate” impairment defined as scoring 2 SDs below age-matched norm. Tests of cognitive function administered at least 3 h after subjects underwent tryptophan challenge, with details of tryptophan challenge not presented in this paper.

Depression / Depressed Mood – Measured via the BDI and an extended version of the HAM-D, administered at least 3 h after tryptophan challenge (tryptophan challenge reported elsewhere).

Mental Status Examination and Neurological Examination – Conducted as part of screening.

Prolactin response After Tryptophan Infusion – Procedures not described in this paper. Prolactin measured at baseline and then after tryptophan infusion.

**Analyses**: Possible relationships between scores on tests of memory (specifically the WMS) and cumulative dose of ecstasy were examined via correlation. Prolactin levels at baseline and prolactin response to tryptophan infusion also reported (procedure not described in full). Comparisons on tests of performance were made on the basis of age-matched norms, and measures of depression scored via published norms. Number of subjects with impairment on each test reported. Otherwise, no formal analyses performed on data.

**Results – Significant Differences**: Tests of Cognitive Function – 5 / 9 subjects showed at least mild impairment on the WMS-Initial paragraph test compared with norms. 4 / 9 (all belonging to group who showed impaired performance on Initial Paragraph) also showed deficits in the Delayed paragraph test, and 3 / 9 had definite mild impairment on the WMS-Delayed Paragraph test. In comparison, 2 / 9 showed mild (1) or moderate (1) impairment on Trail Making test, 4 / 9 showed mild impairment on Tactual Performance test (1, dominant hand, 2, non-dominant hand, 1, both hands). 2 showed mild impairment on location performance test in Tactual Performance test and 1 / 9 mildly impaired on performance of Lafayette Pegboard test. Because of small sample size, authors only consider the findings for the WMS to be significant.

Prolactin Response to Tryptophan and Test Performance – Prolactin response to tryptophan was associated with impaired performance on the WMS-Delayed Figural test, suggesting that tryptophan infusion itself, or prolactin response to tryptophan, might have interfered with test performance.

**Results – No Differences Found**: Mental Status Examination and Neurological Examination – All subjects found to be functioning normally, and no sign of clinical impairment in cognitive function, as evidenced through mean full-scale IQ: (115 ± 9.5) and no difference between verbal and performance IQ. There were no group-related patterns on WAIS-R, Boston Naming Test, Benton Visual Retention Test, Trail Making Test, Tokens Test, Lafayette Pegboard Test, Tactual Performance Test, Finger Oscillation Test, or Grip Strength.

Depression / Depressed Mood – None of the subjects had elevated scores on either the BDI or the HAM-D, with all scores below indicators of clinical depression.

Drug Use Parameters and Test Performance – No relationship between cumulative ecstasy dose (lifetime exposure) and performance on the WMS. There were no associations between prolactin at baseline or in response to tryptophan and performance on the Paragraph tests of the WMS.

**Overall Effects**: A small sample of regular ecstasy users performed within the normal range on tests of general intelligence, learning, language, manual dexterity, eye-hand co-ordination, 5 of 9 subjects performed at least 1 standard deviation below published age-matched norms on tests of immediate and
delayed memory. (Specific references are made to the test of immediate and delayed verbal memory).
There is some indication that a small number of subjects were impaired on various tests of manual speed,
manual dexterity and (possibly) executive function, but there were too few of them in a small sample for this to be considered a “group specific pattern.” Impaired performance on tests of memory was not correlated with cumulative lifetime exposure to ecstasy and it was not associated with prolactin response to tryptophan challenge. None of the subjects participating in this study were diagnosed with affective or anxiety disorders, though they frequently reported previous experiences with depression or anxiety, and BDI and HAM-D scores were well within normal range.

Comments: This paper is one of the first to document possible deficits in cognitive performance in regular ecstasy users. The paper seems to have the qualities of a preliminary study in that the sample size is very small and no matched controls were employed. Unlike later studies without control groups, little use is made of correlational analyses. Correlations were only performed between performance and cumulative exposure to ecstasy (number of lifetime exposures). Because tests of cognitive function were conducted a few hours after tryptophan infusion, it is possible that performance on one or more test was either made worse or better by the tryptophan challenge. The paper is unusual in the number of tests employed for measuring manual dexterity and eye-hand co-ordination. Subjects taking part in this study were selected from another study on the basis of their low levels of 5HIAA in CSF, so caution should be used in generalizing from this study. Study sample is identical to the sample taking part in Price et al.

McCann et al. (1994). Serotonergic neurotoxicity after 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”): A controlled study in humans.


Purpose: Neuropsychological, including pharmacological challenge and personality measures: To measure CSF monoamines in ecstasy users and to examine whether differences in amount of 5HIAA in CSF are related to differences in functional domains presumed to be related to serotonergic function.

Design: Non-experimental (retrospective) 2-group between subjects (across groups) design, with drug-free ecstasy users compared with matched non-user controls, with drug use (ecstasy use versus non-use) serving as a between-subjects factor. All subjects underwent measurements of monoamine metabolites in CSF, prolactin response to tryptophan infusion and measures of response to ischemic pain, and all completed measures of personality.

Subjects: 30 regular ecstasy users recruited nationally through self-referral and 28 non-user controls either recruited by ecstasy user subjects or recruited through local advertisements in the Baltimore / Washington DC area. Matching – On gender, height and weight, and approximately matched on age and education.

Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 25 different occasions over lifetime. Non-users – No past or current ecstasy use, but use of psychoactive drugs other than ecstasy permitted. All Groups – Good health as assessed through physical examination, psychiatric interview, ECG and laboratory analysis. No history of major medical disorder, including neurological, renal, endocrine or hematological illness) and no history of psychiatric disorders, including psychosis or depression, alcohol or substance abuse. Not pregnant, and negative urine and blood screen for major psychiatric drugs. Abstinence from any psychoactive drug for at least 2 weeks prior to study day, with compliance verified by drug screens described above, performed on 1st study day.

Drug Use Parameters – Ecstasy Users – Ecstasy users reported that, on average, they had used ecstasy on 94.4 ± 90.6 occasions over a lifetime (25-300), and that average frequency of use was 4.16 ± 4.79 times a month (.15-20 times monthly.) Average dose of ecstasy taken per occasion was approximately 1.7 ± .8 tablets (.5 – 4 tablets), and average duration of use was approximately 59.8 ± 35.52 months (6 – 192
Correlations – All correlations calculated were Pearson correlations (product moment).

Number of ecstasy users reported using the following drugs: cannabis, 28 / 30; LSD, other hallucinogens, 26 / 30; cocaine, 24 / 30; benzodiazepines, 18 / 30; opiates, 16 / 30; other amphetamines, 13 / 30; sedative hypnotics, 10 / 30; solvents, 8 / 30 and PCP and related drugs, 4 / 30.

Non-Users - Number of non-user controls reported using the following drugs: cannabis, 22 / 28; LSD, other hallucinogens, 9 / 28; cocaine, 8 / 28; benzodiazepines, 6 / 28; opiates, 9 / 28; other amphetamines, 9 / 28; sedative hypnotics, 1 / 28; solvents, 8 / 28 and PCP, related drugs, 2 / 28.

Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender, height and weight, and ecstasy users were approximately matched on age and education level. Gender, as M / F ratio – Ecstasy users, 18 / 12: non-users, 17 / 11. Height, in cm – Ecstasy users, 174.8 ± 9.2 cm: non-users, 175.4 ± 9.5. Weight, in kg – Ecstasy users, 69.9 ± 14.9 kg: non-users, 70.4 ± 10.7 kg. Age. Ecstasy users, no range provided, mean = 32.3 ± 13.6: non-users, no range provided, mean = 27.8 ± 7.8. Educational level – On average, ecstasy users had 15.2 ± 2 years’ education, and non-users had, on average, 16.5 ± 2.8 years’ education.

Measures: Monoamine Metabolites in CSF – Subjects received lumbar puncture on the morning of 3rd study day after overnight fast. Monoamine metabolites in CSF measured via high performance liquid chromatography with electrochemical detection. Metabolites measured were 5HIAA (serotonin metabolite), HVA (dopamine metabolite) and MHPG (norepinephrine metabolite).

Prolactin Response to Tryptophan Challenge – 7 g L-tryptophan i. v. infused over 20 min, and plasma prolactin concentration was measured in blood samples drawn at 15 and .5 minutes before tryptophan infusion and 30, 40, 50, 60, 70, 90 and 120 min after infusion. Date of tryptophan challenge unspecified. Serum prolactin determined via radioimmunoassay.


Personality Assessment – Personality traits measured via MMPI and EPQ, both of which contain scales referring to impulsivity and control. Aggression and hostility was measured via BDHI. Time of administration unspecified.

Analyses: CSF Monoamine Metabolites – Amount of monoamine metabolites initially analyzed via ANCOVA, with age and height serving as covariates and with drug use (ecstasy user versus non-user) serving as a between-subjects variable. Second analysis attempted to control for seasonal variation in monoamine metabolites by analyzing data via 2(drug use) x 4(season) ANCOVA, with age and height serving as covariates. Because raw scores indicated possibility of gender differences in monoamine concentration, CSF monoamine metabolites also analyzed via 2(drug use) x 2(gender) ANCOVA, with age and height serving as covariates. Post-hoc comparisons made with Duncan’s multiple range test.

Prolactin after Tryptophan Infusion – Prolactin values at 15 and .5 minutes before tryptophan infusion averaged. Peak change scores were calculated by subtracting baseline prolactin value from highest prolactin value after tryptophan infusion, and AUC was calculated using the trapezoidal method. Prolactin response to tryptophan challenge measured via ANCOVA, with drug use (ecstasy user versus non-user) as a between-subjects factor and with age, basal prolactin level and plasma L-tryptophan values serving as covariates. Duncan’s multiple range test was used for post-hoc comparisons.

Pain Measures – All 3 measures of pain (sensitivity, endurance and tolerance) analyzed via 2(drug use) x 2(gender) ANOVAs, with drug use and gender serving as between-group factors, and with post-hoc comparisons made via Duncan’s multiple range test.

Personality Assessments – Scores on the MMPI, BDHI and EPQ were analyzed via 2(drug use) x 2(gender) ANCOVA, with age and education as covariates, and with analysis corrected for Type 1 error via Bonferroni method, and with post-hoc comparisons made via Duncan’s multiple range test.

Correlations – All correlations calculated were Pearson correlations (product moment).
Results – Significant Differences: CSF Monoamine Metabolites – When age and height used as covariance, ecstasy users had lower 5HIAA in CSF than did non-user controls. A drug use x gender ANOVA found that while 5HIAA levels lowest in females in ecstasy user group, non-user males had lower 5HIAA levels than non-user females. Female ecstasy users had lower CSF HVA than female non-users, but there was no difference in CSF HVA for males.

Personality Assessments – Ecstasy users scored higher on MMPI Control scale, indicating that ecstasy users were less impulsive than non-users. While there were drug use x gender effects on the alienation, harm avoidance and constraint scales of the MMPI, these are not described. Ecstasy users scored lower on the Indirect Hostility scale of the BDHI than did non-users.

Results – No Differences Found: CSF Monoamine Metabolites – Duration of ecstasy use and CSF 5HIAA were uncorrelated. While number of lifetime doses (cumulative exposure) was negatively correlated with CSF 5HIAA, the correlation was not statistically significant. A drug use x season analysis found no interactions with season. Ecstasy users and non-users did not differ in amount of CSF MHPG. While CSF HVA was lower in ecstasy user females versus non-users, male ecstasy users and non-users had similar values of CSF HVA.

Prolactin after Tryptophan Infusion – Ecstasy users did not differ from non-users in their prolactin response to tryptophan infusion, whether measured as peak change or as AUC.

Pain Measures – Ecstasy users did not differ from non-users on any of the 3 measures; pain sensitivity, pain endurance or pain tolerance.

Personality Assessments – Ecstasy users did not differ from non-users on other MMPI scales, other BDHI scales (such as direct hostility, direct aggression and indirect aggression) and any of the EPQ scales.

Overall Effects: Ecstasy users had lower levels of 5HIAA in their cerebrospinal fluid (CSF), and there was a gender-specific decrease in HVA in ecstasy users, with female ecstasy users having decreased HVA compared to female controls while HVA values were similar for male ecstasy users and non-user controls. Despite the lower 5HIAA values, ecstasy users did not differ from controls on two measures selected for their presumed connection with serotonergic function. Ecstasy users did not have a blunted (or stronger) prolactin response to tryptophan infusion when compared with controls, and all measures of pain reaction, including pain sensitivity, endurance and tolerance were similar for ecstasy users and non-user controls. Non users and ecstasy users differed in some personality scale scores, with ecstasy users scoring higher on the MMPI control scale (meaning they were less impulsive) and lower on the BDHI Indirect Hostility scale. However, the two groups scored similarly on all other MMPI, BDHI and EPQ scales.

Comments: This paper sought to establish links between ecstasy use, lower serotonin metabolites and changes in functions selected for their presumed association with serotonergic function. The findings are thus surprising in that lower levels of the serotonin metabolite 5HIAA was found in ecstasy users, but there were few behavioral correlates of this difference, and the differences that were found between ecstasy users and non-users were opposite those predicted on the basis of theory. Either the assumptions about the strong relationship between the selected functions were incorrect or incomplete, or the measures chosen were not accurate or effective measures. There is also some suggestion that some of the personality differences between the 2 groups were a reflection of the personality characteristics of regular ecstasy users in the late 1980s or early 1990s. The authors explain the discrepancy between their findings of reduced 5HIAA without any behavioral correlates as evidence for selective damage to ascending, but not descending, serotonergic axons. Gender seems to be a more powerful predictor of outcome than past use of ecstasy in several measures, suggesting that it is important to examine studies that rely on data from one gender only (as with Gerra). Such studies may not accurately reflect either serotonergic function or the effects of regular ecstasy use in both genders.


**Purpose:** Brain imaging (PET with ligand binding): To investigate whether MDMA use produces long-term changes in number of serotonin transporter sites by performing PET with a radioligand for the serotonin transporter site.

**Design:** Non-experimental (retrospective) 2-group between subjects design that compared drug free ecstasy users with matched non-user controls, with drug use (ecstasy use versus no ecstasy use) as a between-group factor, and with all subjects receiving PET scans.

**Subjects:** 14 regular ecstasy users and 15 non-users recruited via advertisements in local (Baltimore, MD / Washington, DC) newspapers and on the internet, and referrals. Matching – On gender, age and education.

Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 25 occasions over a lifetime. Non-users – No past or current ecstasy use, but use of other drugs permitted. All Groups – No past or current major medical or psychiatric illness as assessed through physical examination and psychiatric interview, ECG and standard urinary and blood analyses. Abstaining from all psychoactive drugs for at least 3 weeks prior to study period, with compliance verified by urinary and blood screening for drugs on day of admission to study. No claustrophobia, absence of any neuropsychiatric disorders where serotonin function might be impaired, and no cardiac pacemaker.

**Drug Use Parameters – Ecstasy Users** – On average, ecstasy users reported taking ecstasy on 228 occasions (70-400 occasions), with an average dose per use of approximately 3.8 tablets (1.5 – 12.5 tablets). Ecstasy users had an average frequency of use of 6 times a month (1-16 times monthly), and average duration of use, in months, was 55.2 months (18-120 months). Number of days from last use until study day was 133 days (21- 1029 days)

**Group Demographics and Matched Variables** – Ecstasy users matched with non-user controls on gender, age and education. **Gender, as M / F ratio** – Ecstasy users, 9 / 5: non-users, 9 / 6. **Age.** Ecstasy users average age = 26.6 ± 10.5 (range not provided): non-users average age = 28.3 ± 11.7 (range not provided). **Education Level** – Ecstasy users average education level, in years, was 15 ± 2, and non-users average education level, in years, was 16 ± 4. **Use of Other Drugs** – Information on number of other psychoactive drugs used by ecstasy users or non-users not provided, but members of both groups had negative screens for marijuana, amphetamines, opiates, barbiturates, PCP and benzodiazepines on the study day.

**Measures:** PET was performed, with PET co-registered with MRI to more clearly locate and define regions of interest. PET was conducted after injection of [11C]McN-5652. 2 sets of scans were performed on each subject; one with (+)McN-5652 and one with (-)McN-5652. Regions of interest were drawn on PET scans by an experimenter blind to subject’s drug history, with regions being frontal cortex, parietal cortex, temporal cortex, occipital cortex and cingulate, caudate, putamen, thalamus, midbrain, pons, hypothalamus and cerebellum.

**Analyses:** Analyses were performed on model for (+)McN-5652 that consisted of specific binding, non-specific binding and free ligand, and the model for (-)McN-5652 consisted of non-specific binding and free ligand only. Ligand binding data was transformed to log to achieve normal distribution, and data for all regions in controls used to create a pooled coefficient of variation of 22%. Log transformed ligand binding data for 12 brain regions were analyzed via MANOVA, with drug use (ecstasy user versus non-user) as between-group variable, ligand binding data as dependent variables and age and gender as covariates. A 1-way ANOVA was used to examine differences in ligand binding in individual regions, presumably with drug use (ecstasy use versus non-use) serving as a between-subjects factor. **Correlations** – Possible relationships between time since last use, extent of previous use (total lifetime use) and ligand binding data were examined via Pearson’s correlations, with p. set at .05.

**Results – Significant Differences:** Ecstasy users had lower global specific binding for [11C]McN-5652, indicating lower numbers of serotonin (5HT) transporter sites in brain. Decreased serotonin transporter
binding in ecstasy users was found when comparisons were made between [11C]McN-5652 binding in the following brain regions: frontal cortex, parietal cortex, occipital cortex and cingulate, caudate, putamen, midbrain, pons, hypothalamus and cerebellum. Correlations – Extent of ecstasy use (presumably total number of lifetime doses) was negatively correlated with extent of transporter binding, with greater extent of use associated with less serotonin transporter binding.

Results – No Differences Found: Serotonin binding in the temporal cortex and the thalamus, as measured through [11C]McN-5652 binding, was similar for ecstasy users and non-users. Correlations – Time between last use and study day was not related to number of serotonin transporter sites, as measured through [11C]McN-5652 binding.

Overall Effects: When measured via PET with the radioligand [11C]McN-5652 (specific for the serotonin transporter site), ecstasy users had fewer serotonin binding sites than non-user controls. Number of serotonin transporter sites was reduced in a global comparison of ecstasy users and non-users, and number of serotonin transporter sites were also reduced in 10 of 12 ROIs (regions of interest), including most cortical and sub-cortical regions except for the temporal cortex and thalamus. Greater extent of ecstasy use was associated with fewer serotonin transporter sites, but number of days since last use was not associated with quantity of serotonin transporter sites.

Comments: This paper is one of the first to use PET imaging with a radioligand specific for the serotonin transporter site to compare serotonergic functioning in regular ecstasy users and non-user controls. While findings cannot be interpreted as irrefutable evidence of serotonergic neurotoxicity of ecstasy, they do support this hypothesis. Given some of the findings for region-specific differences in cerebral glucose utilization (Obrocki et al., 1999), cerebral blood volume (Reneman et al, 2000a,b), and presence of myo-inositol (e.g. Chang et al, 1999) in ecstasy users versus non-user controls, it is surprising that reduction in serotonin transporter sites is nearly global, affecting 10 of 12 regions of interest. Sample size is small, and so caution should be used in generalizing to the population at large.

McCann et al. (1999). Altered neuroendocrine and behavioral responses to m-chlorophenylpiperazine in 3,4-methylenedioxymethamphetamine (MDMA) users.


Purpose: Pharmacological challenge: To determine whether differences between ecstasy users and non-user controls would be revealed after administering the mixed serotonin agonist mCPP, with differences presumably referring to changes in serotonergic function after regular ecstasy use. Specific hypothesis tested – that if ecstasy users had sustained serotonergic injury, they would exhibit altered neuroendocrine and behavioral responses to mCPP. (Does not specify nature of difference).

Design: Non-experimental (retrospective) 2-group between groups design, wherein drug-free ecstasy users were compared with matched non-user controls on their physiological and subjective responses to mCPP (.08 mg / kg in 20 cc NS). Drug use (ecstasy use versus non-use) was a between-subjects factor. All subjects received mCPP and completed self-report measures of subjective drug effects for mCPP. Design of mCPP Administration – mCPP was administered via a placebo controlled, single-blind, fixed order design, with all subjects receiving saline at Time 1 and mCPP at time 2.

Subjects: 25 regular ecstasy users and 25 non-user controls. Information not provided on recruitment for ecstasy users, but another related study used advertisements in newspapers and the internet and self-referrals. Non-user controls were recruited via advertisements. Matching – On gender, age, education and use of other drugs.

Criteria for Inclusion, Ecstasy Users – Having used ecstasy at least 25 times over lifetime. Non-users – No past or current use of ecstasy, though use of other psychoactive drugs permitted. All Groups – Absence of past or current major medical or psychiatric illness as assessed through physical examination and psychiatric interview, ECG and standard urinary and blood analyses. Abstinence from all
psychoactive drugs for 3 weeks prior to study period, with compliance verified by urinary and blood screening for drugs on day of admission to study. Sample in this study appears to be similar to the sample used in McCann et al, 1999b.

**Drug Use Parameters – Ecstasy Users** – On average, ecstasy users reported that they took ecstasy on 196 \(\pm 24\) occasions over the lifetime (30 – 400 times), and that the average dose per occasion was approximately 3.2 \(\pm 2.8\) tablets (1-12.5 tablets). Ecstasy users reported that on average, they took ecstasy 5 \(\pm 1\) times a month (.6 – 11 times monthly) and that they had used ecstasy for an average of 60 \(\pm 36\) months (12 – 168 months). The average period between the last use of ecstasy and the first study day was 98 \(\pm 203\) days (21-973 days). Other drugs reportedly used by ecstasy users: Cannabis (25 / 25), LSD, other hallucinogens (24 / 25), amphetamines (24 / 25), cocaine (23 / 25), solvents (18 / 25), sedative hypnotics (19 / 25), opiates (14 / 25), PCP, related drugs (5 / 25). **Non-users** – Other drugs reportedly used by non-users: cannabis (20 / 25), LSD, other hallucinogens (11 / 25), amphetamines (10 / 25), cocaine (10 / 25), opiates (10 / 25), sedative hypnotics (7 / 25), solvents (7 / 25), PCP, related drugs (4 / 25).

**Group Demographics and Matched Variables** – Ecstasy users were matched with non-user controls on gender and approximately matched on age and education. **Gender**, as M / F ratio – Ecstasy users, 17 / 8: non-users, 17 / 8. **Age**, Average age of ecstasy users = 26.92 \(\pm 1.95\) (men, 28 \(\pm 4\), women, 27 \(\pm 2\), no range provided). **Education Level**, in years - Ecstasy users, 13.36 \(\pm .59\): non-users, 15.28 \(\pm .42\). **Use of Other Drugs** – While both groups had tried the same types of drugs, save ecstasy, with the same proportion of each group generally using each drug, a smaller number of non-users had tried each drug when compared with ecstasy users in every case (see above). Other **Variables** – Ethnic / racial make-up of ecstasy users, 23 White, 1 African American, 1 “other: non-users, 15 White, 6 African American, 4 “other.” Past psychiatric history – Ecstasy users, dysthymia = 1, PTSD = 1: Non-users, dysthymia = 0, PTSD = 3.

**Measures: Neuroendocrine Response to mCPP** – Fasting subjects received placebo infusion at Time 1 and (approximately 2 h later) received mCPP infusion, with subjects believing randomized presentation of drug. Plasma cortisol and prolactin measured from blood samples drawn at 30 and 15 min pre-drug and 30, 60 and 90 min post-drug, with drug either placebo or mCPP. Cortisol and prolactin concentrations measured via immunoassays.

**Mood** – Lader’s Mood Scale and 8 author-generated 100-mm visual analog scales (VAS) measuring mood states, with each measure administered at 15, 30, 60 and 90 min post-drug (either placebo or mCPP), and all measures administered at baseline (before placebo).

**Panic Symptoms** – Measured via NIMH Panic Symptoms Scale, administered at baseline and 90 min post-drug (placebo or mCPP). Subjects asked to rate symptoms “at their worst” as mild, moderate or severe; presence of panic attacks also recorded within each group.

**Self-reported Drug Effects (“Side Effects”)** – Measured via NIMH Self-Rating Symptom Scale, measuring emotional and physiological drug effects and author-devised 21 item questionnaire designed to measure self-reported physical effects, with measures administered at baseline (pre-placebo) and at 15, 30, 60 and 90 min post-drug (placebo or mCPP).

**Analyses: Neuroendocrine Response to mCPP** – Only male subjects included in analyses of cortisol and prolactin response to mCPP. Cortisol and prolactin response analyzed with a repeated measures ANCOVA, with drug use (ecstasy user versus non-user) as a between-group factor, drug infusion (placebo versus mCPP) and time (time of sample) as within-subjects factors and with one covariant (baseline cortisol or prolactin). Post-hoc comparisons made via Bonferroni method and p. set at .05. Correlates made between “extent of ecstasy use” (definition unspecified, but may refer to overall lifetime occasions or estimated cumulative dose) and prolactin response to mCPP infusion.

**Mood** – Mood analyzed via repeated measures ANCOVA with one between-group factor, with drug use (ecstasy user versus non-user) as between-group factor and with drug infusion (placebo or mCPP) and time (time of sample) as within-subjects factors, and with baseline mood measures as covariates. Post-hoc comparisons made via Bonferroni method, with p. set at .05.
Panic Symptoms – Subjects scored positively on panic symptom scale if they rated 4 or more panic-related symptoms as moderate or severe. Ecstasy users compared with non-users using Fisher’s exact test, with comparisons made at placebo and after mCPP infusion.

Self-reported Physiological Effects (“Side Effects”) – Self-reported side effects analyzed via repeated measures ANCOVA, with drug use (ecstasy use versus non-use) as a between-group factor and with drug infusion (placebo or mCPP) and time (time of sample) as within-subjects factors, and with baseline side effect / symptom measures as covariates. Post-hoc comparisons made via Bonferroni method, with p. set at .05.

Results – Significant Differences: Neuroendocrine Response to mCPP – All findings relating to neuroendocrine response to mCPP refers to analyses employing male subjects only. Baseline cortisol was lower in ecstasy users than in controls. Cortisol response to mCPP infusion blunted in ecstasy users compared with controls (lower cortisol after mCPP). Prolactin response to mCPP infusion was blunted in male ecstasy users compared with same-sex controls.

Mood – Lader Mood Scales: Ecstasy users had higher scores on Lader “attentiveness” scale at baseline than non-users. After mCPP infusion, ecstasy users rated selves higher than non-user controls on Lader Mood “content,” “energetic,” “happy,” and “quick-witted” scales. Overall, ecstasy users rated mood more positively than did non-users after mCPP. Ecstasy users rated themselves higher on Lader Mood “alert,” “content,” “amicable,” “tranquil,” “quick-witted” after mCPP, with scale ratings increasing over time after mCPP infusion, but not after placebo. Analyses using peak changes from baseline found that after placebo, ecstasy users rated selves higher on Lader Mood “interested” but on no other scales. After mCPP infusion, ecstasy users rated selves higher on 11 of 16 Lader Mood scales compared with controls. VAS: After mCPP infusion, ecstasy users rated selves less sad and less tired on VAS measures when compared with non-user controls. When ecstasy users and non-users were compared on peak change scores after mCPP, ecstasy users rated selves as less tired and less sad on VAS compared with controls.

Panic Symptoms – Non users were more likely to meet criteria for panic attacks than were ecstasy users after mCPP infusion. 1 ecstasy user and 8 controls experienced a panic attack after mCPP infusion.

Drug Effects, “Side Effects” – NIMH Self-Rating Scale: At baseline, ecstasy users rated themselves as more “elated” and less “worried” than non-user controls. After mCPP, ecstasy users had higher scores on “elated” and lower scores on “sad,” “slowed down” “uncomfortable mentally” and “worried.” Overall ecstasy users reported more pleasant effects after mCPP than did non-users, and fewer unpleasant effects, and the same pattern of self-ratings was true when ratings were compared over time of sample (30, 60, 90 min post-drug). After placebo, ecstasy users only differed in self-rating of “feel mistrustful or suspicious,” with direction of difference unspecified. Physical Symptoms: Ecstasy users differed from non-users on ratings of “dry mouth,” (lower rating), “nausea” (lower rating) and “poor appetite” (no information provided, probably lower rating). After mCPP infusion, ecstasy users reported less of these symptoms than did non-users: drowsiness, poor appetite, increased appetite, stiffness, tiredness, weakness. After mCPP infusion, ecstasy users reported more sexual thoughts or interest than did non-users.

Results – No Differences Found: Neuroendocrine Measures – All findings refer to analyses employing male subjects only. No difference in plasma cortisol values between male ecstasy users and same-sex non-users after placebo. There were no differences between the 2 groups in prolactin concentration at baseline, or in prolactin response to placebo. Extent of ecstasy use was not correlated with changes in prolactin after mCPP or with changes in cortisol after mCPP, with extent of ecstasy use undefined; in prior studies, defined as total lifetime occasions used). Ecstasy users and non-users had similar plasma mCPP values.

Mood – Lader Mood Scales: Ecstasy users and non-users did not differ on all other Lader Mood scales (clear-headed, content, energetic, gregarious, happy, interested, proficient, relaxed, strong, tranquil) at baseline. After mCPP, ecstasy users and non-users rated selves similarly on some (unspecified) Lader Mood scales. When peak change from baseline analyzed after placebo, ecstasy users and non-users rated selves similarly on all Lader Mood scales except “interested,” and after mCPP, ecstasy users and non-users rated selves similarly on 4 of 16 Lader Mood scales. VAS: There were no differences between
ecstasy users and controls on all VAS at baseline or after placebo. After mCPP, ecstasy users and non-users provided similar VAS ratings on 6 (undescribed) VAS scales.

Panic Symptoms – There were no differences between ecstasy users and non-users on number of panic symptoms after placebo. No subjects from either group experienced a panic attack after placebo.

Drug Effects and Side Effects – NIMH Self-Rating Scale: Ecstasy users and non-users did not differ in their self-ratings on 19 (undescribed) other items on the NIMH Self-Rating measure. Ecstasy users did not differ from non-users on 23 of the 24 items on the NIMH self-Rating Scale or any of 6 sub-scales. Physical Symptoms: Ecstasy users and non-users reported a similar number of physical symptoms after placebo and baseline on 23 of 26 items. After mCPP, ecstasy users and non-users did not differ in their reports of experiencing 19 other physical symptoms on the NIMH Self-Rating scale.

Overall Effects: Prolactin and cortisol response to mCPP was blunted in ecstasy users, and this remained true even though ecstasy users had lower cortisol levels at baseline. Differences in neuroendocrine response to mCPP could not be explained via plasma mCPP level, as they were similar in both groups. However, extent of ecstasy use was not associated with extent of blunted prolactin or cortisol response after mCPP. Ecstasy users were more likely to experience mCPP as producing positive effects, such as alertness, contentedness and feeling quick-witted. They were less likely than non-users to report feeling tired or sad after mCPP, and they were less likely than non-users to report feeling slowed down, mentally uncomfortable or stiff. While the two groups did not differ in reports of panic symptoms at placebo, non-users were more likely than users to report panic symptoms and to experience panic attacks after mCPP infusion. Non-users reported a greater number of unpleasant physical symptoms after mCPP infusion, such as weakness, nausea and drowsiness, while ecstasy users reported fewer negative symptoms and greater sexual thoughts after mCPP. Since ecstasy users also rated themselves as less “worried” and more “elated” in general, and described their mood as more positive generally, they may have had fewer concerns about the effects of mCPP than the non-user controls. The authors’ hypothesis was partially confirmed. Ecstasy users demonstrated blunted neuroendocrine response to mCPP, and their experience of the subjective effects of mCPP was different from that reported by non-users. However, the hypothesis is bi-directional, and did not specify expectations about the nature of the predicted change. The results do not rest on confirmed serotonin injury, as stated in the hypothesis, as serotonin injury has only been implied via by blunted neuroendocrine response to mCPP challenge, and not confirmed.

Comments: This paper attempts to replicate and expand upon earlier findings comparing ecstasy users with non-user controls on a challenge with a serotonin releaser. (An earlier study used d-fenfluramine challenge, and the subjective effects of the challenge drug were not measured in that study). Neuroendocrine responses are measured in male subjects only, because the authors were concerned with fluctuations in prolactin related to the menstrual cycle. The authors propose that the differences in neuroendocrine and behavioral responses to mCPP in ecstasy users are evidence for altered serotonin systems. The major alternative hypotheses they mention are greater exposure to drugs and greater sensation seeking in ecstasy users. However, it is also possible that ecstasy users may have reported a “conditioned” response to mCPP, as some of its physical effects are similar to those reported for ecstasy. Non-users, who were specifically selected for lack of experience with ecstasy, would not have “learned” to associate these physical effects with elevated mood or positive effects. Some of the individuals participating in this study also participated in a paper from the same year that assessed cognitive performance.

McCann et al. (1999). Cognitive performance in 3,4-methylenedioxymethamphetamine (MDMA) users: A controlled study.

**Purpose:** Cognitive function (general): To examine whether ecstasy use affects other cognitive functions besides or in addition to visual and verbal memory and to see whether cognitive functions other than those mediated by the serotonin system might be affected by regular ecstasy use

**Design:** Non-experimental (retrospective) 2-group between-subjects design where drug-free ecstasy users were compared with matched non-user controls. Drug use (ecstasy use versus no use) served as a between-subjects factor. All subjects completed test battery designed to assess cognitive functions. (Test administration was part of a more extensive study of neuroendocrine and other functions in ecstasy users and non-users).

**Subjects:** 22 regular ecstasy users recruited by word of mouth / self-referral and 22 non-user controls recruited via local advertisements in the Baltimore / Washington DC area. **Matching** – On age, gender, education and use of other drugs. Sample seems to be similar to that used in McCann et al, 1999a. **Criteria for Inclusion, Ecstasy Users** – Having used ecstasy at least 25 times over lifetime. **Non-users** – No past or current ecstasy use, though use of other psychoactive drugs permitted. **All Groups** – Absence of past or current major medical or psychiatric illness as assessed through physical examination and psychiatric interview, ECG and standard urinary and blood analyses. Abstinence from all psychoactive drugs for 3 weeks prior to study period, with compliance verified by urinary and blood screening for drugs on day of admission to study. (Nicotine use permitted before and during study to avoid effects due to nicotine withdrawal).

**Drug Use Parameters** – **Ecstasy Users** – On average, ecstasy users reported that they took ecstasy on 215 ± 33 occasions over a lifetime (30 – 725 times), and that the average dose per occasion was approximately 2.7 ± .4 tablets, or 272± 40 mg (1-10 tablets). Ecstasy users reported that on average, they took ecstasy 5.72 ± .61 times a month (.8 – 15 times monthly) and that they had used ecstasy for an average of 54.24 ± approx. 9 months (12 – 168 months). The average time since last use of ecstasy and the first study day was 97.37 ± 45.78 days (21- 1029 days). **Other Drugs** – Other drugs reportedly used by ecstasy users: Cannabis (22 / 22), LSD, other hallucinogens (22 / 22), amphetamines (21 / 22), cocaine (21 / 22), solvents (17 / 22), sedative hypnotics (15 / 22), opiates (13 / 22), PCP, related drugs (6 / 22). **Non-users** – Other drugs reportedly used by non-user controls: cannabis (19 / 23), LSD, other hallucinogens (11 / 23), amphetamines (10 / 23), cocaine (10 / 23), opiates (10 / 23), sedative hypnotics (7 / 23), solvents (7 / 23), PCP, related drugs (4 / 23).

**Group Demographics and Matched Variables** – Ecstasy users matched with non-users on gender, and approximately matched on age, education level and use of other drugs. **Gender,** as M / F ratio – Ecstasy users, 15 / 7: Non-users, 16 / 7. **Age:** Ecstasy user average age = 26.23 ± 1.99 (range not provided). Non-user average age = 30.35 ± 1.98. (Non-users older than ecstasy users). **Education Level,** in years: Ecstasy users had, on average, 13.36 ± .63 years, non-users had 15.22 ± .45 years. **Use of Other Drugs** – Both ecstasy users and non-users had tried other psychoactive drugs, but in nearly all cases, a greater number of ecstasy users had tried other drugs than non-users. Only use of opiates and PCP roughly equivalent in both samples.

**Measures:** **CSF Monoamine Metabolites** – CSF extracted through lumbar puncture (Day of study and time of puncture not provided). Monoamine metabolites in CSF measured via high performance liquid chromatography with electrochemical detection. Metabolites measured were 5HIAA, HVA and MHPG. Samples were assayed without awareness of participant drug history. **Tests of Cognitive Function** – Measured via Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR-PAB), a computerized test battery designed for testing people with wide range of reading and arithmetic skills, including people who only possess basic skills. This test battery contains: Time Wall task (time estimation), Serial Add and Subtract (machine-paced mental arithmetic), Logical Reasoning (self-paced, subjects indicate which of two target statements is incorrect), Manikin task (visuospatial rotation, subject indicates hand that a human figure is using to hold target), Code Substitution (similar to WAIS Digit Symbol: self-paced, indicate learn number-code correspondence, then translate code without key for maximum points, but can press button to view key), Matching to Sample (Pick 1 of 2 visual arrays that match previously presented target), and Delayed Recall (At conclusion of
test battery, perform Code Substitution again without code). WRAIR-PAB administered 3 times daily for all 5 study days, with test battery taking approximately 20-30 min to complete.

**Analyses: CSF Monoamine Metabolites** – Analysis of 5HIAA in ecstasy users and controls compared with 2-tailed student’s t-test. CSF 5HIAA value also correlated with peak accuracy, speed and “throughput” scores (see below) on all 7 cognitive tasks.

**Tests of Cognitive Function** – Analyses excluded test performance on 4th day of study due to administration of mCPP on 4th day. All 3 daily administrations of the WRAIR-PAB were averaged within each day, producing 3 time points (1 per day). Baseline = Performance on Day 1, learning curve = performance on Day 2 and peak = Performance on Day 3. Data then analyzed via 2(Drug use: ecstasy user versus non-user) x 3(Time: Day 1 vs. Day 2, Day 3) repeated measures ANOVA, with drug use serving as between-group factor and time of administration as within-subjects factor. Post-hoc comparisons made via Bonferroni method. Comparisons also made on speed, accuracy and “throughput” score, where throughput = number of questions answered per minute (speed) x number of correct answers (accuracy). If significant effects due to drug use were found on any one task, those test scores were further analyzed separately for speed and accuracy of response. **Regressions** – Baseline (Day 1) and peak (Day 3) performance scores (accuracy, speed, throughput) regressed on drug use status, lifetime (total) ecstasy dose, weekly dose and monthly dose.

**Results – Significant Differences:** CSF Monoamine Metabolites – Ecstasy users and non-user controls differed on amount of CSF 5HIAA, with ecstasy users < controls.

**Tests of Cognitive Function** – Ecstasy had lower test scores overall on the Logical Reasoning and the Code Substitution task (for all 3 days). Ecstasy users had lower test scores on Serial Add and Subtract on Learning (Day 2) and Peak (Day 3) days. Ecstasy users had lower test scores for Delayed Recall at Baseline (Day 1), but not for Learning or Peak days. **Accuracy** – Ecstasy users were less accurate (made more errors) on Code Substitution and Delayed Recall on Baseline day. **Speed** – Ecstasy users performed the Serial Recall task more slowly on Learning (Day 2) and Peak (Day 3) days than did non-user controls.

**Regression** – Total lifetime number of ecstasy doses was associated with performance on Code Substitution task only, with greater number of doses associated with lower speed and “throughput” scores on the Peak day (Day 3).

**Results – No Differences Found:** CSF Monoamine Metabolites – Ecstasy users and non-user controls had similar amounts of CSF HVA and MHPG. CSF 5HIAA values were found to be unrelated to task performance on any of the 3 study days measured.

**Tests of Cognitive Function** – Performance measured on Time Wall, Manikin and Matching to Sample tasks were similar in ecstasy users and non-users, with similar performance seen on all 3 days (baseline, learning and peak). Ecstasy users and non-users had similar Baseline (Day 1) performance scores on Serial Add and Subtract task. Ecstasy users had similar scores on Learning and Peak days on Delayed Recall task. **Accuracy** – Ecstasy users were as accurate on Serial Add and Subtract and Logical Reasoning tasks as non-users (members of both groups made similar numbers of errors). **Speed** – There were no differences between speed of performance for ecstasy users and controls for Code Substitution, Delayed Recall or Logical Reasoning. **Regression** – There were no associations (positive or negative) between performance on all other WRAIR-PAB tests and total number of ecstasy doses, weekly dose or monthly dose of ecstasy.

**Overall Effects:** Ecstasy users had comparatively less 5HIAA, a serotonin metabolite, in CSF than did non-user controls. When compared on a test battery designed to measure cognitive performance, it was found that ecstasy users performed worse on all testing days on two of seven tests (Logical Reasoning and Code Substitution). Ecstasy users performed poorly on two other tests, but only on some testing days. While ecstasy users did less well on Delayed Recall (performing the Code Substitution task again, without code, at the end of the test battery) on the first day, the two groups maintained similar performance on Days 2 and 3. On the other hand, both groups showed similar performance on Serial Add and Subtract for Day 1, but ecstasy users performed less well (or non-users performed better) on Days 2 and 3. While ecstasy users had lower CSF 5HIAA and performed less well on certain tasks, amount of 5HIAA was not correlated with task performance on any of the 3 days. Decrement in performance by
ecstasy users on some tests (Code Substitution, Delayed Recall) was due to greater number of errors on baseline day, whereas poor performance on another task (Serial Add and Subtract) was due to slower responses compared to those of non-users on Days 2 and 3. The two groups did not differ on task performance for a task of visuospatial rotation (Manikin task), task of time estimation (Time Wall) or a Matching to Sample task. Total number of lifetime doses was negatively correlated with peak performance on Code Substitution, but it not with any other task, and number of days since last use was not associated with performance on any of the WRAIR-PAB tests. The lack of association between lower levels of 5HIAA and decrements in test performance can be interpreted as evidence that regular ecstasy use affects cognitive functions not directly mediated by the serotonin system. Decreased performance on at least one test (Logical Reasoning) suggests decrements in areas outside of verbal or visual memory, but the number of functions assessed by any one test is less clear.

Comments: This paper appears to be a combined replication of several studies performed by the same authors, including a comparison of CSF monoamine metabolites and performance on cognitive tests. In contrast to a previous study measuring monoamine metabolites, this study only found decreased 5HIAA in ecstasy users, and it did not find gender differences with respect to HVA concentration. The findings in this paper can be interpreted as evidence for a dissociation between the effects of regular ecstasy use on the serotonin system and on cognitive function. However, evidence concerning deficits in cognitive function outside of memory seems less certain. It would appear that performance on 2 of the 4 tests relies upon memory (Code Substitution and Delayed Recall) and performance on a third test might involve immediate recall (Serial Add and Subtract). This seems to leave only one task demonstrating performance decrements in ecstasy users that is truly unrelated to memory (Logical Reasoning). The authors remark that differences in performance are subtle, and that ecstasy users do not report any difficulties with everyday functioning. As was true in other user comparison studies performed by the same author, use of other drugs in ecstasy users is much higher than drug use in the non-user sample.

Morgan (1998). Recreational user of “Ecstasy” (MDMA) is associated with elevated impulsivity (Study 1).


Purpose: Neuropsychological, including mood, personality and cognitive function: To determine whether a history of recreational ecstasy use is specifically associated with changes in functional domains believed to be associated with serotonin (5HT) function by comparing ecstasy users with polydrug user and no drug user controls.

Design: Non-experimental (retrospective) 3-group between subjects (across groups) design, with ecstasy users compared with 2 groups of matched controls, polydrug users who had never used ecstasy (polydrug user controls) and individuals who had never used illicit drugs (no-drug user controls), with drug use as a between subjects factor. All groups were compared on measures of mood, anxiety, anger / hostility, impulsivity (psychometric and behavioral) and cognitive function, and all subjects completed questionnaires and test batteries.

Subjects: 16 ecstasy users, 12 polydrug users and 16 no-drug users residing in the Swansea (Wales) area, with members of all 3 groups recruited via posters and advertisements and by word of mouth. Matching – On gender, age, height, weight, education level and estimated IQ (NART score). Criteria for Inclusion, Ecstasy Users – Had used ecstasy on at least 20 separate occasions. Polydrug Users – No past or current use of ecstasy, but drug use pattern that is otherwise similar to that of ecstasy users. No-drug controls – No prior history of ecstasy use and no use of other drugs save alcohol and nicotine. All Groups – No past or current major medical or psychiatric illnesses, not pregnant, and no alcohol or substance abuse. No more than 25 incorrect answers on NART and attending university or being a university graduate. No information on required drug-free period, but Morgan, 1999 (containing
Drug Use Parameters – Ecstasy Users – On average, ecstasy users reported that they had taken an average of 35.6 ± 17.5 tablets over the lifetime (range not provided), and that the average dose used per occasion was 1.12 ± .34 tablets (range not provided). Ecstasy users reported that on average, they took ecstasy 2.94 ± .93 times a month (range not provided) and that they had used ecstasy for an average of 25.44 ± 16.32 months (range not provided). The average period between the last use of ecstasy and the first study day was 20.4 ± 33.6 days (range not provided). The average maximum amount of ecstasy used on 1 occasion, in tablets = 2.28 ± 1.25 tablets. Other drugs used by ecstasy users, reported as average amount per wk / per month / per year, and duration of use, in years: Alcohol, 67.12 units per month, duration 8.31 years, cigarettes, 64.81 per wk, no duration information, cannabis, 59.75 joints per month, 5.69 years, amphetamines, 17.2 grams per year, 2.56, LSD, 6.19 trips per year, no duration information. Polydrug Users – Drug use reported as average amount per wk / per month / per year, and duration of use, in years: Alcohol, 85.67 units per month, duration 7.25 years, cigarettes, 71.67 per wk, no duration information, cannabis, 50.5 joints per month, 4.67 years, amphetamines, 19.2 grams per year, 2.42, LSD, 18.33trips per year, no duration information. Both MDMA users and polydrug users also used psilocybian mushrooms and benzodiazepines infrequently. Ecstasy users more likely to use cocaine than polydrug users, though use was low (exact figures not presented here).

Group Demographics and Matched Variables – Ecstasy users, polydrug users and no-drug users were matched on gender, age, weight, height, education level and NART score. Ecstasy users were matched with polydrug users on use of other (non-ecstasy) drugs. Gender, as (approximate) M / F ratio: Ecstasy users, 8 / 8: polydrug users, 7 / 5: no-drug users, 7 / 9. (Author presented data as average of binary coded data where 1 = male and 2 = female, with ecstasy users = 1.50, polydrug users = 1.42, no-drug users = 1.62.) Age. Ecstasy users’ average age = 20.94 ± 1.88, polydrug users average age = 20.25 ± 1.48, no-drug users average age = 21.87 ± 6.09. Height, Weight – Height in cm, weight in kg: Ecstasy users, 170 ± 10 cm, 61.26 ± 9.63 kg, polydrug users, 172.3 ± 7.65 cm. 62.22 ± 7.18 kg, no-drug users, 171.3 ± 9.99 cm, 69.15 ± 12.91 kg. Education Level – Ecstasy users had approximately 15.5 years education, polydrug users had approximately 14.5 years education and no-drug users had approximately 14.5 years education. (Original data coded 1 = passed basic high school exam, 2 = passed advanced high school exam, 3 = university degree, with ecstasy users = 2.94 ± .25, polydrug users = 2.67 ± .49, no-drug users = 2.69 ± .6).

Estimated IQ (from NART Score) – Ecstasy users = 114.9 ± 5.6, polydrug users = 112.3 ± 4.76, no-drug users = 113.5 ± 6.41

Measures: Mood – Current (state) mood measured via author-devised self-report questionnaire with 9 items, with some items addressing positive mood (happy, joyful) and others addressing negative mood (depressed, frustrated). Anxiety was measured via STAI and anger was measured with the State-Trait Anger Expression Inventory (STAXI).

Personality: Psychometric – Trait anxiety measured via STAI and trait anger / hostility measured through STAXI. Impulsiveness, venturesomeness (risk taking) and empathy measured via IVE.

Executive Function / Cognitive Function – Measured through the Cambridge Neuropsychological Test Automated Battery (CANTAB), a suite of tests performed on touch-screen computers. CANTAB tests intended to assess cognitive function associated with frontal lobe function. The CANTAB includes: Tower of London (TOL) – Variation of “Tower of Hanoi” puzzle. Subject asked to move balls from “pockets” on screen using the smallest number of moves, with each set presenting an increasingly difficult task (2 moves – 5 moves). TOL also compares “yoked control” where each step of self-generated solution is replayed and subject follows each move). Subjects scored on “number of excess moves” (more than minimum required), “proportion of perfect solutions” (number of solutions using minimum moves), ‘initial thinking time” (time elapsed from presentation to first touch of screen), “subsequent thinking time per move” (time between first move and completion of problem). “Pure planning” scores calculated by subtracting simple movement time from “initial thinking” (“motor initiation”) and “subsequent thinking” (“motor execution”) time. Spatial Span – Test of visual working
memory. Subjects asked to reproduce sequence of events via touch-screen, with test terminated if subject unable to correctly reproduce all sequences at one level, with 3 presentations given for each level. Spatial span scored for highest possible span, number of sequence errors made and number of usage errors made (pressing a box not illuminated during presentation). TOL and Spatial Span tasks counterbalanced to prevent order effects.

**Impulsivity, Behavioral Measure** – Impulsivity measured via another CANTAB test, the Matching Familiar Figures Test (MFF20). Sample and 6 potential matches presented simultaneously, with only one correct response (identical match), and sample must be matched with target. If incorrect, asked to try again. Subjects scored on time to first response, the first alternative indicated and number of errors before correct response. Scores used in analysis were: mean latency to first response, total number of errors, and “I score,” calculated as Z score of Total Errors – Z score of Mean Latency Before First Response.

**Analyses:** All measures (mood, personality, cognitive function, impulsivity) analyzed via separate multiple analyses of variance (MANOVAs) with drug use (ecstasy versus polydrug versus no-drug) serving as between-subjects factor and each score serving as a dependent variable. Post-hoc comparisons made via Duncan’s multiple range test.

**Results - Significant Differences:**

**Personality** – Both ecstasy users and polydrug users were more venturous (risk-taking, novelty-seeking) than no-drug subjects (ecstasy users = polydrug users > no-drugs),

**Impulsivity, Behavioral** – There were differences in number of errors and in “I score” (impulsivity) due to drug use, with ecstasy users < polydrug users = no drug subjects.

**Results - No Differences Found:**

**Mood** – No differences on the author-devised mood measure, with all 3 groups (ecstasy users, polydrug users, no-drugs) making similar responses. There were no differences in STAI (anxiety) scores due to drug use; STAI scores for ecstasy users, polydrug users and no-drug subjects did not differ. There were no differences in STAXI (anger / hostility) scores due to drug use (ecstasy users, polydrug users and no-drug subjects had similar scores).

**Personality** – As noted above, 3 groups did not differ in STAI (anxiety) or STAXI (anger / hostility) scores. There were no differences in “impulsiveness” or “empathy” scores of the IVE, with ecstasy users, polydrug users and no-drug subjects had similar scores.

**Cognitive Function (Executive Function)** – There were no differences in total spatial span, number of sequence errors or number of usage errors between all 3 groups (ecstasy users, polydrug users, no drugs). No difference in scores of “number of excess moves,” “initial thinking time,” “proportion of perfect solutions,” or “thinking time per move,” so that all 3 groups (ecstasy users, polydrug users and no drug subjects) performed similarly on TOL task.

**Impulsivity, Behavioral** - Ecstasy users, polydrug users and no-drug subjects did not differ in latencies to first response on MFF20.

**Overall Effects:** Ecstasy users, polydrug users who had never taken ecstasy and a set of controls without any history of drug use scored similarly on measures of mood and personality and on two measures associated with frontal lobe function. Specifically, they reported similar current mood states on a self-report questionnaire, and members of all 3 groups had similar levels of trait and state anxiety. None of the groups differed in degree of state or trait anger or hostility, and all three groups reported similar levels of impulsivity and empathy on a self-report measure. As might be expected, given their drug history, both polydrug users and ecstasy users scored similarly on a measure of venturousness. All three groups performed similarly on the “spatial span” and “Tower of London” tasks featured in the CANTAB, a test battery designed to measure frontal lobe function (apparently including attention, memory and executive function). However, when compared on the “Matching Familiar Figures” test, considered a behavioral measure of impulsivity, ecstasy users committed more errors than polydrug user or no-drug controls, and they had higher “impulsivity” scores on the MFF20.

**Comments:** Study 1 in this paper is as surprising for what it failed to find as it is for what it did find. While other studies have found altered mood or cognitive function in ecstasy users, the ecstasy users in this study only differed in impulsivity, and only when it was assessed via behavioral measure. The findings in this study suggest that behavioral measures may not be measuring the same construct tapped...
by self-report measures. However, that does not mean that the behavioral measure is necessarily “better” than the self-report measure, as a task involving matching to sample could also serve as an assessment of visual search strategy or even of visual non-spatial memory. Differences in age and education were minimal in this study (in fact, all participants were either university students or graduates), reducing the potential influence of differences in educational level. Perhaps the lack of many differences between the 3 groups indicates that differences found in other studies may have arisen from other factors, such as differences in age, education or drug use patterns. A few individuals reported using ecstasy within a week of the study, so that the difference in impulsivity could potentially be due to residual drug effects.

Morgan (1998). Recreational user of “Ecstasy” (MDMA) is associated with elevated impulsivity (Study 2).


Purpose: Neuropsychological, including mood, personality and cognitive function: To determine whether preliminary findings concerning the effects of ecstasy use on various domains (including increased impulsivity) could be replicated in a second study using the same study design but with a larger sample.

Design: Non-experimental (retrospective) 3-group between subjects (across-groups) design, with drug ecstasy users compared with 2 groups of matched controls; polydrug users with no history of ecstasy use (polydrug user controls) and people with no history of illicit drug use (no-drug users), with drug use as a between subjects variable. All groups completed self-report measures of impulsivity and health complaints, and all groups underwent behavioral assessments of impulsivity.

Subjects: 25 ecstasy users, 20 polydrug (no ecstasy) users and 19 no-drug (drug-free) users residing in the Swansea (Wales) area, with members of all 3 groups recruited via posters, advertisements and word of mouth. Matching – On gender, age, education, height, weight, and estimated IQ. Ecstasy users and polydrug users approximately matched on use of other drugs, excluding ecstasy. Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 20 separate occasions. Polydrug Users – No past or current use of ecstasy, but similar drug use histories to those reported by ecstasy users. No-drug Users – No past or current use of ecstasy and little or no past or current use of other psychoactive drugs, but similar on other matched variables to ecstasy users and polydrug users. All Groups – In good health, including absence of current or past major medical or psychiatric illness (verification unspecified, either through examination or through self-report). Absence of asthma, dyslexia and migraine, and no alcohol or opiate dependence, and not pregnant. Attending university or being a university graduate, making no more than 25 errors on the NART test. Abstinence from any psychoactive drug except for nicotine on the study day, with compliance verified by self-report on study day.

Drug Use Parameters – Ecstasy Users – On average, ecstasy users reported that they had taken an average of 49.6 ± 33.2 tablets over a lifetime (20-160), and that the average dose per occasion was 1.47 ± .78 tablets (range not provided). Ecstasy users reported that on average, they took ecstasy 4.36 ± 1.15 times a month (range not provided) and that they had used ecstasy for an average of 49.4 ± 15.2 months (range not provided). The average period between the last use of ecstasy and the study day was 65.1 ± 85.7 days (range not provided). The average maximum amount of ecstasy used on 1 occasion, in tablets, 3.78 ± 2.17. Other drugs used by ecstasy users, reported as average amount per wk / month/ year, and duration of use, in years: Alcohol, 34.94 units per wk, 7.9 years, cigarettes, 65.8 per wk, 6.07 years, cannabis, 13.74 joints per week, 6.14 years, amphetamines, 1.97 grams per month, 4.46, psilocybe mushrooms, 204 per year, no duration information, LSD, 2.63 trips per year, 4.23 years, inhalants, 2.5 a month, no duration information, cocaine, 2.6 grams a year, no duration information. 8 subjects reported some use of benzodiazepines, 3 reported some use of barbiturates and 2 reported taking ketamine with ecstasy.

Polydrug Users – Average drug use per week / month/ year and duration of use per year: Alcohol, 43.25 units per wk, 8.67 years, cigarettes, 73.71 per wk, 6.17 years, cannabis, 9.31 joints per week, 5.17 years,
amphetamines, 1.2 grams per month, 2.65, psilocybe mushrooms, 124 per year, no duration information provided, LSD, 2.95 trips per year, 2.12 years, inhalants, 1.13 “hits” per month, no duration information, cocaine, .3 grams a year, no duration information.

Group Demographics and Matched Variables – Ecstasy users, polydrug users and no-drugs groups matched on gender, age, height, weight, and estimated IQ (via NART score). Ecstasy users and polydrug users matched on use of other drugs (except ecstasy). Gender, as approximate M / F ratio – Ecstasy users, 13 / 12, polydrug users, 8 / 12, no-drug controls, 8 / 11 (see note for Study 1 on gender coding scheme: here, ecstasy users = 1.48, polydrug users = 1.70, no-drug = 1.63). Age. Ecstasy users, average age = 22.28 ± 2.48, polydrug users, average age = 23 ± 4.71, no-drugs, average age = 21.74 ± 2.94. Height. Weight – Height in cm, weight in kg: Ecstasy users, 173.3 ± 8.88 cm, 65.1 ± 9.9 kg, polydrug users, 170.3 ± 8.42 cm, 62.2 ± 9.3 kg, no-drugs controls, 172.3 ± 7.91 cm, 67.4 ± 10.8 kg. Education Level – Average number of years of education, in approximate years: Ecstasy users, 15.5 years, polydrug users, 15.5 years, no-drug controls, 14.5 years. (See note on “Study 1” for education level coding: ecstasy users = 2.8 ± .5, polydrug users = 2.95 ± .22, no-drugs = 2.68 ± .58). Estimated IQ, as derived from NART score: Ecstasy users = 113.1 ± 3.13, polydrug users = 116.1 ± 5.06, no drug controls = 115.1 ± 5.15. Ecstasy users have lower NART scores (hence lower estimated IQ) than members of the other 2 groups.

Measures: Mood / Health Complaints – Measured via GHQ, a measure of current psychological health, containing 12 mood and health-related items. Personality Traits. – Measured via IVE, a self-report measure with scales for empathy, impulsivity and venturesomeness. Cognitive Function – Measured via Tower of London, described in “Study 1” (Solve puzzle in minimum of moves, thinking time, errors and planning measured). TOL administered on twice, with the MFF20 placed between the 2 administrations, to see whether groups could be differentiated after subjects had grown familiar with task. Test of memory (Rivermead Behavioral Memory Test Battery) also employed, but method and results not described in this paper). Impulsivity, Behavioral – Measured via Matching Familiar Figures (MFF20) described above (Subject matches stimulus to 1 among 6 targets, with latency to first response, number of errors and “I score” (impulsivity score) calculated for each subject.

Analyses: Same procedure described for Study 1. Data analyzed via MANOVA, with drug use as between-groups variable, and with post-hoc comparisons made with Duncan’s multiple range test. Relationships between variables analyzed via Pearson correlation coefficient.

Results: Significant Differences: Mood / Mental Health – Ecstasy users and polydrug users scored lower on the GHQ than did no-drug subjects, but ecstasy users did not have significantly lower GHQ scores than no drug subjects. (Ecstasy users = polydrug users < no-drug controls). However, ecstasy user scores were lower than polydrug user scores. Personality - Ecstasy users and polydrug users scored higher on measures of trait impulsivity and venturousness than did non-users, but ecstasy users did not have significantly higher impulsiveness or venturesomeness scores than polydrug users (ecstasy users = polydrug users > no-drugs).

Results: No Differences Found: Personality – There were no between-group differences on empathy scores, with ecstasy users, polydrug users and no drug subjects scoring similarly. Cognitive Function / Executive Function – No drug controls had a longer “initial thinking time” on the TOL than did ecstasy users or polydrug users, but only on the first administration of the TOL, and the difference was a trend only and did not reach statistical significance. There were no differences in “number of excess moves,” “proportion of perfect solutions” or “thinking time per move” for either the first or the second administration of the TOL. Ecstasy users, polydrug users and no drug controls scored similarly on this measure. Impulsivity, Behavioral Measure – Ecstasy users made a greater number of errors than did polydrug users on the MFF20, though ecstasy users’ number of errors were not significantly different from the number of errors made by no-drug controls. Ecstasy users, polydrug users and no-drug controls did not differ on mean latency to first response or on “I score” on the MFF20.
Overall Effects: Ecstasy users and polydrug users had higher scores on trait impulsivity and venturousness than no-drug users. (In study 1, ecstasy users and polydrug users only had higher venturesomeness scores). Ecstasy users and polydrug users scored significantly lower on a measure of psychological health than no-drug users. All three groups performed equally well on the Tower of London (TOL) task, though there was a tendency for non-drug users to take more time thinking before the first move during the first, but not the second, administration of the TOL. Ecstasy users made more errors than polydrug users on the MFF20, a behavioral measure of impulsiveness, but the number of errors they made was not significantly different than the number of errors made by no-drug controls.

Comments: Some of the findings first seen in Study 1 are confirmed in this replication, while there are differences in other areas. Ecstasy users are again found to be more impulsive than the no-drug group, but Study 2 results are less certain, since ecstasy users did not differentiate themselves from polydrug users on the self-report measure of impulsivity and they did not have higher “I scores” than the other 2 groups. The lower scores on a measure of psychological health found in this study are more consonant with findings in other studies, yet they stand in contrast with the lack of difference in current mood state reported in Study 1. Even after employing larger samples and a greater number of ecstasy users who had not recently used the drug before the study, Study 2 finds differences between the self-report and behavioral measures of impulsiveness. However, in this study, it seems that there is slightly more similarity between the self-report and the behavioral measure of impulsiveness.

Morgan (1998). Recreational user of “Ecstasy” (MDMA) is associated with elevated impulsivity
(Analysis of pooled data from Studies 1 and 2).


Purpose: Neuropsychological, with focus on impulsivity: To use the larger sample provided by pooling data from Study 1 and Study 2 to investigate the effects of ecstasy on impulsivity and cognitive function and to clarify the relationship, if any, between self-report and behavioral measures of impulsivity.

Design: Analysis using data pooled from Study 1 and Study 2, using a 2 (Study) x 3 (Group) design. Both studies used retrospective 3-group designs with drug use (ecstasy use, polydrug use without ecstasy use or no drug use) as a between-subjects factor.

Subjects: 41 regular ecstasy users, 32 polydrug users with no past or current ecstasy use and 35 non-users residing in the Swansea area, with participants in all 3 groups recruited via local advertisements and word of mouth. Matching – See Study 1 and Study 2; subjects matched within study on gender, age, education level, height, weight, and estimated IQ. Ecstasy users and polydrug users approximately matched on use of other drugs, excluding ecstasy.

Criteria for Inclusion – See criteria used for including subjects in Study 1 and Study 2.

Drug Use Parameters – See information on drug use parameters within Study 1 and Study 2.

Group Demographics and Matched Variables – Ecstasy users, polydrug users and non-user controls matched on gender, age, education level, height, weight and estimated IQ, but matching took place within each study.

Measures: Personality Traits – Measured via IVE, as described above.

Impulsivity, Behavioral – Measured via MFF20, previously described (subject matches stimulus to 1 among 6 targets, with latency to first response, number of errors and “I score” calculated for each subject.

Cognitive Function / Executive Function – Measured via TOL, as previously described, (solve puzzle in minimum of moves, with thinking time, number of errors and planning measured). Only the first administration of the TOL in Study 2 used for pooled analysis.

Analyses: IVE scores, MFF20 scores and TOL scores analyzed via MANOVA, with a 2(study: study 1 versus study 2) x 3(Group: ecstasy users, polydrug users, no-drug users) between-factor design. Correlations performed with Pearson correlation coefficient.
Effects of Overall Ecstasy Consumption on Impulsivity - Using data pooled from both studies, ecstasy users divided on the basis of lifetime ecstasy consumption (in tablets) of 20-30 tablets (n = 15), 30-60 tablets (n = 10) and 60-160 tablets (n = 16). IVE impulsivity scores and MFF20 performance analyzed via 1-way ANOVA with lifetime ecstasy consumption as between-group variable.

Results – Significant Differences: Study Effects – The polydrug users and non-drug users of Study 2 made more errors on the MFF20 than did polydrug users and non-drug users in Study 1. Personality Traits – Ecstasy users had higher impulsivity scores than polydrug users or no-drug controls (ecstasy users > polydrug users, non-users). Ecstasy users and polydrug users had higher scores on the Venturesomeness scale than did non-users (ecstasy users, polydrug users > non-users). Impulsivity, Behavioral – Ecstasy users committed a greater number of errors and thus attained higher “I scores” on the MFF20 than either the polydrug users or no-drug controls (ecstasy users > polydrug users, non-users).

Effects of Overall Ecstasy Consumption on Impulsivity – Subjects with overall consumption of 30-60 tablets of ecstasy had higher scores on trait impulsivity than those who had taken 30 tablets or less. Correlational Analyses – On the MFF20, “mean latency to first response” scores and total numbers of errors were negatively correlated (shorter latency associated with more errors).

Results – No Differences Found: Study Effects – Performance was similar for each of the 3 drug use groups across the 2 studies on the IVE, the TOL, and 2 scores on the MFF20 (Latency to 1st response and “I score”). This means that groups can be successfully combined across study (i.e. ecstasy users in study 1 with ecstasy users in study 2). Personality Traits – Non-users, polydrug users and ecstasy users all scored similarly on the Empathy scale of the IVE. Cognitive Function / Executive Function – Ecstasy users, polydrug users and no-drug controls all scored similarly on all of the TOL performance scores (number of excessive moves, thinking time, or planning time). Impulsivity – Members of the 3 groups (ecstasy users, polydrug users, no-drug controls) did not differ on latency to first response on the MFF20. Effects of Overall Ecstasy Consumption on Impulsivity – There were no differences on MFF20 performance between ecstasy users who had taken 20-30 tablets, those who had taken 30-60 tablets those who had taken over 60 tablets. Correlational Analyses – While “initial think time” in TOL was positively correlated with “mean latency to first response” in MFF20 before Bonferroni corrections, the two scores were no longer significantly correlated after Bonferroni method corrections used. There were no other significant correlations between IVE scores, TOL scores or MFF20 scores. Trait impulsivity measured via IVE was not correlated with “I score” or number of errors committed on the MFF20.

Overall Effects: Subjects from Study 1 and Study 2 could be safely pooled, as there was only one difference in performance across studies, with polydrug users and no-drug controls in Study 2 making more errors than did members of these groups in Study 1. Ecstasy users and polydrug users in the combined analysis had higher scores on the IVE venturesomeness scale than did non-drug users. The pooled group of ecstasy users had higher impulsivity scores than did polydrug users or no-drug controls, and they also demonstrated more impulsivity when performing the MFF20 task. There still were no differences in performance on the TOL task, said to be a test of executive function. When ecstasy users were categorized on the basis of lifetime tablet consumption, lifetime ecstasy consumption was related to trait impulsivity, as measured via IVE, but not to behavioral impulsivity, as measured through MFF20. Comments: Aside from offering further confirmation of increased behavioral, and perhaps trait, impulsiveness in ecstasy users, analysis of the pooled data allows for an examination of the relationship between overall ecstasy use and degree of impulsiveness. Furthermore, the lack of a correlation between trait and behavioral measures of impulsivity suggests that the two measures are not tapping into the same construct. The combined analysis is notable for using relatively large sample sizes in a between-group comparison study. Employing a larger sample size and the addition of a group of polydrug user controls.
gives strength to the findings of increased impulsivity, but not decreased executive function, in regular ecstasy users.


Purpose: Cognitive function (Memory): To investigate whether a history of ecstasy use, and not polydrug use, is specifically associated with deficits in immediate and delayed recall by comparing test performance by ecstasy users, polydrug users who have not used ecstasy and people who have not used any illicit drugs on a measure of memory. Specific hypothesis tested: that ecstasy users would perform less well than polydrug user and non-user controls.

Design: Non-experimental (retrospective) 3-group between subjects (across groups) design wherein drug-free ecstasy users are compared with two groups of matched controls, one polydrug user group and one no-drugs user group. All subjects completed a test for immediate and delayed recall.

Subjects: 25 ecstasy users, 22 polydrug (no ecstasy) users and 19 no-drug (drug-free) users, with members of all 3 groups recruited via posters, advertisements and word of mouth. Matching – On gender, age, education level, height, weight, and estimated IQ. Ecstasy users and polydrug users approximately matched on use of other drugs, excluding ecstasy.

Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 20 separate occasions. Polydrug Users – No past or current use of ecstasy, but with drug use histories similar to those reported by ecstasy users. No-drug Controls – No prior history of ecstasy use, little or no past or current use of other psychoactive drugs, but similar on other matched variables to ecstasy users and polydrug users. All Groups – In good health, including absence of current or past major medical or psychiatric illness (verification unspecified, either through examination or through self-report), and not pregnant. Absence of asthma, dyslexia and migraine, and no alcohol or opiate dependence. Attending a university student or being a university graduate, Making no more than 25 errors on the NART test. Abstinence from any psychoactive drug except for nicotine on the study day, with compliance verified by self-report on study day.

Drug Use Parameters – Ecstasy Users – On average, ecstasy users reported that they had taken an average of 49.6±33.2 tablets over the lifetime (20-160), and that the average dose per occasion was 1.47±.78 tablets (range not provided). Ecstasy users reported that on average, they took ecstasy 4.36±1.15 times a month (range not provided) and that they had used ecstasy for an average of 49.4±15.2 months (range not provided). The average period between the last use of ecstasy and the study day was 65.1±85.7 days (range not provided). The average maximum amount of ecstasy used on 1 occasion, in tablets, 3.78±2.17. Other drugs used by ecstasy users, reported as average amount per wk / per year, and duration of use, in years: Alcohol, 34.94 units per wk, 7.9 years, cigarettes, 65.8 per wk, 6.07 years, cannabis, 13.74 joints per week, 6.14 years, amphetamines, 23.68 grams per year, 4.32, psilocybe mushrooms, 203.6 per year, 2.44 years, LSD, 2.63 trips per year, 3.19 years, inhalants, 30.03 “hits,” per year, 2.02 years, cocaine, 2.6 grams a year, 1.36 years. Polydrug Users – Average drug use per week / year and duration of use per year: Alcohol, 42.95 units per wk, 8.5 years, cigarettes, 67.3 per wk, 6.15 years, cannabis, 9.28 joints per week, 5.52 years, amphetamines, 12.09 grams per year, 2.73, psilocybe mushrooms, 112.3 per year, 1.25 years, LSD, 2.68 trips per year, 1.43 years, inhalants, 176 “hits,” per year, 1.18 years, cocaine, .27 grams a year, .27 years. No Drug Controls – Average alcohol use, per wk = 14.97 units, duration of use in years, 5.79 and cigarettes, 36.75 per week, 3.18 years (1 non-user admitted 1 use of cannabis at least 1 year before study). Duration of LSD use longer in ecstasy users than in polydrug users, and some ecstasy users, but no polydrug users, had reported using benzodiazepines and barbiturates.

Group Demographics and Matched Variables – Ecstasy users, polydrug users and no-drug controls matched on gender, age, height, weight, education and NART score. Ecstasy users and polydrug users...
matched for drug use, excepting ecstasy use. Gender, as approximate M / F ratio – Ecstasy users, 13 / 12: polydrug users, 10 / 12: no-drug subjects, 9 / 10. (Gender presented in text as “average” with 1 = M, 2 = F, but ratio for ecstasy users known from previous paper; Ecstasy users = 1.48, polydrug users = 1.68, non-users = 1.58). Age. Ecstasy users, average age = 22.28 ± 2.51 years: polydrug users, average = 22.86 ± 4.52 years: no-drug, average = 21.74 ± 2.94 years. Height, Weight, with height in cm and weight in kg – Ecstasy users, 172.3 ± 8.88 cm, 65.1 ± 9.9 kg: polydrug users, 170.3 ± 8.48 cm, 64.4 ± 14.2 kg: No-drug controls, 172.3 ± 7.91 cm, 67.4 ± 10.8 kg. Education Level – Ecstasy users, approximately 15.5 years (2.8 ± .5): polydrug users, approximately 15.5 years, (2.95 ± .21): no-drug, approximately 14.5 years (2.68 ± .58). Education level 1 = Basic high school exam, 2 = Advanced high school exam, 3 = University degree. NART Score – Average score for ecstasy users = 35.9 ± 2.52, average score for polydrug users, 39.1 ± 4.73, average score for no-drug user, 37.5 ± 4.15. When compared with polydrug users and no-drug users, ecstasy users were found to have significantly lower NART scores than the other 2 groups, indicating that they were not matched on this variable. Other Variables – 16 / 25 ecstasy users reported usually taking ecstasy when in a large group, 8 / 25 reported usually using ecstasy when in small groups and 1 / 25 reported usually using ecstasy when alone. 21 / 25 ecstasy users reported that there were long-term (sub-acute) side effects to ecstasy use, while 4 / 25 reported no long-term side effects. When asked whether they viewed ecstasy as safe, 5 / 25 responded “yes,” 8 / 25 responded “no” and 12 / 25 responded “not sure.”

Measures: Immediate and delayed recall measured via Rivermead Behavioural Memory Test (RBMT), with subjects writing down as much as they could recall from audiotaped story immediately after presentation and again 40-50 minutes after presentation, with subjects performing unrelated tasks between the measures. Recall scored by number of ideas correctly recalled.

Analyses: Recall scores analyzed via between subjects / repeated measures ANOVA with drug use (ecstasy use, polydrug use or no drug use) as a between-subjects variable and with immediate and delayed recall as within-subjects variables. Possible relationships between drug use parameters and recall scores assessed via Pearson’s correlation coefficient. Recall scores also analyzed via ANCOVA, with any items that appeared to be related to performance serving as covariates.

Post-hoc Analysis of Ecstasy Users by Time since Last Use – Ecstasy users divided into 3 groups with reference to period of time since last use, with subjects divided into those who had last used ecstasy within the month (13), those who last used ecstasy between 1 and 6 months before the study (9) and those who had last used ecstasy 6 months or earlier before the study (3). A between subjects / repeated measures ANOVA was performed, with time since last use as a between group variable and scores on immediate and delayed recall as within-subjects variables.

Results – Significant Differences: Ecstasy users had lower Immediate Recall scores than did polydrug users or no-drug controls (ecstasy users < polydrug users = no-drugs). Ecstasy users also had lower Delayed Recall scores than members of the other 2 groups (ecstasy users < polydrug users = no drug users). Cannabis consumption per week was negatively associated with performance on immediate recall for ecstasy users only, with greater cannabis use associated with decrements in performance. Duration of LSD use was positively associated with estimated lifetime consumption of ecstasy (total lifetime uses or cumulative dose). Duration of LSD use was also negatively correlated with performance on delayed recall for ecstasy users, but not for polydrug users, with longer duration of LSD use indicating decrements in delayed recall. While duration of LSD use proved to be a significant covariate, differences between ecstasy users and polydrug users on immediate and delayed recall scores remained when duration of LSD use entered into analysis. Performance on immediate recall, but not delayed recall, was negatively correlated with a composite of average dose per session and duration of use, with greater amount per month x duration associated with lower performance on the test of immediate recall.

Post-hoc Analysis of Ecstasy Users by Time Since Last Use – Those who had taken ecstasy at least 6 months before study performed better on both immediate and delayed recall than subjects who had last taken ecstasy within the month or those who had taken ecstasy 1 – 6 months ago.
Purpose: Brain imaging (PET): To investigate whether long-term ecstasy use has any relationship with alteration in brain glucose metabolic rate, considered a marker of global and regional brain activity.

Results – No Differences Found: NART score did not correlate with either immediate recall or delayed recall. Cannabis consumption per week did not correlate with performance on immediate or delayed recall for the polydrug users; the relationship between cannabis use and performance on delayed recall only existed for ecstasy users. Duration of LSD use was unrelated to performance on immediate or delayed recall for polydrug users. Duration or consumption of all other drugs (amphetamines, psilocybe mushrooms, alcohol, consumption of LSD per year, inhalants, cocaine) were all uncorrelated with performance on immediate or delay recall measures. Use of benzodiazepines and barbiturates (restricted to ecstasy users) was uncorrelated with immediate or delayed recall. Total lifetime consumption of ecstasy was not correlated with performance on measure of immediate or delayed recall. There were negative associations between average ecstasy dose per occasion and performance on the immediate recall measure, and between duration of ecstasy use (in years) and performance on immediate and delayed recall, but neither of these associations reached statistical significance. Performance on delayed recall was unrelated to the composite variable of average dose per session x duration of use.

Overall Effects: A group of ecstasy users matched for gender, age, education and (to some degree) use of other drugs did less well on measures of immediate and delayed recall when compared with polydrug users who had not used ecstasy and people who had never used any illicit drugs. Amount of cannabis consumed per week was associated with reduced performance on immediate recall, but only for ecstasy users, and not for polydrug users. However, amount of cannabis used per week was not associated with reduced or increased performance on delayed recall for either ecstasy users or polydrug users. Duration of LSD use, which is moderately related to lifetime ecstasy use, was negatively associated with performance on delayed, but not immediate, recall. However, there was no relationship between duration of LSD use and performance on either measure of recall for polydrug users. The author found some tentative evidence for a relationship between the combination of average dose per session and duration of use and effects on immediate, but not delayed, recall in ecstasy users. Ecstasy users who had abstained from ecstasy for at least 6 months before the study day did best on both measures of immediate and delayed recall when compared with those who had last used ecstasy within six months of the study day.

Comments: This is one of several (and possibly the first) paper that employed 2 comparison groups, polydrug users and non-user controls, when examining the effects of ecstasy use on performance on a test of memory. By restricting subjects to university students or graduates and by using a cut-off for NART score, the author also attempted to select subjects with the same level of education and general intelligence. This paper supports the existence of a relationship between ecstasy use and decrements in performance on tasks involving memory that is independent of polydrug use. The findings might even be interpreted as supporting an interaction between ecstasy and other drugs on memory, given the susceptibility of ecstasy using subjects, but not polydrug using subjects, to associations between weekly cannabis use or duration of LSD use and reductions in recall. The effects of ecstasy use on memory may be time-dependent, with people who had abstained from ecstasy for over 6 months performing better on tests of memory than those who had taken ecstasy within the month or between 1 and 6 months before the study day. However, since there were only 3 such users, compared with larger numbers of people taking ecstasy closer to the time of study, conclusions based on this analysis alone should be viewed with caution. Nearly all of the subjects participating in this study also participated in Study 2 of Morgan, 1998.


Purpose: Brain imaging (PET): To investigate whether long-term ecstasy use has any relationship with alteration in brain glucose metabolic rate, considered a marker of global and regional brain activity.
Overall ecstasy consumption, defined as number of tablets taken in a lifetime, did not predict the extent of the changes in brain metabolism, and neither did the time since last use of ecstasy.

**Design**: Non-experimental (retrospective) 2-group between subjects (across groups) design, with ecstasy users compared with matched non-user controls, with drug use (ecstasy use versus non-use) serving as a between-subjects factor and with all subjects receiving brain scans.

**Subjects**: 7 ecstasy users recruited via out-patient substance abuse unit and 7 non-user controls recruited from a sample of patients with tumors who routinely received whole-body PET scans, with both samples probably residing in or near Hamburg (Germany). Matching – On age and gender.

Criteria for Inclusion, Ecstasy Users – No specific criteria for inclusion referring to parameters of ecstasy use provided; all subjects used ecstasy more than once over their lifetimes, and all used ecstasy more consistently than other drugs. Non-users – No past or current use of ecstasy, and no history of alcohol or substance abuse. All Groups – No past or current major neurological or psychological illness, as assessed through psychiatric interview, BDI and symptom checklist, and abstinence from psychoactive drugs before or on the study day (drug-free period not specified), with compliance verified through urine drug screen performed at unspecified time before or on study day.

**Drug Use Parameters** – Ecstasy users reported an overall lifetime use of 12-840 tablets, producing an estimated range of occasions of 12-620 uses (assuming a use pattern of 1 – 2 tablets per occasion). Information on average dose per use and frequency of use not provided. Average duration of ecstasy use not provided, but range of use was reported at 1-39 months. The time period between last use of ecstasy and the study day was 60-480 days. An unspecified number of ecstasy users also reported using cannabis, amphetamines and cocaine in “varying doses,” but using these drugs less often (or in lesser amounts) than ecstasy use. Non-user controls – Selected for absence of history of drug use.

**Group Demographics and Matched Variables** – Ecstasy users matched on gender and age. Gender, as M / F ratio – Ecstasy users, 5 / 2: non-users, 6 / 1. Age. Ecstasy users’ average age not provided, range was 19-29 years. Average age and precise age range for non-users not specified, but required age range to be 16-30. Other variables – No information on education level provided.

**Measures**: PET scans performed with 2[18F]-fluoro-2-deoxy-D-glucose (FDG), a radioactive tracer for glucose metabolism. Volumes of interest (VOIs) selected from both cortical and subcortical structures. VOIs were amygdala, caudate nucleus, cingulate, hippocampus, putamen, Brodmann 10 and Brodmann 11, with areas examined on both L and R hemispheres. Maximum FDG uptake measured in all individuals.

**Analyses**: Average maximum uptake was calculated for both groups (ecstasy users and non-users). Group means were compared via unpaired 2-tailed t-test. Possible correlations between PET data and two drug use parameters (number of tablets consumed over lifetime, time since last use) were examined via correlation, procedure not described but probably Pearson correlation coefficient.

**Results – Significant Differences**: Glucose metabolism in the L hippocampus was lower in ecstasy users than in non-users. Ecstasy users also had increased glucose metabolism when compared with non-users in Brodmann area 11, but only after increasing p. level.

**Results – No Differences Found**: While there was decreased glucose metabolism in the amygdala (L, R), cingulate (L, R) and R hippocampus in ecstasy users, compared with non-users, these differences did not differentiate all ecstasy users from all non-users. While ecstasy users experienced an increase in glucose metabolism when compared with controls in the caudate nucleus (L, R), the putamen (L, R) and Brodmann area 10, these differences did not reach statistical significance. Neither positive nor negative associations were found between overall ecstasy consumption and changes in brain glucose metabolism or between time since last use and changes in brain glucose metabolism.

**Overall Effects**: While differences between glucose metabolism in ecstasy users and non-user controls were found in every area studied (decreases in amygdala, cingulate and hippocampus, increases in Brodmann 10, Brodmann 11, caudate and putamen), the only differences that differentiated all ecstasy users from all non-user controls was decreased glucose metabolism in the left hippocampus and perhaps increased glucose metabolism in Brodmann area 11. The consequences of these differences in terms of mood or cognitive function is unknown, although the hippocampus plays a role in learning and memory. Overall ecstasy consumption, defined as number of tablets taken in a lifetime, did not predict the extent of the changes in brain metabolism, and neither did the time since last use of ecstasy.
**Comments:** To date, this is the only study employing PET scans with FDG rather than a serotonin-specific radioligand. However, the results may be somewhat comparable to SPECT scans that measure cerebral blood flow or volume. The authors did not examine what relationship, if any, these changes in regional cerebral glucose metabolism had on mood or cognitive function, though they did select for individuals with no psychiatric illness. The changes the authors found were persistent enough to remain at least 2 months after the last use of ecstasy. However, the sample size used in this study is very small, and controls were not matched with ecstasy users on the basis of drug use. Furthermore, members of both groups (ecstasy users and non-users) were selected from specific and potentially non-representative groups; ecstasy users were all enrolled in an outpatient substance abuse treatment program and non-users were all people with tumors. Caution should be used when generalizing to broader populations.

**Parrott & Lasky (1998).** Ecstasy (MDMA) effects on mood and cognition; Before, during and after a Saturday night dance.


**Purpose:** Mood and cognitive function acutely over time: To investigate the acute and chronic effects of ecstasy on mood and cognition in humans by taking measures at 4 time points occurring before and after ecstasy self-administration in a night-club environment.

**Design:** Non-experimental (retrospective) 3-group mixed between-subjects / within-subjects design, comparing self-selected regular ecstasy users, novice ecstasy users and matched non-user controls, with drug use (regular ecstasy use, novice ecstasy use, non-use) as a between-group variable, and time as a within-subjects factor. Measures were taken at baseline, at a night-club (on-drug for ecstasy users) and at 2 and 7 days post-club, with all subjects completing measures of mood, memory and visual search. (See also “Retrospective Studies” for an account of Parrott & Lasky focusing more on the acute and sub-acute effects of ecstasy over time).

**Subjects:** 15 regular ecstasy users, 15 novice ecstasy users and 15 non-user controls residing in the London (England) area, recruited through snowball technique. **Matching** – On age, gender, use of other drugs, and sub-culture (night-club patrons).

- **Criteria for Inclusion, Regular ecstasy users** – Having used ecstasy 10 or more times in lifetime.
- **Novice ecstasy users** – Having used ecstasy 1-9 times in lifetime.
- **Non-Users** – No past or current ecstasy use.

**All Groups** – Regularly visiting a large nightclub in London area. Use of alcohol and other drugs permitted in all groups, but not required. On baseline test, abstinence from ecstasy for 1 week prior to testing and abstinence from all other drugs for 24 h before testing, with compliance verified through self-report only.

**Drug Use Parameters** – No information is provided on number of occasions or tablets used over a lifetime, frequency of use per month or duration of use. As noted in “Criteria for Inclusion,” novice ecstasy users reported using ecstasy on 1-9 occasions (no average provided) and regular ecstasy users reported using ecstasy on 10 or more occasions, no average or largest number of occasions for regular ecstasy users provided. Average dose per use for regular ecstasy users was 1.8 tablets: average dose per use in novice ecstasy users was 1.45 tablets. The day since last use before baseline is not reported: assessments were made acutely during / after ecstasy use, 2 days and 7 days after ecstasy use, with abstention from ecstasy and other drugs verified via self-report only. Information on use of other drugs not reported for overall use, but the text indicates that members all 3 groups had used cannabis, cocaine or amphetamines at least once in a lifetime. On assessment 2 (at club), subjects reported using the following drugs: cannabis, (2 regular ecstasy users, 1 novice ecstasy user and 3 non-user controls), cocaine (4 regular ecstasy users, 2 novice ecstasy users and 2 controls) and amphetamines (1 novice user), alcohol (6 regular ecstasy users, 5 novice ecstasy users, 10 non-user controls). Number of drinks reported in each group: Regular users, 3.7 drinks, novice users, 2.7 drinks, controls, 5 drinks,
Group Demographics and Matched Variables – Regular ecstasy users, novice ecstasy users and non-user controls were matched on age, gender and sub-culture (patron at specific London night club). Gender, as M / F ratio – Regular ecstasy users: 7 / 8: novice ecstasy users, 7 / 8: non-users, 5 / 10. Age. Average age for regular ecstasy user = 21.4, no range provided, average age for novice ecstasy user = 22.8, no range provided, average age for non-user = 21.3, no range provided. Overall age range for 3 groups combined = 19-30. Sub-Group – Regular ecstasy users, novice users and non-users all recruited from population of individuals who frequented a large night club in London. Other Variables – Use of cannabis and other psychostimulants (amphetamine, cocaine) reported by members of all 3 groups on Assessment 2 (“club” night), and members of all 3 groups had used other illicit drugs at least once in a lifetime, with cannabis use, amphetamine and cocaine use specifically reported. Non-user controls consumed more alcoholic drinks than regular or novice ecstasy users at assessment 2 (“club” assessment) and regular ecstasy users consumed more drinks than novice ecstasy users on assessment 2. No information provided about education level for any subjects in any of the 3 groups.

Measures: Mood – Author-generated visual analog scales (VAS) presented via palm-top computer, with scales containing 16 items addressing current mood, with VAS administered once at each session (baseline (1), at club (2), 2 days post-club (3) and 7 days post-club (4). On-drug measures for ecstasy users taken 2 to 4 h post-ingestion for 22 / 30 ecstasy users and 8-16 h post-ingestion in 8 / 30 ecstasy users.

Memory and Visual Search – Memory – Assessed via auditory word recall (listen to tape-recorded list, and after 30 sec, write down all words recalled from 20-word list in any order). 2 lists presented per session, with 8 different lists presented overall. Visual Search – (locate target embedded in array of distracters and touch with light pen as rapidly as possible). Test had “easy” and “difficult” form, with “easy” task using differently shaped distracters and difficult task using somewhat similarly shaped distracters. 4 increasingly large arrays presented, but only the smallest and largest arrays used for analysis. Both measures taken at baseline, at club (2), 2 days (3) and 7 days (4) post-club. On-drug measures for ecstasy users taken 2 to 4 h post-ingestion for 22 / 30 ecstasy users and 8-16 h post-ingestion in 8 / 30 ecstasy users.

Analyses: Mood – Each item on VAS analyzed separately via 2-way between subjects / within-subjects ANOVAs, with drug use (regular ecstasy use, novice ecstasy use and non-use) serving as between-group factor and session (Assessment 1, 2, 3 or 4) as a within-subjects factor. Within-session comparisons for each item on the visual analog scales made via 1-way ANOVA, with drug use serving as between-group factor. Post-hoc comparisons on within-session analysis made via Duncan’s test.

Memory and Visual Search – Memory and visual search tasks analyzed via 2-way between subjects / within subjects ANOVA, with drug use (regular ecstasy use, novice ecstasy use or non-use) serving as a between-group factor and session (Assessment 1, 2, 3 or 4) as a within-subjects variable. Within-session performance was compared across 3 groups (regular ecstasy user, novice ecstasy user and non-user) via 1-way ANOVA with drug use serving as a between-group factor, with post-hoc comparisons made via Duncan’s test.

Results – Significant Differences: Mood – At baseline, ecstasy users reported being more clear-headed than non-users (regular > novice > non-user) and novice ecstasy users reported being more sad than either non-users or regular ecstasy users. On assessment 2 (at club), both regular and novice ecstasy users reported feeling more abnormal, sober and steady than non-users. There was a trend for regular and novice ecstasy users to indicate they were less sad and depressed during Assessment 2 (at club). On Assessment 3 (2 days post-club), ecstasy users reported feeling more depressed, sad, unsociable, unpleasant, and abnormal; in most cases, regular ecstasy users and novice ecstasy users scored closer to each other than to controls (abnormal, sad, unsociable). Novice ecstasy users reported feeling more depressed, less good-tempered and more unpleasant than both regular ecstasy users and non-user controls. On Assessment 4 (7 days post-club), regular and novice ecstasy users reported feeling more drowsy than non-users (regular < novice < non-user). Overall, regular and novice ecstasy users reported feeling more sad than non-users. Members of all 3 groups felt more good tempered, sociable and less sad on Assessment 2 (at club) than at other times of assessment.
Memory and Visual Search – Members of all 3 groups recalled fewest words at club (Assessment 2) than during any other session (Baseline, Assessment 3 or Assessment 4). Regular and novice ecstasy users recalled fewer words than non-users across all 4 assessments (baseline, at club, 2 and 7 days post-club), but with regular ecstasy users performing worse than novice ecstasy users (regular users < novice users < non-users). Only on Assessment 2 (At club), ecstasy users took longer to perform the visual search task than non-users, with regular ecstasy users performing more poorly than novice ecstasy users.

Results – No Differences Found: Mood – At baseline, there were no significant differences between members of all 3 groups on 14/16 visual analog scale items. At assessment 2 (at club), there were no differences between members of all 3 groups on 13/16 scales. On assessment 3 (2 days post-club), there were no differences between all 3 groups on: calm, clear-headed, drowsy, energetic, ill, interested, quick-witted, sober, steady and well-coordinated. On Assessment 4 (7 days post-club), there were no differences between all 3 groups on 15/16 scales. There were no between-group differences in mood that extended across all 4 assessments.

Memory and Visual Search – Regular ecstasy users, novice ecstasy users and non-users performed at similar levels on the visual search days at baseline, at Assessment 3 (2 days post-club) and on Assessment 4 (7 days post-club).

Overall Effects: Ecstasy acutely reduced sadness and sub-acutely produced deterioration in mood 2 days after use, with mood returning to baseline 7 days after use. In several cases (feeling depressed, feeling less good tempered), scores of novice ecstasy users were more affected 2 days post-club than were those of regular ecstasy users. Ecstasy acutely reduced recall and visual search, with regular ecstasy users performing less well than novice users, and novice users performing less well than controls. Ecstasy users had lower performance scores on word recall than non-users in across-group comparisons at each assessment, with regular ecstasy users having the lowest recall scores and non-user controls the highest recall scores. Ecstasy acutely reduced attention (assessed in visual search), probably due to difficulty concentrating. Performance on the visual search task returned to baseline both at 2 days and 7 days post-drug.

Comments: While the overall design used in the study reported here was retrospective, with groups divided on the basis of drug-use rather than assigned to drug use condition, the authors attempt to use a prospective design to study the acute and sub-acute effects of ecstasy over time. The advantage of using this design in comparing users with non-users is that there is some chance of separating “residual drug effects” from more persistent ones. The authors also sought to compare people with a higher lifetime exposure to ecstasy with people who had a lower lifetime exposure. It is particularly interesting that while novice ecstasy users reported greater negative mood on Assessment 3 than did regular ecstasy users, regular ecstasy users recalled fewer words than did novice users on all sessions. These findings suggest that changes in mood and cognitive function after ecstasy use do not necessarily reflect changes in the same neural substrates. The authors believe that their data supports the case for alterations in memory even after using ecstasy on no more than 9 occasions, but they also believe that single large doses and frequency of use are the most important contributors to ecstasy related cognitive deficits. The sample size in this study is small, so some caution should be used in generalizing to the population at large. Regression analyses using drug use parameters may also be more informative means for learning about the effects of these parameters on cognitive function or other variables, particularly in a study where subjects were not formally assigned to a specific drug use condition.


Purpose: Cognitive function, general: To investigate whether MDMA use affects cognitive functions.
Design: Non-experimental (retrospective) 3-group between subjects design comparing regular ecstasy users, novice ecstasy users and matched non-user controls, with drug use serving as a between-subjects factor. All subjects completed a battery of tests assessing several cognitive functions.

Subjects: 10 regular ecstasy users, 10 novice ecstasy users and 10 non-user controls residing in the London (England) area, with members of all 3 groups recruited via snowball technique (either through direct acquaintance with researchers or via word of mouth through friends). Matching – On age and approximately matched on gender and education.

Criteria for Inclusion, Ecstasy Users – Having used ecstasy on 10 or more occasions over a lifetime. Novice ecstasy users – Having used ecstasy on 1-9 occasions over a lifetime. Non-users – No past or current use of ecstasy. All Groups – Abstention from ecstasy or other psychoactive drugs on the study day, with compliance verified via self-report only.

Drug Use Parameters – No information provided concerning average dose of ecstasy per use, frequency of use or duration of use (in months). As noted above, novice ecstasy users reported using ecstasy 1-9 times (no average provided) and regular ecstasy users reported using ecstasy 10 or more times (no average provided, and greatest number of occasions per lifetime unknown). Time elapsed since last use is not provided, though subjects reported being drug-free on study day.

Group Demographics and Matched Variables – Regular ecstasy users, novice ecstasy users and controls matched on the basis of age and approximately matched on the basis of gender. Gender, as M / F ratio – Regular ecstasy users, 8 / 2, novice ecstasy users, 5 / 5, non-users, 4 / 6. Age. No average ages provided for any group. Regular ecstasy users ages ranged from 18-25 year, novice ecstasy users age range, 20-25, and non-users age range was 21-30 years. There were more women non-users than regular ecstasy users. Other variables – While no information is formally provided on education level, author states that most subjects were university students or their friends; estimated education level in years across all 3 groups is approximately 14.5 years.

Measures: Cognitive function measured via sub-set of tasks selected from the Cognitive Drug Research (CDR) test battery, a computerized test battery consisting of speeded tasks. Simple Reaction Time – Press appropriate key as rapidly as possible after target word (“YES”) appeared on screen. Choice Reaction Time – Press “Yes” key as rapidly as possible on appearance of “Yes” on screen and press “No” key as rapidly as possible when “No” appears on screen, with “Choice Reaction Time” presented at 2 points in assessment. Immediate Word Recall – Write down as many words as can recall immediately after viewing a 15-word list presented on computer screen, with score = total number of words recalled. Number Vigilance Task – Press “Yes” key as rapidly as possible when target number matches stimulus, with potential targets presented in succession, with target detection and reaction time scored. Sternberg task – Indicate presence of number in previously presented list by pressing “Yes” key, with potential targets presented after stimulus (not simultaneously, as in Number Vigilance), and with reaction time scored. Delayed recall – Write down as many words as can still recall from original “Immediate recall” list, with score = total number of words recalled

Analyses: All tasks on the cognitive test battery were analyzed via separate 1-way ANOVAs, with drug use (regular ecstasy use versus novice ecstasy use and non-use) as a between-group subject, with post-hoc comparisons made via Duncan’s test.

Results – Significant Differences: Ecstasy users differed from non-users on performance on both the immediate and the delayed word recall task, with regular and novice ecstasy users recalling fewer words than non-users both on the immediate and the delayed recall task. Novice ecstasy users recalled significantly fewer words than non-users and regular ecstasy users recalled slightly (but not significantly) more words than regular ecstasy users.

Results – No Differences Found: There were no differences between regular ecstasy users, novice ecstasy users and non-users on the following tasks: simple reaction time, choice reaction time (at first or second time point), number vigilance task or Sternberg task response time. There were no differences between regular ecstasy users, novice ecstasy users and non-users on target detection in the number vigilance task.
Overall Effects: Regular ecstasy users, novice ecstasy users and non-users all performed equally well on tests of simple and complex reaction time, vigilance and visual search and immediate visual recall. However, after being presented with a list of words, regular and novice ecstasy users recalled fewer words immediately after list presentation and at a later point in time. The effect of drug use was equally present for both novice and regular ecstasy users, but there was a tendency for regular ecstasy users to recall fewer words than novice users.

Comments: This paper is one of several that seeks to compare cognitive performance both between ecstasy users and non-user controls and between “regular” and “novice” ecstasy users, with categories defined via self-reported number of occasions where ecstasy was used over a lifetime. It is surprising to find that “novice” ecstasy users show the same pattern of deficits in immediate and delayed verbal recall as do “regular” ecstasy users. Either the effects of ecstasy on memory are produced after a small number of exposures or some other drug use parameter not measured here produced these effects. Unfortunately, the authors do not present information on other drug use parameters found to correlate with deficits in cognitive function in other studies, such as duration of use, frequency of use, or time elapsed since last use. Additionally, it is unclear whether use of other psychoactive drugs was similar across all 3 groups or whether there were differences in use of other drugs, such as cannabis. While the groups were approximately matched for gender, there were more men in the regular ecstasy group than in the novice user or non-user group, and non-users tended to be older than either group of users.

Parrott et al. (2000). Psychobiological problems in heavy ‘Ecstasy’ (MDMA) polydrug users.

Parrott, A. C., Sisk, E., & Turner, J. J. D. (2000). Psychobiological problems in heavy ‘ecstasy’ (MDMA) polydrug users. Drug and Alcohol Dependence, 60, 105-110

Purpose: Psychiatric health (presence of symptoms): To investigate whether extent of ecstasy use affects presence of psychiatric symptoms in light ecstasy users, heavy ecstasy users and in non-user controls. Design: Non-experimental (retrospective) 3-group between subjects design comparing groups of matched light ecstasy users, heavy ecstasy users and non-user controls, with drug use (light use, heavy use or no use of ecstasy) as a between-subjects factor, and with all subjects completing measures of mood and psychiatric symptoms. Subjects: 12 heavy ecstasy users, 16 light ecstasy users and 22 non-users residing near Cork (Ireland), recruited via “snowball technique” (word of mouth and through direct acquaintance with researchers). Matching – On age and gender. Criteria for Inclusion, Heavy Ecstasy Users – Having used ecstasy on 20-1000 occasions. Light Ecstasy Users – Having used ecstasy on 1-20 occasions. Non-users – No past or current use of ecstasy, but use of other drugs permitted. All groups – Participation in “youth subculture” in small town near Cork, Ireland, and using no psychoactive drugs on study day, with compliance verified through self-report only. No other criteria given for inclusion, though it appears that members of all 3 groups are matched on use of drugs other than ecstasy. Drug Use Parameters – Heavy ecstasy users reported using ecstasy on an average of 371 occasions in a lifetime (30-1000), with no information on average dose per session. Light ecstasy users reported using ecstasy on an average of 6.8 occasions (1-20), no information on dose per use provided. No information provided on frequency or duration of ecstasy use or time since last use. Other Drugs – Percentage of individuals in each group who used each drug listed: alcohol, heavy users 92%, light users 100%, non-users 100%, tobacco, heavy users 92%, light users, 82%, non-user, 50%, cannabis, heavy users, 100%, light users, 87%, non-users, 82%, amphetamines, heavy users, 83%, light users, 69%, non-users, 36%, cocaine, 75%, light users, 56%, non-users, 14%, LSD, heavy users, 83%, light users, 69% non-users, 18%, magic mushrooms, heavy users, 75%, light users, 31%, non-users, 27%, barbiturates / benzo diazepines, heavy users, 33%, light users, 12%, non-users, 0%, opiates, heavy users, 25%, light users, 25%, non-users, 14%, steroids, 8%, light users, 0%, non-users, 5%, solvents, heavy users, 50%. 

Page 337 of 367
light users, 31%, non-users, 14%. There were differences in drug use pattern for LSD and cocaine, and for amphetamines and magic mushrooms, with heavy ecstasy users > light ecstasy users > non-users.

**Group Demographics and Matched Variables** – Heavy ecstasy users, light ecstasy users and non-users matched on age, gender and approximately matched on use of drugs other than ecstasy. **Gender**, as M / F ratio – Heavy ecstasy users, 7 / 4, 1 undeclared: light ecstasy users, 6 / 10: non-users, 11 / 10, 1 undeclared. **Age**. Average age of heavy ecstasy users = 20.8 ± 2.2 (range not provided), average age of light ecstasy users = 20.9 ± 1.6 (range not provided), average age for non-users = 23.2 ± 4.9 (range not provided.)

**Measures:** **Psychiatric Symptoms** – Measured via SCL-90, a self-report measure addressing symptoms related to major psychiatric illnesses.

**Daily Life Events** – Author-designed Uplifts, Hassles, Stresses & Cognitive Failures questionnaire, designed to measure frequency of occurrence of the life events listed over the last month.

**Personality** – Impulsiveness, venturesomeness and empathy assessed via IVE.

**Analyses:** **Psychiatric Symptoms** – Data analyzed by 1-way ANOVA, with drug use (heavy ecstasy use, light ecstasy use, non-use) as between-subjects factor. Post-hoc comparisons made with Tukey’s test.

**Daily Life Events** – Score on each scale analyzed via 1-way ANOVA with drug use (heavy ecstasy use, light ecstasy use, non-use) as between-subjects factor. Post-hoc comparisons made via Tukey’s test.

**Personality** – Each scale on the IVE analyzed via 1-way ANOVA with drug use (heavy ecstasy use, light ecstasy use, non-use) serving as between-subjects factor. Post-hoc comparisons made via Tukey’s test.

**Results – Significant Differences:** **Psychiatric Symptoms** – Heavy ecstasy users scored higher on specific SCL-90 scales than did non-users. These included somatisation, obsessionality, anxiety, hostility, phobic-anxiety, paranoid ideation, psychoticism, poor appetite and restless / disturbed sleep, with heavy ecstasy users > non-users. Light ecstasy users differed from non-user controls on 2 SCL-90 scales, paranoid ideation and psychoticism, with light ecstasy users > non-users.

**Daily Life Events** – None found. However, cognitive failure scores increased across groups (heavy ecstasy users > light users > non-users), but differences did not reach statistical significance.

**Personality** – Heavy ecstasy users scored higher on the Impulsivity scale on the IVE than did non-users, with heavy users > non-users.

**Results – No Differences Found:** **Psychiatric Symptoms** – No differences found between heavy users and non-users on only 2 SCL-90 scales (depression, interpersonal sensitivity). No differences found between light users and non-users on 8 of 10 SCL-90 scales, including depression, anxiety, somatisation, phobic-anxiety, obsessionality, interpersonal sensitivity, hostility, disturbed appetite / sleep. SCL-90 scores for light users intermediate between those of non-users and heavy users.

**Daily Life Events** – There were no differences between all 3 groups on the Uplifts, Hassles, Stresses & Cognitive Failures scale for all 4 scales. Heavy ecstasy users had higher scores on the cognitive failures scale than did light ecstasy users, and light ecstasy users scored higher on cognitive failures than non-users, but this difference in scores did not reach significance.

**Personality** – All 3 groups (heavy ecstasy user, light ecstasy user, non-user) did not differ on venturesomeness or empathy scale scores on IVE. Light ecstasy users did not differ from non-users on impulsivity scale, though scores were higher, and they also did not differ from non-users on empathy or venturesomeness scale scores.

**Overall Effects:** When compared on number of self-reported psychiatric symptoms, heavy ecstasy users reported a greater number of symptoms than did light ecstasy users and non-user controls. Self-reported symptoms covered a wide array of problems, including anxiety-related symptoms, hostility related symptoms, psychoticism and signs of disturbed appetite and sleep. Light ecstasy users reported symptoms at a level that was intermediate between heavy users and non-user controls, but this difference rarely reached statistical significance except in the case of symptoms of psychoticism and paranoid ideation, with both greater in light users than in non-user controls. Heavy ecstasy users scored higher on the IVE impulsivity scale when compared with non-users, but there were no differences in venturesomeness or empathy between the 3 groups. Heavy ecstasy users, light ecstasy users and non-users reported experiencing similar numbers of uplifts, hassles, stresses and cognitive failures in the past...
Other Variables – Controls were selected from a larger pool of subjects from a study conducted 7 years previous to the study with MDMA users and matched via age.

While members of the 3 groups did not differ in the number of daily life stressors they experienced, there was a trend for self-reported cognitive failures to increase with ecstasy use.

Comments: This paper reports one of several studies that seek to investigate differences arising from the extent of ecstasy use as well as differences arising from ecstasy use in general. This paper presents more evidence in support of an association between ecstasy use and higher impulsivity. This paper also found that heavy ecstasy users experienced a greater number of psychiatric symptoms, despite their failure to report a greater number of daily life stressors (stresses and hassles) than light ecstasy users or non-users. It is surprising that one self-report measure of psychiatric symptoms found differences across groups while another self-report measure of daily life events did not produce across-group differences, since people experiencing symptoms of depression, anxiety, or paranoid ideation would be expected to report more daily life stressors than people without these psychiatric symptoms. Unlike a similar study conducted by Schifano et al. (1998, 2000), ecstasy users in this study had not sought medical help for their substance use. Members of all 3 groups, including the non-users, were sampled from a population that is more representative of young ecstasy users than that of Schifano. Drug use was comparable in all 3 groups, yet ecstasy users, especially those classified as heavy users, did use more drugs than did non-users, and this was particularly true for use of stimulants and hallucinogens. Hence some caution might be used in generalizing study results to the population at large.


Purpose: Measure of metabolites in CSF: to examine monoamine metabolites in ecstasy users and non-user controls to discover whether regular ecstasy use alters the amount of brain monoamines.

Design: Non-experimental (retrospective) 2-group between-subjects (across groups) design comparing ecstasy users with matched non-user controls, with drug use (ecstasy use versus no ecstasy use) serving as between-subjects factor and with all subjects receiving lumbar puncture.

Subjects: 5 ecstasy users and 17 non-user controls. No information is provided on recruitment of ecstasy users; perhaps performed via word of mouth. Non-users recruited from a larger study previously conducted in the Palo Alto (California) area that already involved lumbar puncture. Matching – On age and perhaps gender (not enough information provided to be certain).

Criteria for Inclusion, Ecstasy Users – Having used ecstasy at least once in a lifetime. Non-users – No past or current use of ecstasy. All Groups – Abstinence from all psychoactive drugs for 6 weeks (ecstasy users) to 2 weeks (controls), with abstinence verified through self-report. No information provided concerning restrictions, if any, based on mental or physical health, though ecstasy users denied any long-term effects on their behavior or emotional state.

Drug Use Parameters – Ecstasy users reported taking ecstasy on 1 to 33 occasions over a lifetime, with average number of occasions approximately 22.5 (excluding subject reporting 1 use only) or 18.2 (including low-dose subject). Dose per use ranged from 1 tablet to approximately 1.6 tablets (converted from self-reported dosage by mg where 1 tablet estimated at 125 mg), no average value provided. No information is provided concerning frequency of use, but duration of use was approximately 18 months (no range provided). No information on number of days since last use; requested to be drug-free for 30-60 days before study day.

Group Demographics and Matched Variables – Ecstasy users and non-users matched on age, and perhaps matched on gender. Gender, as M / F variable. Ecstasy users, unknown. Possibly 5 / 0: non-users, 17 / 0.

Age: Ecstasy users average age not provided, (20 – 33 years), non-users average age = 26 ± 3 (20-33 years).

Other Variables – Controls were selected from a larger pool of subjects from study conducted 7 years previous to study with MDMA users and matched via age.
Measures: Concentrations of 5HIAA, HVA and MHPG in CSF. Subjects underwent lumbar puncture in the morning after an overnight fast. Metabolite levels assessed via combined gas chromatography and mass spectrometry.

Analyses: No formal analyses reported; nature of data suggests either an unpaired t-test or a non-parametric test comparing means across groups (ecstasy users and non-users). A correlation (undescribed) was performed between extent of ecstasy use (number of occasions used over a lifetime) and concentration of 5HIAA in CSF.

Results – Significant Differences: None found.

Results – No Differences Found: There were no differences between ecstasy users and non-user controls in CSF concentration of 5HIAA, HVA or MHPG. Extent of ecstasy use did not correlate with amount of 5HIAA found in CSF.

Overall Effects: When values for the serotonin metabolite 5HIAA, the dopamine metabolite HVA and the norepinephrine metabolite MHPG were measured in a sample of 5 ecstasy users and an age-matched sample of non-user controls, comparisons across user groups found values for all 3 metabolites to be similar in both groups. There was no association between extent of ecstasy use and level of 5HIAA in CSF.

Comments: This is the first paper that attempted to detect alteration or damage of the serotonergic system in ecstasy users by measuring the concentration of 5HIAA in cerebrospinal fluid. The technique is used much less frequently in later papers, probably because of its invasiveness and unpleasantness for participants. Later papers (e.g. McCann et al., 1994; McCann et al., 1999; Ricaurte et al., 1990) in contrast with this paper, did find differences between 5HIAA in regular ecstasy users and 5HIAA values in non-user controls. The samples in this study are matched for age only, and little information is provided about other variables, such as general health or complete drug use history. It is even possible that the samples were not matched on gender, as information is only provided on the gender of non-user controls, who were all male. Non-user controls outnumber ecstasy users by a factor of 3, and controls were drawn from a study not specifically designed for comparisons between controls and ecstasy users. Caution should be used in generalizing from this study to the population at large.

Price et al. (1989). Neuroendocrine and mood responses to intravenous L-tryptophan in 3,4-methylenedioxymethamphetamine (MDMA) users: Preliminary observations.


Purpose: Pharmacological challenge: To investigate whether ecstasy use has altered serotonergic function through measuring prolactin response to L-tryptophan challenge in ecstasy users and controls.

Design: Non-experimental (retrospective) 2-group design, with ecstasy users compared with matched non-user controls, with drug use (ecstasy use versus no ecstasy use) as a between subjects factor, and with all subjects receiving L-tryptophan challenge.

Subjects: 9 regular ecstasy users and 9 non-users, with non-users recruited via local advertisements in the New Haven (Connecticut) area, and ecstasy users recruited nationally, perhaps through self-referral or via snowball technique (information not provided). Matching – On gender, age.

Criteria for Inclusion, Ecstasy Users – Current or past history of ecstasy use, specific extent, duration or cumulative dose requirements unspecified. Non-users – No current or prior history of ecstasy use, absence of substance abuse. All Groups – Good health as established via physical examination, neurological examination and standard laboratory tests, absence of major medical or psychiatric illnesses, and abstinence from use of psychoactive drugs for at least 3 weeks prior to study day, with compliance verified through self-report only. (Some ecstasy users reported infrequent marijuana use during this period).
Drug Use Parameters – No information is provided on number of times (occasions) ecstasy had been used in a lifetime, cumulative exposure (originally listed in grams) indicates ecstasy users took an average of 130 ± 131 tablets over a lifetime (13.3 ± 13.4 g). Ecstasy users reported taking approximately 1.3 ± .4 tablets per occasion (.5 – 2 tablets per occasion). Some ecstasy users (exact number of users not provided) reported taking occasional doses of 5 tablets or more per occasion. Average frequency of use was reported at 1.9 ± 1.7 times per month (.3 – 5 times per month) and duration of use was reported to be 61.2 ± 27.6 months (24 – 84 months). Day since last use not reported; if ecstasy users complied with requested drug-free period, last day of use estimated at 21 days prior to study day. An unspecified number of ecstasy users also used cannabis, as indicated in “Criteria for Inclusion” section.

Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender and age. Gender, as M / F ratio – Ecstasy users, 7 / 2: non-users, 7 / 2. Age – Ecstasy users, average age = 34 ± 7 (22-47 years): non-users, average age, 33 ± 8 years (22-48 years).

Measures: Prolactin Response to L-Tryptophan – Subjects received an infusion of 7 g tryptophan in 500 mL saline, with duration of infusion at 3 h. Blood samples taken at 15 and .5 min before infusion and at 30, 40, 50, 60, 70, and 90 min after start of infusion. Plasma prolactin assessed through radioimmunoassay. Different assays used for detecting prolactin in ecstasy users and controls, with low intra-assay and inter-assay coefficients of variation.

Mood – Current mood state experienced during tryptophan infusion measured via 11 visual analog scales (VAS, with items for happy, sad, drowsy, nervous, calm, depressed, anxious, energetic, fearful, mellow, high). Measures administered at 15 and .5 minutes before infusion and at 30, 40, 50, 60, 70 and 90 minutes after start of infusion.

Analyses: Prolactin Response to L-Tryptophan – Baseline values averaged, and peak change scores calculated by subtracting baseline average from highest prolactin value after tryptophan infusion. AUCs calculated via trapezoidal rule. Because of non-normal data distribution, comparisons over time of sample (within subjects) analyzed via Wilcoxon signed-rank test (non-parametric test) and comparisons across group (between subjects) examined via Wilcoxon ranked sum (non-parametric test.) Correlations were performed using Spearman’s P.

Mood – Analyzed via repeated-measures ANOVA, with group (ecstasy user versus non-user) as a between subjects factor and time of administration (15, .5 min before infusion and 30, 40, 50, 60, 70 and 90 min after start of infusion) as a within-subjects factor. No information provided on test used for post-hoc comparisons. Correlations were performed using Spearman’s P.

Results – Significant Differences: Prolactin Response to Tryptophan Infusion – When compared with baseline values, peak prolactin levels after tryptophan infusion were significantly higher in non-user controls, but not in ecstasy users. Prolactin at baseline was positively correlated with peak prolactin values after tryptophan infusion, with higher baseline prolactin associated with higher peak prolactin after tryptophan infusion. Difference between AUC and baseline was significantly different for non-user controls, but not for ecstasy users.

Results – No Differences Found: Prolactin Response to Tryptophan Infusion – Ecstasy users and non-user controls did not differ on baseline prolactin concentration. Ecstasy users and non-user controls did not differ in peak plasma prolactin value after tryptophan infusion. When baseline plasma prolactin values were compared with peak prolactin values after tryptophan infusion, values were not significantly different in ecstasy users, though they were in non-user controls. There was no correlation between prolactin values at baseline and peak prolactin values after tryptophan infusion for ecstasy users. While the AUC values for ecstasy users’ prolactin was higher than at baseline, this difference did not reach statistical significance. There were no significant differences between ecstasy users and non-user controls for prolactin AUC after tryptophan infusion. Baseline plasma prolactin, peak plasma prolactin after tryptophan infusion and prolactin AUC were not correlated with duration of ecstasy use, frequency of ecstasy use or estimated cumulative dose for ecstasy users.
Mood – There were no differences between ecstasy users and non-users in the subjective effects of tryptophan infusion as reported via visual analog scales. Members of both groups reported feeling more drowsy, less energetic and less happy during / after the infusion than before the infusion.

Overall Effects: Increased prolactin was seen in ecstasy users and in non-user controls. The difference between baseline prolactin values in non-user controls was great enough to be statistically significant, but the difference between baseline values and peak prolactin after tryptophan in ecstasy users was not great enough to be considered statistically significant. Ecstasy users appear to have a blunted prolactin response to tryptophan infusion, yet a formal comparison of the two groups concluded that prolactin response to L-tryptophan did not significantly differ between the two groups. Both ecstasy users and controls reported decreased happiness and energy and increased drowsiness after tryptophan infusion, with no differences in the subjective effects of tryptophan as experienced by members of either group.

Comments: This paper attempts to detect altered serotonergic function in ecstasy users via L-tryptophan challenge. However, there are a number of difficulties with the study. According to the authors, samples comprised of men tend to have modest prolactin values after tryptophan challenge, making it difficult to spot between-group differences in an already low value (a “floor effect.”) Due to non-normative distribution, non-parametric tests were used instead of parametric tests. On the other hand, ecstasy user participants were selected on the basis of having low 5HIAA values in CSF. These individuals also appeared in Krystal et al, 1992. While most controls resided near the study location, some ecstasy users resided in different locations and had traveled to New Haven to participate in the study. Furthermore, not enough information is provided about use of other psychoactive drugs, such as cannabis, amphetamines or hallucinogens, in either group. Data concerning prolactin response after ecstasy use continues to be inconclusive, though later studies (i.e. Gerra, 1999, Gerra et al, 2000) suggest that ecstasy users have a blunted prolactin response to serotonergic drugs.

Reneman et al. (2000). Memory disturbances in “Ecstasy” users are correlated with an altered brain serotonin transmission.


Purpose: Brain imaging (SPECT with ligand), cognitive function (memory): To see whether regular ecstasy use alters serotonergic function and performance on a test of memory, with density of 5HT2A receptors measured via SPECT scans using the radioligand, [123-I]-5-I-R91150.

Design: Non-experimental (retrospective) 2-group between subjects design comparing ecstasy users with matched non-user controls, with drug use (ecstasy use versus no ecstasy use) serving as a between-subjects factor and with all subjects undergoing SPECT scans and completing measures of memory.

Subjects: 5 regular ecstasy users and 9 non-user controls residing in the Amsterdam (Netherlands) area, with subjects in both groups recruited via local advertisements. Matching – On age, approximately matched for gender and education.

Criteria for Inclusion, Ecstasy Users – Having used at least 50 tablets over lifetime. Non-users – No past or current use of ecstasy, no history of substance use or abuse for any other illicit drug. All groups – Healthy, not pregnant, absence of past or current major medical or psychiatric illness, including conditions that preclude informed consent. Absence of claustrophobia and conditions where serotonin function is implicated. Abstinence from all psychoactive drugs for at least 2 weeks prior to study day, with compliance verified by urinary drug screen performed at unspecified time before or on study day. Drug Use Parameters – Average number of tablets consumed over a lifetime was 218 tablets (50-500), with no information on average dose per use. No information is provided concerning frequency or duration of ecstasy use. Average time since last use, in days, was approximately 138 days (4.6 months), (approximately 60-360 days).
Group Demographics and Matched Variables – Groups matched on age and approximately matched on gender and education. Gender, as M / F ratio – Ecstasy users, 4 / 1: non-users, 4 / 5. Age. Ecstasy users average age = 23.6 ± 5.3 years, non-users 22.8 ± 2.9 years. Education level, in years – Average education level in ecstasy users = 13 ± 6 years; average education level in non-users = 15 ± 5 years. There were more female non-users than there were female ecstasy users, and ecstasy users had attained fewer years of education than non-users.

Measures: SPECT – Scans performed with the 5HT2A receptor radioligand, [123-I]-5-I-R91150 co-registered with MRI scans. Frontal, parietal and occipital areas were selected as regions of interest (ROIs) and the cerebellum and temporal area selected as ROIs in another template. An investigator blind to subjects’ drug use histories performed ROI analysis, with the cerebellum used as a reference due to presumed lack of 5HT2A receptors. “Specific” binding for each ROI calculated as “mean” ROI binding / cerebellar binding = 5HT2A binding ratio.

Memory – Assessed via RAVLT, a test of verbal memory, with immediate recall measured via Logical Memory sub-test and delayed memory measured via Delayed Recall and Recognition sub-tests. RAVLT administered day before conducting SPECT imaging. (Personal communication to R. Doblin indicates memory also assessed via WMS-Recall and Rivermead Behavioral Memory Test (RBMT)).

Analyses: SPECT – Specific binding figures derived from the formula above were compared between ecstasy users and non-users via Mann-Whitney U test (non-parametric test), with p. set at .05.

Memory – Analysis not specifically described. Each RAVLT sub-test score was compared between ecstasy users and controls, apparently also with the Mann-Whitney U test. Other test scores (as with WMS-Recall and RBMT) probably treated to similar analyses.

Correlations between SPECT and Test Performance – Possible relationships between performance on RAVLT and [123-I]-5-I-R91150 binding (indicating 5HT2A receptor density) performed via Spearman’s R (ranked coefficient). Subsequent correlations also employed demographic variables (gender, age, education) and drug use parameters (extent of previous MDMA use).

Results – Significant Differences: SPECT – Specific [123-I]-5-I-R91150 binding in the occipital cortex was higher in ecstasy users than in non-users.

Memory – Ecstasy users had lower scores on RAVLT Recall than did non-users, indicating that ecstasy users recalled fewer words after a delay than did non-user controls.

Correlations between SPECT and Test Performance – Score on RAVLT-Recall sub-test were positively correlated with mean cortical 5HT2A binding (as indicated through [123-I]-5-I-R91150 binding), with higher Recall scores associated with greater mean cortical 5HT2A binding. Correlations also employing subjects’ age, gender or education did not modify the relationship between RAVLT-Recall score and mean cortical 5HT2A binding. Extent of past ecstasy use (unspecified, either total lifetime ecstasy consumption, duration of use or some combination of these drug use parameters) did not modify the relationship between RAVLT-Recall score and mean cortical 5HT2A binding. Hence the relationship between increased 5HT2A binding and memory scores is not strongly affected by age, gender, education or extent of ecstasy use.

Results – No Differences Found: SPECT – While specific [123-I]-5-I-R91150 binding was higher in ecstasy users across other ROIs, (frontal, temporal and parietal areas), these differences in binding did not reach statistical significance.

Memory – Ecstasy users and non-users did not differ on their performance on the Immediate Recall and Recognition sub-tests of the RAVLT. (Personal communication to R. Doblin indicates that there were also no differences between ecstasy users and non-users on test performance for the RBMT and the WMS, but this data is not presented in the paper).

Correlations between SPECT and Test Performance – Performance on RAVLT-Recall was unrelated to mean cortical 5HT2A binding (as indicated through [123-I]-5-I-R91150 binding) in non-user controls, despite there being a relationship between recall score and 5HT2A binding for ecstasy users.

Overall Effects: 5HT2A receptor binding, assessed via SPECT using a radioligand specific to the 5HT2A receptor, was greater in the occipital area for ecstasy users than for controls. Though ecstasy users and non-users performed similarly on measures of immediate recall and a test of visual and verbal memory,
ecstasy users also scored lower on a measure of delayed verbal recall. In ecstasy users, greater mean cortical 5HT2A binding was associated with higher performance on the measure of delayed recall, yet mean cortical 5HT2A binding was neither positively nor negatively correlated with performance on the test of recall in non-users. Gender, age, education and prior use of ecstasy were not correlated with performance on Recall and did not change the association between mean cortical 5HT2A binding and Recall score.

**Comments:** This paper appeared as a “rapid communication,” and the information here has been supplemented with further information sent as a personal communication to Rick Doblin. The relationship between mean cortical 5HT2A binding and RAVLT recall score is especially interesting because the alteration in 5HT2A binding is correlated with better performance rather than worse performance on a test of verbal memory. These findings could be used in support of a role for 5HT2A receptor density either as a pre-existing protective factor or as an adaptive or compensatory factor that reduces the effects of ecstasy use on delayed recall. However, the sample size in this study is small, and insufficient information is offered concerning use of other psychoactive drugs in either group. Hence it is possible that the findings arose out of differences in use of other drugs. Caution should be used in generalizing from this small sample to the population at large.

Reneman et al. (2000). MDMA (“Ecstasy”) and its association with cerebrovascular accidents; Preliminary findings.


**Purpose:** Brain imaging (SPECT with ligand): To investigate the effects of ecstasy on brain 5HT2A receptor density by performing SPECT scans with [123-I]-R91150 on two groups of ecstasy users ("current" and "ex" users) and on non-user controls.

**Design:** Non-experimental (retrospective) 3-group between subjects (across groups) design comparing current ecstasy users with former ecstasy users and matched non-user controls, with drug use (ecstasy use or no ecstasy use) and recency of drug use (current ecstasy use, past ecstasy use, no ecstasy use) serving as between subjects factors, and with all subjects undergoing SPECT and MRI scans.

**Subjects:** 10 recent regular ecstasy users, 5 former regular ecstasy users and 10 non-user controls residing in the Amsterdam (Netherlands) area recruited via advertisements in local newspapers. Matching – On age.

**Criteria for Inclusion, Current ecstasy users** – Having used at least 50 ecstasy tablets over a lifetime and last use of ecstasy between 1 week and 2 months prior to study day. **Former (“Ex”) Ecstasy Users** – Having used at least 50 ecstasy tablets over a lifetime and last use of ecstasy at least 2 months prior to study day. **Non-users** – No past or current use of psychoactive drugs, including ecstasy, though some reported using cannabis. **All Groups** – Healthy, not pregnant, absence of past or current major medical or psychiatric illness, including conditions that preclude informed consent. Absence of claustrophobia and conditions where serotonin (5HT) function is implicated. Abstention from all psychoactive drugs for at least 1 week prior to study day, with compliance verified by urinary drug screen performed at unspecified time before or on study day.

**Drug Use Parameters** – Current Ecstasy Users. Current ecstasy users took, on average, 139 ± 129 tablets over a lifetime (no range provided), with no information provided on average dose per use. Average frequency of use, assessed as use in last 3 months, was approximately .3 ± .26 tablets per month (1 ± .8 in 3 months), (range not provided) with no information on duration of use provided. Last use of ecstasy prior to study day, in days, 49 ± 35 days. **Former (Ex) Ecstasy Users.** Ex-ecstasy users reported taking, on average 218 ± 201 tablets over a lifetime (no range provided), with no information provided on average dose per use. Average frequency of use, assessed as use in last 3 months for ex-ecstasy users was
Overall Effects: Density of 5HT2A receptors was found to be lower in current ecstasy users, people who had last used ecstasy less than 2 months before the study day than in ex-ecstasy users, people who had last approximately .13 ± .2 tablets per month (.4 ± .6 tablets in last 3 months), (range not provided) with no information on duration of use provided. Last use of ecstasy prior to study day, in days, 126 ± 105 days. Other Drugs: For current users, average amount of alcohol drunk in last 3 months, in units = 27 ± 31 units, tobacco = 57 ± 45 cigarettes, cannabis = 20 ± 29 joints, cocaine, 6 ± 15 lines, LSD = 1 ± 1.7 times. For ex-users, average amount of alcohol drunk in last 3 months, in units (approximately) = 38 ± 33 units, tobacco = 54 ± 44 cigarettes, cannabis = 46 ± 39 joints, cocaine, .8 ± 2 lines, LSD = Either not reported or not used. Non-Users – Average amount used in last 3 months, alcohol, in units = 41 ± 38 in last 3 months, tobacco, in cigarettes = 17 ± 20 in last 3 months, cannabis, in joints = 3 ± 6 in last 3 months. Group Demographics and Matched Variables – All 3 groups matched on age. Age. Average age of current ecstasy users = 27 ± 5: average age of ex-eczasy users = 24 ± 5: Average age of non-users = 23 ± 3 (Non-users slightly younger than either group of ecstasy users). Other Variables – Gender, as M / F ratio – Current ecstasy users, 7 / 3: ex-eczasy users, 4 / 1: non-users, 4 / 6. Measures: SPECT-Radioligand Binding – Scans performed with the 5HT2A receptor radioligand, [123-I]R91150, co-registered with MRI scans. Frontal, parietal and occipital areas were selected as regions of interest (ROIs) and the cerebellum and temporal area selected as ROIs in another template. An investigator blind to subjects’ drug use histories performed ROI analysis, with the cerebellum used as a reference due to presumed lack of 5HT2A receptors. “Specific” binding for each ROI calculated as “mean” ROI binding / cerebellar binding = 5HT2A binding ratio. Regional Cerebral Blood Volume (CBV) – Performed on a sub-sample of 5 ecstasy users (4 men, 1 woman, average age = 25 ± 5, 3 (of 10) current users and 2 (of 5) former users and 6 controls (3 women, 3 men, average age = 22 ± 1. MRI scans made by 1.5 T scanner with gadolinium-based contrast material, with scans made 6 h before SPECT. rCBV maps derived on a voxel by voxel basis with dynamic imaging software, rCBV / white matter calculated for each ROI (L, R frontal and occipital cortices, white matter, putamen, globus pallidus), where mean CBV for region divided by unilateral mean white matter. High ratio = vasodilatation, low ratio = vasoconstriction. Analyses: SPECT-Radioligand Binding – Examined via 1-way between subjects (across groups) ANOVA, with comparisons made between current ecstasy users, ex-eczasy users and non-users, with p. value set at .05. Regional CBV – CBV across groups (current ecstasy users, ex-eczasy users and non-users) analyzed via unpaired student’s t test, with p. value set at .05. Relationship between Ligand Binding and rCBV – Mean radioligand binding was correlated with CBV values using Spearman’s rank correlation. Correlations or regressions (unspecified) also performed where gender, age and extent of ecstasy served as covariates. Results – Significant Differences: SPECT-Radioligand Binding – [123-I]R91150 binding in each of the 3 groups differed from ligand binding in 1 other group. Current ecstasy users had lower mean ligand binding values than ex-eczasy users. Ex-eczasy users had higher mean ligand binding values than did non-users, (ex-eczasy users = > non-users = > current ecstasy users.) Regional CBV – CBV was higher in ex-eczasy users than in current ecstasy users. Ex-eczasy users also had higher rCBV than non-users, but in certain (unspecified) brain areas only. Relationships between Ligand Binding and rCBV – 5HT2A receptor density (measured via ligand binding) was positively correlated with rCBV in the globus pallidus and occipital cortex in current ecstasy users, but not in non-users. Age, gender and extent of previous ecstasy use (presumably total number of tablets consumed over lifetime) did not modify the relationship between 5HT2A receptor density and rCBV in either the globus pallidus or the occipital cortex. Results – No Differences Found: No differences were found between CBV for current ecstasy users and controls in all brain regions studied (frontal, parietal and occipital regions). Relationships between Ligand Binding and rCBV – 5HT2A receptor density was uncorrelated with rCBV in any brain region studied in non-users. Overall Effects: Density of 5HT2A receptors was found to be lower in current ecstasy users, people who had last used ecstasy less than 2 months before the study day than in ex-eczasy users, people who had last
used ecstasy more than 2 months before the study day. However, people defined as “ex-ecstasy users” had greater density of 5HT2A receptors than did non-users. Thus the greatest difference in 5HT2A receptor density, as measured through [123-I]-R91150 binding, was between “current” and “former” ecstasy users. Regional CBV was found to be higher in ex-ecstasy users than regional CBV in non-users or current ecstasy users, though it should be noted that the sample of ex-ecstasy users who underwent rCBV recording was very small (2 individuals). In current ecstasy users, but not in non-user controls, 5HT2A receptor density is positively correlated with rCBV in the globus pallidus and the occipital cortex. Age, gender and number of ecstasy tablets taken over a lifetime did not moderate the relationship between 5HT2A receptor density and rCBV in the areas listed above.

**Comments**: This paper could be considered a companion to the previous Reneman paper. The “ex-ecstasy users” who participated in this study appear to be the ecstasy user group featured in the first Reneman imaging paper. It should be noted that in contrast to findings with individuals who have not used ecstasy in at least 3 months, those who have used ecstasy more recently (within 2 months) show a decrease in 5HT2A receptor binding density rather than an increase in 5HT2A density. Because the authors did not report memory findings in this paper, it is hard to draw conclusions about the relationship between 5HT2A receptor density and performance on measures of memory. Differences in CBV in ex-ecstasy users are used as the basis for hypotheses concerning associations between ecstasy use and cerebrovascular accidents, mentioned in the title of the paper. To date, there have been reports of cerebrovascular accidents acutely after ecstasy use, but no signs that chronic use of ecstasy increases risk of cerebrovascular accident. While matched for age, the samples were not matched for gender, and the sample of ex-ecstasy users is smaller than the other 2 samples (5 versus 10). Furthermore, conclusions drawn about regional cerebral blood volume are based on a sub-sample of 11 (3 current users, 2 ex-users and 6 non-users). Caution should be used in drawing conclusions about the general population from this study, particularly in the case of data on rCBV.

**Ricaurte et al. (1990). Aminergic metabolites in cerebrospinal fluid of humans previously exposed to MDMA: Preliminary observations.**


**Purpose**: Metabolites in CSF: To evaluate the neurotoxic potential of MDMA (ecstasy) in humans by comparing levels of 5HIAA in the cerebrospinal fluid of ecstasy users and non-using controls.

**Design**: Non-experimental (retrospective) 2-group between subjects (across groups) design with ecstasy users compared with matched non-user controls, with drug use (ecstasy use or no ecstasy use) as a between subjects variable. All subjects underwent lumbar puncture.

**Subjects**: 33 regular ecstasy users and 24 people with lower back pain who had not used ecstasy. No recruitment information provided for either group. However, other studies conducted by this author recruited ecstasy users nationally, while non-user controls probably resided in the Baltimore (MD) / Washington, DC area. Matching – On gender

**Criteria for Inclusion, Ecstasy Users** – Prior or current use of ecstasy, with no restrictions on extent of use stated (all users had taken >10 tablets, so using ecstasy on at least 10 occasions may have been a requirement.) Non-Users – No past or current use of ecstasy, undergoing myelography for diagnostic purposes relating to low back pain. **All Groups** – No current major medical or psychiatric illness, as assessed through physical examination, neurological examination and laboratory analyses. Abstinence from all psychoactive drugs for at least 2 weeks before study day, with compliance verified through self-report only.

**Drug Use Parameters** – On average, ecstasy users had used ecstasy on 52 ± 45 occasions (11-219), with average usual dose per use of 1.25 ± .4 tablets per use (may be 1 ± .3 due to subjects’ belief that 1 tablet = 125 mg) (.5 – 2 tablets). 12 / 33 individuals reported using higher doses. Maximum dose used was
(approximately) 7 tablets (or 5.6 tablets, if 1 tablet = 125 mg) per occasion. Average frequency of ecstasy use was $1.25 \pm 0.25$ times a month, reported as intervals of $3.4 \pm 1.8$ weeks. 13 of 33 reported occasional daily use for 5-7 days. Average duration of use, in months, was $42 \pm 22.8$ months (6 – 96 months). Time elapsed, in days, since last use was, on average, 116.9 ± 163.1 days (14 – 728 days). Other Drugs – ‘Most’ ecstasy users were also polydrug users. Ecstasy users also used these drugs: marijuana, LSD, mescaline and psilocybin (no information on percentage of group using each). Occasionally used were: MDE (“Eve”), 2-CB, and sporadic use of cocaine, other stimulants.

Group Demographics and Matched Variables – Ecstasy users and non-users matched on gender. Gender, as M / F ratio – Ecstasy users, 21 / 12: non-users, 14 / 10. Other variables – Age. – Average age of ecstasy users = 36 ± 10 (19 – 71): average age of non-users = 45 ± 14 (21-73). Non-users were approximately 9 years older than ecstasy users.

Measures: Drug Analysis – 16 / 33 subjects brought 1 sample of ecstasy they had purchased (1 / 33 brought sample plus “suspect” pill sold as ecstasy, but producing different effects). Material analyzed via thin-layer chromatography, gas chromatography / mass spectrometry with nitrogen-phosphorus detector. Clinical Assessment – Asked to report on functional domains believed to be associated with serotonergic function, including sleep, pain perception, sexual behavior, aggression, mood regulation, appetite and food preference. Subjects also asked about any recent (post-ecstasy) tendency toward impulsiveness, obsessiveness or cognitive decline. However, no psychometric measures used to assess any of the dimensions listed above.

Monoamine Metabolites in CSF – Lumbar puncture performed from morning until late afternoon, without any requirement for overnight fast or bed-rest, but with conditions of lumbar puncture matched between controls and ecstasy users. Concentrations of 5HIAA, HVA and MHPG measured through HPLC (high-performance liquid chromatography) with electrochemical detection. Proteins and Cell Counts in CSF – Amount of total protein concentration and cell count (white blood cells, lymphocytes, polymorphnuclear cells) performed in CSF of ecstasy users only.

Analyses: (Metabolites in CSF only). Comparisons between ecstasy users and non-users made via 2-tailed Student’s t-test. Correlations were carried out with Pearson’s correlation coefficient. Correlations performed between CSF 5HIAA values and number of occasions of ecstasy use, duration of use and time since last use.

Results – Significant Differences: Monoamine Metabolites in CSF – Ecstasy users had lower levels of 5HIAA than controls (26% less 5HIAA).
Clinical Assessment – There was no formal comparison between non-users and ecstasy users, and most reported no problems in the functional domains asked about. However, 3 of 33 ecstasy users reported experiencing psychiatric symptoms. 1 complained of “depression,” 1 of “poor concentration and bad memory” and 1 of “diminished creativity.” All believed their ecstasy use played a role in producing symptoms but also identified other causes as well.

Results – No Differences Found: Monoamine Metabolites in CSF – Non-users and ecstasy users had similar levels of HVA and MHPG in CSF. While women in both groups had higher 5HIAA values than men in both groups, this difference did not reach statistical significance.

Protein and Cell Count in CSF (Ecstasy Users Only) – Total protein count for ecstasy users was within the normal range for ecstasy users. Protein level was slightly elevated in 5 / 33 subjects, but only 1 / 33 had protein level 2 times greater than upper limit of normal protein level. Cell counts (immune cell counts) were within normal limits for all but 1 subject (1 of 33). (This subject also had high protein levels in CSF, but no sign of meningeal irritation).

Correlations – 5HIAA level in CSF was neither positively nor negatively correlated with lifetime number of occasions of ecstasy use. Amount of 5HIAA in CSF was unrelated to duration of ecstasy use. Level of 5HIAA in CSF was neither positively nor negatively correlated with self-reported time since last use of ecstasy.

Clinical Assessment – No formal analysis compared non-users with ecstasy users on the basis of self-reported symptoms, and only 3 of 33 ecstasy users reported complaints concerning any of the functional
domains they were asked about. Ecstasy users did not have complaints about disturbed appetite or sleep, increased or decreased aggressiveness, changes in sexual behavior or in pain perception.

**Results – Other:** All ecstasy samples provided (16 / 16) contained MDMA. “Suspect” pill contained MDA.

**Overall Effects:** Regular ecstasy users had lower levels of 5HIAA than did people with lower back pain with no history of ecstasy use. However, both groups had the same levels of the dopamine metabolite HVA and the norepinephrine metabolite MHPG. Total protein level and cell counts, performed on ecstasy users only, found that the majority of the ecstasy users had values within the normal range. Only 1 subject had protein levels that were twice the normal level, and only 1 subject (also at the high end of elevated protein levels) had a high immune cell count, but no sign of infection. A majority of ecstasy users reported no symptoms related to serotonergic function (sleep disturbance, mood disorders, aggression, impulsivity, change in appetite, pain or sexual behavior). Only 1 of 33 complained of depression and 2 of 3 complained of decline in cognitive function (poor concentration, decline in creativity). Since these were not measured in non-user controls and normative data on these complaints not provided, it would appear that there is no significant increase in these complaints. All samples of material purchased as “ecstasy” (in the late 1980s – 1990) were identified as MDMA except for 1 pill, identified as MDA.

**Comments:** This is an early paper attempting to associate ecstasy use with alteration in serotonergic function, here measured via the fairly invasive and unpleasant method of measuring metabolites in cerebrospinal fluid via lumbar puncture, as well as a clinical assessment. Because of the invasiveness of this technique, the authors had to use non-user controls receiving the procedure for diagnostic purposes. It is possible that people with lower back pain might differ from healthy controls in cerebrospinal monoamine metabolites or in measures of psychological health. No formal comparisons were made between ecstasy users and non-users on assessment for psychiatric complaints, and so it is difficult to tell whether the number of complaints (3 of 33 in ecstasy users) is within the expected range for people of the same gender and age group. The paper is also notable for its attempt to identify at least some of the material people purchased as ecstasy, and it appears that most or all of the material was MDMA. While the findings in this paper might support the case for regular ecstasy / MDMA use producing reduction in 5HIAA and changes in physiological or mental health.


**Purpose:** Cognitive function, general: To investigate the effects of regular ecstasy use and regular cannabis use, independent of ecstasy use, on memory and attentional processes by comparing performance on tests of reaction time, memory and attention in ecstasy users, cannabis users and non-user controls.

**Design:** Non-experimental (retrospective) 3-group between subjects (across-groups) design comparing ecstasy users (who had all used cannabis) with 2 matched control groups; cannabis users and people with no history of drug use (non-users). All subjects completed a test battery assessing memory and attentional processes and the Cognitive Failures Questionnaire.

**Subjects:** 15 regular ecstasy users, 15 cannabis users who had never taken ecstasy and 15 individuals who had never taken any illicit drugs. All subjects resided near the Sunderland (England) area and members of all 3 groups were recruited via “snowball” technique (word of mouth and direct acquaintance with the researchers). Matching – On gender, age, socioeconomic status and educational level. Ecstasy users and cannabis users matched on cannabis use.

**Criteria for Inclusion, Ecstasy Users –** Having used ecstasy on at least 5 occasions. Abstinence from ecstasy for at least 2 months prior to study day and abstinence from cannabis for at least 1 month prior to
study day, with compliance with both requests verified via self-report only. **Cannabis Users** – Regular use of cannabis, with regular use undefined, perhaps using cannabis on 5 or more occasions. No past or current use of ecstasy, and abstinence from cannabis for at least 1 month prior to study day, with compliance verified via self-report only. **Non-users** – No use of any psychoactive drugs, including either ecstasy or cannabis. **All Groups** – Abstinence from any psychoactive substance on study day, with compliance verified through self-report only. Absence of psychiatric illness reported for all 3 groups, but unclear as to whether this was a criterion for study participation. **Drug Use Parameters** – **Ecstasy Users** – Ecstasy users taken ecstasy on an average of 20 occasions (range not provided) over a 5 year period, with no information provided on average dose per use. Duration of use, on average, was 60 months, (range not provided) with no information provided concerning frequency of use, though using the numbers above provides a rough calculation of approximately .3 occasions per month. Time since last use was at least 60 days (precise information not provided). **Other Drugs** – Ecstasy users also reported using cannabis on an average of 4 days a week, with an average duration of use of 10 years. (No information on dose per use). Time of last use prior to study day was reported as at least 30 days. Use of these drugs reported on less than 5 occasions: LSD (3 / 15), amphetamines (2 / 15) and cocaine (3 / 15). **Cannabis Users** – Cannabis users reported using cannabis on an average of 4 days a week for an 11-year period. (No information on dose per use). Time of last use prior to study day was at approximately 30 days. **Group Demographics and Matched Variables** – Ecstasy users, cannabis users and non-users all matched on gender, age, socioeconomic background and educational level. Ecstasy users and cannabis users matched on frequency of cannabis use. **Gender**, as M / F ratio – Ecstasy users, 8 / 7: cannabis users, 8 / 7: non-users, 9 / 6. **Age**. Average age of ecstasy users, 31 ± 4 years (23-44 years); cannabis users, 30 ± 6 years (21-43 years); non-users, 32 ± 4 years (26-39 years). **Socioeconomic Status** – Subjects in all groups reported to be working in “professional careers.” **Educational Level**, as number of people with this amount of education and approximate years (provided via personal communication) – GCSE (“school leaving” exam), ecstasy users = 3, cannabis users = 2, non-users = 3 (approx. 10 years), “A” levels (high school pre-college), ecstasy users = 2, cannabis users = 3, non-users = 4 (approximately 12 years), post-college, graduate school, ecstasy users = 3, cannabis users = 2, non-users = 1. Average education, ecstasy users = 2.6 (approx. 15), cannabis users = 2.6 (approximately 15 years), non-users = 2.4 (approximately 14.5 years). **Measures** – Tests of Reaction Time – Via computerized tests devised specifically for this study. Subjects press spacebar after seeing or hearing a target (white circle for visual RT, simple tone for auditory RT). Subjects press number corresponding to number (from 1 to 9) displayed on screen for test of complex RT. **Tests of Memory** – Assessed via WMS. This scale consists of Figural Memory (match to sample with designs as targets), Logical Memory (Subject listens to and retells story by memory, scored on total number of ideas recalled from story), Visual Paired Associates, Verbal Paired Associates (learn associations), Visual Reproduction (Draw picture from memory), Digit Span, Visual Memory Span (Subject watches and reproduces sequences of taps of colored squares). Delayed recall is tested by a second presentation of Logical Memory, Visual Reproduction, Visual Paired Associates and Verbal Paired Associates. **Index Scores** – Calculated using weights provided by the WMS record form. Index scores calculated for General Memory, Verbal Memory, Visual Memory, Delayed Recall and Attention and Concentration. **Self-Reported Cognitive Deficits** – Measured via Cognitive Failures Questionnaire. **Analyses**: All data (tests of reaction time, WMS Index scores, WMS sub-test scores and Cognitive Failures Questionnaires) analyzed via 1-way ANOVA, with drug use (ecstasy use, cannabis use or no drug use) as between-subjects factor. Post-hoc comparisons were made via Newman-Keuls procedure. **Results – Significant Differences**: Tests of Memory – Both groups of drug users (ecstasy users and cannabis users) had lower General Memory index scores (ecstasy users, cannabis users < non-users), but since Verbal Memory is part of this score, the difference reflects differences in Verbal Memory. Verbal memory score differed across all three groups, with ecstasy users, cannabis users < non-users. Ecstasy
users and cannabis users performed less well on the Logical Memory sub-test than did non-users. There were differences in Delayed Recall index score, with ecstasy users, cannabis users < non-users. Ecstasy users and cannabis users did not perform as well on Logical Memory II. Ecstasy users performed less well on Verbal Paired Associates II and Visual Paired Associates II when compared with cannabis users and non-user controls (ecstasy users < cannabis users < = non-users).

**Results – No Differences Found:** Tests of Reaction Time – Ecstasy users, cannabis users and non-users performed similarly on all tests of RT: visual reaction time, auditory reaction time and complex reaction time.

Tests of Memory – There were no differences between any of the 3 groups on performance of the Verbal Associates sub-test. All 3 groups (ecstasy users, cannabis users, non-users) scored similarly on the Visual Memory Index of the WMS and on all sub-tests that made up this score (Figural Memory, Visual Associates-Immediate, Visual Reproduction). Attention and Concentration index score was similar for all 3 groups, including performance on all components (Mental Control, Digit Span, Visual Memory Span). All 3 groups scored similarly on Visual Reproduction II (delayed visual reproduction).

Self-Reported Cognitive Deficits – Ecstasy users, cannabis users and non-users all scored similarly on the Cognitive Failures Questionnaire, indicating that the 3 groups did not differ in respect to self-reported everyday difficulties with cognitive function.

**Overall Effects:** Immediate verbal recall, but not immediate visual recall, was worse in cannabis users and ecstasy users (who also used cannabis) when compared with controls who had never used either drug. However, ecstasy users, but not cannabis users, performed less well on tests of delayed recall, in the verbal and visual domain. Neither ecstasy use or cannabis use seemed to affect immediate visual recall or attention and concentration, with all three groups scoring similarly on index scores and tests of these areas. Members of all 3 groups also performed equally well on tests of simple and complex reaction time. While ecstasy users and cannabis users each performed less well on some tests of memory, neither group reported an increased number of difficulties related to problems with memory or cognition, as assessed in the Cognitive Failures Questionnaire.

**Comments:** Like Croft and Gouzoulis-Mayfrank, Rodgers has sought to separate the effects of cannabis from the effects of ecstasy on cognitive function by employing 2 matched control groups, one consisting of regular cannabis users who have never used ecstasy and one consisting of individuals with no history of drug use. The findings in this paper support the existence of two independent drug-related effects, with cannabis affecting immediate verbal recall and ecstasy (perhaps interacting with cannabis) affecting delayed recall. There were no attempts to correlate one or more parameter of ecstasy or cannabis use with performance on tests of cognitive function. The author suggests that some of the effects attributed to cannabis in both ecstasy and cannabis users may be related to cannabis withdrawal. The paper is notable in being moderately successful in matching ecstasy users and cannabis users on use of cannabis and other drugs, and making sure that members of both drug-using groups were not regular users of drugs other than ecstasy or cannabis. Samples used in this study are larger than those used in other studies, but the samples are small enough to warrant some caution when extrapolating the findings to larger groups of ecstasy and cannabis users.


**Purpose:** Psychiatric health, cognitive function, general, epidemiological; to investigate the subjective effects of ecstasy and ecstasy usage patterns and possible psychopathological consequences of regular ecstasy use in the context of polydrug use. (See “Non-Clinical Studies” for a summary of the paper focusing on the subjective effects and epidemiology of ecstasy use in a sample of polydrug users).
**Design:** Non-experimental (retrospective) 2-group between subjects (across groups) design comparing drug free ecstasy users with matched non-user controls, with drug use as a between-subjects factor, and with all non-users and sub-set of users completing tests of memory and executive function. (Comparisons are also made between ecstasy users with and without psychiatric problems, also using a retrospective 2-group between subjects design wherein subjects are divided into “problematic” and “problem-free” ecstasy uses on the basis of diagnosis with at least one psychiatric problem).

**Subjects:** 10 out of 150 ecstasy users seeking treatment for substance abuse, consecutively presented in N. Italian addiction unit and 20 non-user controls. **Matching** – On age and education.

**Criteria for Inclusion, Ecstasy Users** – Using ecstasy at least once. **Non-Users** – No past or current of any illegal drugs, including ecstasy, but similar age and education as ecstasy users. **All Groups** – No other criteria stated, though all subjects received physical and psychiatric examinations.

**Drug Use Parameters** – Information for sub-set of 10 ecstasy users unavailable. Information here is for sample of 150 users sampled in study, with some information presented only after categorization by presence of psychiatric problems. Ecstasy users took an average of 11 tablets over a lifetime (1-125), 1 in 4 had taken 50 or more tablets overa lifetime; no information on average dose per use provided, though author reports that most “usually” used 1 tablet per occasion. Average duration of ecstasy use was 8.125 months (.25-24 months). Frequency of use, in tablets per month, ranged from approximately .48 to 6 tablets per month, with no overall average presented (problem-free users = 1 per month, problematic users = 4 per month). Largest single intake ranged from 1 to 5 tablets, with problem-free users average = 1 tablet, problematic users = 3 tablets. Time of last use prior to study day not provided. **Age when First Used** – Average age when ecstasy was first consumed = 19 years. **Other Drugs Used** – 58% had used opiates. Percentage of problematic and non-problematic users who also reported use of these substances: cannabis, 66% and 78%, cocaine, 56% and 63%, and 30% of problematic users and 57% of non-problematic users had used other drugs (nitrites, other amphetamines, and psychedelics).

**Group Demographics and Matched Variables** – While the author indicates that 10 ecstasy users and 20 non-users were matched by education, specific information is not provided about the demographics of either group or years of education attained by members of either group. **Gender**, overall, as M / F ratio is 124 / 26. **Age**, average age = 23.2. 48% of overall sample of ecstasy users were employed, 21% were students and 31% were unemployed. The degree to which ecstasy users and non-users were matched for age or education cannot be assessed, due to lack of information. About non-users

**Measures:** **Memory** – (10 ecstasy users and 20 non-users only) Assessed via RBMB (Rivermead Behavioral Memory Battery).

**Executive Function (Planning Abilities)** – (10 ecstasy users and 20 non-users only) Assessed via Tower of London (TOL) task.

**Psychiatric Symptoms** – (Overall ecstasy user sample only) Assessed via psychiatric interview, with focus on symptoms believed to be related to serotonin function, including mood, sleep, aggression, impulsivity and appetite disorders, and cognitive decline. Percentage of ecstasy users reporting psychiatric disorders compared with number of ecstasy users not reporting any psychiatric disorders.

**Analyses:** **Memory and Executive Function** – Not clearly reported, but probably unpaired Student’s t test. **Psychiatric Symptoms** – Relationship between being diagnosed with at least 1 psychiatric symptom and demographic variables analyzed via t-test. The effects of drug use parameters (lifetime use, frequency of use, duration of use, largest single intake) on presence versus absence of psychiatric complaints analyzed via Mann-Whitney U test. The effect of other drug use on diagnosis with at least 1 psychiatric symptom was analyzed via chi-square.

**Results – Significant Differences:** **Memory** – Ecstasy users had lower scores on the RBMB than did non-drug users.

**Executive Function** – Ecstasy users had lower scores on the TOL test than did non-drug users.

**Psychiatric Symptoms** – See “Non-Clinical Studies” for more detailed description of findings. Depression, psychotic disorders and cognitive decline were the most frequently diagnosed problems. 48% were categorized as “non-problematic users” and 52% were deemed to be problematic users. Ecstasy users diagnosed with at least 1 psychiatric symptom were more likely to report their first use of
ecstasy at a younger age than those without psychiatric symptoms were. Ecstasy users with at least 1 psychiatric problem had a taken ecstasy on a greater number of occasions than ecstasy users without psychiatric problems (lifetime use of 47 versus 3 tablets). Ecstasy users with psychiatric problems reported a higher frequency of use (weekly or more often) than ecstasy users without psychiatric problems who used ecstasy once per month or less often. Ecstasy users with psychiatric problems reported a longer duration of use (4-24 months) compared with users without any psychiatric symptoms (duration of 4-12 months). Ecstasy users diagnosed with at least 1 psychiatric problem more likely to have taken a larger “maximum dose” of ecstasy than those without psychiatric problems (average maximum use of 3 tablets versus maximum use of 1 tablet).

**Results – No Differences Found: Psychiatric Symptoms** – See “Non-Clinical Studies” for more details. Gender and weight did not increase or decrease likelihood of having at least 1 psychiatric symptom (though it appears that while men are equally split between “problematic” and “problem free” users, there are more women with psychiatric symptoms than there are women without them. There were no differences in lifetime use of benzodiazepines, opiates or cocaine and being diagnosed with at least 1 psychiatric symptom (i.e. being a problematic user). Overall use of other drugs neither increased nor decreased the likelihood of being diagnosed with at least 1 psychiatric symptom.

**Overall Effects:** A sub-set of 10 ecstasy users drawn from a larger sample of 150 did not perform as well on a test of memory (the RBMT) or a test of executive function (the TOL) as did 20 individuals with no history of drug use. 27% of a sample of 150 ecstasy users reported experiencing some cognitive decline after ecstasy use. 53% of larger sample (150 ecstasy users) also diagnosed with psychiatric problems after ecstasy use, with diagnoses correlated with subject’s age, all parameters of ecstasy use examined (age at first use, frequency of use, duration of use, overall lifetime consumption and maximum dose per use). Ecstasy users with at least 1 psychiatric symptom were more likely to use some drugs (cannabis, alcohol, LSD and stimulants) but not others (benzodiazepines, opiates, cocaine), even though raw percentage data suggest that users with psychiatric problems use opiates at a much higher rate than ecstasy users who were not diagnosed without problems.

**Comments:** This paper is more notable for its exploration of the acute and sub-acute effects of ecstasy in polydrug users than it is for its exploration of the effects of ecstasy use on cognitive function. While the authors present findings supporting the existence of cognitive deficits after ecstasy use, they do not provide enough information about either group of participants for a thorough evaluation of these claims. Given the demographics of the entire sample, it seems highly likely that the sub-set of ecstasy users tested were polydrug users, while non-users had no history of illicit drug use. This raises the issue of whether differences in memory or executive function in this sample arise out of regular ecstasy use or from regular use of other drugs, such as stimulants or opiates. Since all ecstasy users came from a sample of polydrug users who were seeking help for substance abuse, it is unclear as to whether this sample is representative of ecstasy users in general. Because the sample in this paper is unlikely to be representative of ecstasy users in general, findings probably cannot be generalized to the population at large. Sample size is also small as well.

Semple et al. (1999). Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA (“Ecstasy”) users.


**Purpose:** Brain imaging (SPECT with ligand): To investigate the effects of regular ecstasy use on amount of serotonin and dopamine transporter binding, as measured via SPECT with a radioligand sensitive to both the serotonin and the dopamine transporter. **Specific Hypothesis Tested** – That regular ecstasy use would produce abnormalities in serotonin transporter (SERT) binding but would not produce abnormalities in dopamine transporter binding.
**Design:** Non-experimental (retrospective) 2-group between subjects (across groups) design comparing regular ecstasy users and a matched group of polydrug users with no history of ecstasy use, with drug use as a between-subjects variable, with all subjects completing tests of cognitive function and receiving SPECT scans.

**Subjects:** 10 regular ecstasy users and 10 polydrug users with no past or current use of ecstasy residing in the Edinburgh (Scotland) area. Members of both groups were recruited from amongst the dance event / rave community via advertisements, word of mouth and contact with independent (public health) drug agency volunteers. **Matching** – On gender, age, education, estimated IQ (through NART), drug use and lifestyle.

**Criteria for Inclusion, Ecstasy Users** – Lifetime consumption of at least 50 ecstasy tablets, having taken ecstasy for a year or longer and current regular use of ecstasy. Abstinence from ecstasy for at least a week prior to study day, with compliance verified by hair sample taken before study day. **Non-Users** – No past or current use of ecstasy, but use of other drugs permitted. **All Groups** – Being male, between ages of 18-35, and without past or current psychiatric or medical illnesses. No history of head injury or neurological health problems, as assessed via neurological examination.

**Drug Use Parameters** – Ecstasy users had taken, on average, 672 ± 647 tablets of ecstasy over a lifetime (50-1800), with no information provided on average dose per occasion. Average frequency of use not provided. Duration of use not reported, (estimated range, 12 – 120 months, from inclusion criterion and text). The time since last use of ecstasy, prior to study day, was 18 ± 8 days (6 – 28 days). **Other Drugs** – Average weekly use of cannabis in ecstasy users, in 1/ 16 oz = 3 16th oz, in ecstasy users 2.3 16th oz in non-users. Daily use: 6 / 10 ecstasy users, 4 / 10 non-users. Weekly use, 3 / 10 ecstasy users, 3 / 10 non-users. Monthly use, 0 ecstasy users, 2 / 10 non-users. Irregular, 1 / 10 non-users, 1 / 10 non-users. Amphetamine, mean weekly use for ecstasy users = 1.3 g and for non-users, 7 g. Weekly use of amphetamine, 3 / 10 ecstasy users, 0 non-users. Monthly use of amphetamine, 3 / 10 ecstasy users, 1 / 10 non-user. Irregular use 4 / 10 ecstasy users, 9 / 10 non-users. Ecstasy users drank 19.8 ± 10 units of alcohol weekly and smoked 15.4 ± 5.2 cigarettes a day; non-users drank 15.1 ± 12.8 units of alcohol weekly and smoked 11.5 ± 8 cigarettes a day. Both groups reported occasional use of LSD, “magic mushrooms” and cocaine (figures not reported).

**Group Demographics and Matched Variables** – Ecstasy users matched with non-users on gender (all male), age, height, weight, education, estimated IQ via NART score, drug use, personality factors and GHQ score responses. **Gender**, as M / F ratio – Ecstasy users, 10 / 0: Non-users, 10 / 0. **Age**. Average age of ecstasy users = 25.5 ± 4.4, average age of non-users = 24.2 ± 5.2. **Height, Weight**. Height in cm, weight in kg – Ecstasy users, 177 ± 8.6 cm, 72.1 ± 10.4 kg: Non-users, 174.5 ± 6.8 cm, 72.4 ± 9.1 kg. **Education Level**, in years – Ecstasy users = 14.7 ± 2.3 years, non-users = 15 ± 2.5 years. Estimated IQ from NART score: Ecstasy users, 107.6 ± 8.2, non-users = 109.7 ± 7.8. **Personality Measures** (Assessed via short form of Eysenck Personality Questionnaire, or EPQ). Average extroversion score for ecstasy users = 8.4 ± 3.1 and for non-users 7.4 ± 3.6. Average neuroticism score for ecstasy users = 4.3 ± 3.3 and for non-users, 3.2 ± 3.1. Average psychoticism score for ecstasy users = 4.7 ± 1.7 and for non-users = 4.5 ± 2.2. “Lie” score, for ecstasy users = 2.4 ± 1.5, and for non-users = 3.7 ± 2.7. Authors report subjects matched on General Health Questionnaire score, but scores not provided.

**Measures:** Tests of Cognitive Function – Reaction time (RT) and psychomotor speed tested via Trails A and CANTAB simple RT tests. **Visual memory** tested via CANTAB Delayed Matching to Sample test. **Verbal memory** measured via California Verbal Learning Test (verbal memory test, similar to RAVLT with immediate and delayed recall of items). Attention measured via WMS-R Digit Span. **Executive function** assessed via CANTAB Spatial Working Memory test, Trails B, verbal fluency (FAS word generation) test and Stroop task.

**Imaging** – Performed via SPECT with the radioligand [123I]-betaCIT, which binds to serotonin and dopamine transporter. The first scan was performed 90 minutes after ligand injection and the second was performed 21-23 h after injection. Specific binding to serotonin and dopamine transporter was calculated. An ROI analysis was carried out by an individual blind to study hypotheses, using a reference ROI at
should be noted that the study had a large attrition rate, with many potential subjects dropping out or being difficult to locate before the study was completed. It is interesting that the authors find differences

cerebellar area. ROI unspecified but included: Frontal (L, R), anterior cingulate (L, R), anterior temporal (L, R), middle temporal (L, R), occipital (L, R), calcarine (L, R), posterior cingulate (L, R), caudate (L, R), putamen (L, R), thalamus (L, R), caudate and putamen on Day 2 (L, R) and caudal midbrain / pons (R?).

Analyses: Tests of Cognitive Function – Not clearly reported, but involved a parametric between-group test of significance, such as ANOVA or Student’s t-test, with drug use (ecstasy use versus no ecstasy use) as a between-groups factor. Number of tablets taken over a lifetime was correlated with scores on each test of cognitive function.

Imaging – ROI data examined via ANCOVA, with drug use (ecstasy use or non-use) as between-group factor and white matter or cerebellar binding counts as covariant.

Correlations – A correlation was performed on lifetime ecstasy dose and specific binding to the serotonin transporter site (SERT). A correlation was performed on time since last use and ligand binding.

Results – Significant Differences: Tests of Cognitive Function – In ecstasy users, larger lifetime doses of ecstasy were associated with reduced performance on CVLT (verbal memory). Larger lifetime doses of ecstasy were also associated with lower scores on the CANTAB Spatial Working Memory test (authors define as test of executive function), indicating deficits in verbal memory and either spatial working memory or executive function associated with lifetime dose of ecstasy. These negative associations between lifetime ecstasy use and performance on CVLT and Spatial Working Memory task are unmodified when estimated IQ is entered into equation.

Imaging – Ecstasy users had reduced binding for SERT sites in 4 of 22 brain regions (left occipital, calcarine (L, R) and R posterior cingulate. Time since last ecstasy use was correlated with extent of binding in many (unspecified) regions, and specifically L calcarine region. Statistical parameter modeling confirmed findings of ROI analysis and also revealed a positive correlation between time since last use of ecstasy and ligand binding in the mid-line limbic areas (but authors later report absence of correlation between time since last use and tracer binding in these areas).

Results – No Differences Found: Tests of Cognitive Function – There were no differences between ecstasy users and non-users on simple RT test, Trails A, Matching to Sample (visual memory), Digit Span (attention), Trails B (executive function), verbal fluency and Stroop task.

Imaging – Ecstasy users and non-users were found to have similar SERT binding in 18 of 22 brain regions examined via ROI, including frontal (L, R) anterior cingulate (L, R), anterior and middle temporal (L, R), R occipital, L posterior cingulate, caudate, putamen, thalamus (all 3 bilaterally), caudate and putamen on Day 2 (L, R) and R caudal midbrain / pons. There was no relationship between lifetime ecstasy dose (in tablets) and ligand binding at any brain region assessed. Ecstasy users did not differ in dopamine binding in any brain region examined.

Overall Effects: A SPECT scan using a radioligand apparently sensitive to both serotonin and dopamine transporter sites found reduced serotonin transporter binding in the left occipital area and bilaterally in the calcarine and cingulate area in ecstasy users, but not matched non-user controls. Time since last ecstasy use was negatively correlated with serotonin binding in some areas and perhaps positively correlated with binding in other areas. While there were differences between the two groups in serotonin binding, there were no differences between these groups in dopamine binding. Both ecstasy users and non-users scored similarly on tests of reaction time, attention, memory (visual and verbal) and executive function. Yet lifetime (overall) use of ecstasy was correlated with poorer performance in tests of verbal memory and a test of executive function or spatial working memory. The authors’ hypothesis was confirmed; ecstasy users differed from polydrug users who had not used ecstasy on the basis of serotonin transporter binding and not dopamine transporter binding. However, the hypothesis did not predict where differences in serotonin transporter binding would appear.

Comments: This paper is notable for using two very carefully matched groups, both drawn from the same population (relatively young individuals involved in the dance event culture in the Edinburgh area). This strategy would seem to strengthen the validity of differences found between the groups. However, it should be noted that the study had a large attrition rate, with many potential subjects dropping out or being difficult to locate before the study was completed. It is interesting that the authors find differences
in serotonin transporter binding while finding no differences in cognitive function between the groups. Instead, overall lifetime use of ecstasy was more closely related to performance on tests of memory and executive function than simply using 50 or more tablets of ecstasy. The authors made an unusual choice of radioligand for their studies, choosing one that binds to both serotonin and dopamine transporter sites. They sought to distinguish binding at the 2 sites by performing scans at 2 different times, but the success of this procedure is unclear (see Heinz & Jones, 2000). Though the samples were carefully matched, they are small and contain males only; hence some caution should be used when generalizing from the findings in this study to the population at large or to both genders.

Tuchtenhagen et al. (2000). High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent Ecstasy (MDMA) users.


Purpose: Electroencephalography (evoked potentials), personality: To investigate the effects of regular ecstasy use on serotonin system functioning by comparing ecstasy users with two control groups (cannabis users and non-drug users) on auditory evoked potentials and personality characteristics. Specific hypothesis tested – that ecstasy users should be more likely than cannabis users or non-user controls to exhibit a relationship between intensity (volume) of sound and aspects of AEP (tangential NI / P2 source activity).

Design: Non-experimental (retrospective) 3-group; between-subjects (across groups) design comparing regular ecstasy users with 2 matched control groups, cannabis users and people who used no drugs (non-users). Drug use (ecstasy and cannabis use, cannabis use alone or no drug use) served as between-subjects factor. All subjects underwent recording of auditory evoked potentials.

Subjects: 28 regular ecstasy users, 28 cannabis users and 28 individuals with no past or current drug use, with all subjects recruited via personal contacts with people in the Aachen (Germany) dance scene and via snowball technique. (Same sample studied in Gouzoulis-Mayfrank et al, 2000). Matching – On gender, age, approximately matched on education level. Ecstasy users and cannabis users matched on cannabis use.

Criteria for Inclusion, Ecstasy Users – Having used ecstasy regularly for 6 months or more, with minimum frequency of use at twice per month within the last 2 years, or having used ecstasy on at least 25 occasions in the past 2 years. No regular use of other legal or illegal drugs except for cannabis, (regular use defined as once a month or more in last 6 months) and no heavy use of alcohol (defined as self-reported severe drunkenness at least twice a month). Abstinence from ecstasy for at least 7 days prior to study day, with compliance verified through drug screen (unspecified, probably urinary) on day of study. Cannabis users – No current or prior use of ecstasy, and matched with ecstasy users on extent of cannabis use (not all members of the “cannabis user” control group used cannabis because not all ecstasy users were cannabis users). No regular use of any other psychoactive drugs, with regular use defined above, and no heavy use of alcohol, as defined above. Non-users – No past or current use of ecstasy, cannabis or any other legal or illicit drug. All groups – Absence of any major psychiatric or medical illness and no organic brain disorder, as screened via medical history and psychiatric interview. Both ecstasy users and cannabis users required to abstain from cannabis use on day of study. While drug screen is performed on study day, people with positive screens for cannabis were not excluded from the study.

Drug Use Parameters – Ecstasy users reported an average lifetime use of 93.4 ± 119.9 ecstasy tablets (20-500), and they used an average dose of 1.4 ± .9 tablets per occasion (.5 – 3.5 tablets per occasion). Average frequency of use was 2.4 ± 1.6 times per month (.75 – 8 times), and average duration of use in
months was 27 ± 18 months (6-60). Self-reported length of drug-free period before study day, in days was 41 ± 71 days (7-365 days, median 23 days). On average, people first took ecstasy at age 19.4 ± 3.8 years (14-27). 26 / 28 ecstasy users were regular ecstasy users and 2 / 28 were sporadic ecstasy users. Cannabis use – 22 ecstasy users were regular cannabis users, 1 used cannabis sporadically and 5 did not use cannabis. In matched cannabis user group, 23 were regular cannabis users, 2 were sporadic cannabis users and 3 did not use cannabis. Cannabis was used on 20.7 ± 11.5) days a month by ecstasy users and 20.9 ± 10.2 days per month by cannabis users. Duration of cannabis use extended for 66.6 ± 37 months for ecstasy users and for 35.1 ±24 months for cannabis users. Ecstasy users had last used cannabis 4.3 ± 5.3 days (median 2 days) before the study day and cannabis users last used cannabis 4 ± 15.5 days (median 1 day) before the study day. Age at onset of cannabis user for ecstasy users was 16.6 ± 2.9 years, and for cannabis users 17.1 ± 2.4 years. 17 ecstasy users and 20 cannabis users tested positive for presence of THC in urine on study day, and 11 ecstasy users and 8 cannabis users tested negative for THC in urinary analysis.

Group Demographics and Matched Variables – Ecstasy users matched with both cannabis user and non-user controls on gender, age and education level. Gender, as M / F ratio – ecstasy users, 16/12: cannabis users, 15/13: non-users, 17 / 11. Age. Ecstasy users, 18-29, mean = 23.25, cannabis users, 18-31, mean = 22.9, non-users, 18-30, mean = 23.5. Education level. Little / no secondary school – 1 ecstasy user, 0 cannabis users, 0 non-users: “Basic” school-leaving exam – 2 ecstasy users, 2 cannabis users, 0 non-users: “intermediate” school-leaving exam – 8 ecstasy users, 5 cannabis users, 8 non-users: “highest” school-leaving exam – 16 ecstasy users, 20 cannabis users, 20 non-users: university degree – 1 ecstasy user, 1 cannabis user, 0 non-users. Average education, ecstasy users = 3.5 (approx. 11 years), cannabis users = 3.7 (approx. 12 years), non-users = 3.7 (approx. 12 years). Cannabis Use – Ecstasy users matched with cannabis-user controls on cannabis use.

Measures: Personality Traits – Impulsiveness and novelty seeking measured via Sensation Seeking Scale (SSS –V) and Barratt Impulsiveness Scale before evoked potential recordings performed.

Evoked Potential Recording – Subjects passively listened to tones without paying special attention to stimuli. 1 kHz tones presented binaurally, with each tone lasting 30 ms and randomized within sweep. 4 blocks of stimuli were presented, with tones varying in intensity (60, 70, 80 and 90 dB). Each block presented tone of greater intensity due to limitations of AEP recording equipment. Raw data transformed into appropriate format for dipole source analysis, and filtered with low pass and high past filters. A source model formed from grand mean data from non-user controls tested against data, and the goodness of fit (adequacy, appropriateness) of the model for all 3 groups tested. Since model explained data for members of all 3 groups, it was used in later analysis.

Analyses: Personality Traits – Scores on the SSS-V and the Barratt Impulsiveness Scale were compared across groups using an ANOVA (unspecified, presumably 1-way for each score) with drug use (ecstasy and cannabis use versus cannabis use and no drug use) as between-group factor. Post-hoc comparison’s made via Scheffe’s test.

Relationships between Personality Traits and Evoked Potentials – Scores on the SSS-V and the Barratt Impulsiveness Scale correlated with differences calculated for AEP for increasingly loud tone (i.e. 70 – 60 dB, 80 – 70 dB, etc), using the Pearson correlation coefficient.

Dipole Source Model and Evoked Potential Recording – Latencies and amplitudes for each of the 2 dipole sources for the N1 / P2 components were analyzed via 2-way repeated measures ANOVA. Drug use (ecstasy and cannabis use, cannabis use or no drug use) as a between-group factor and tone intensity (60, 70, 80 or 90 dB) as a within-subjects factor. Due to artifacts, ANOVA examining dipole source modeling used 23 ecstasy users, 25 cannabis users and 27 non-users.

Drug Use Parameters and Dipole Source Evoked Potential Recording – Pearson’s correlation coefficient used to examine the relationship between parameters of ecstasy and cannabis use and the intensity-dependence (alteration according to loudness of sound) of the N1 / P2 evoked potential. Correlations performed on arithmetic differences in amplitude of each tone presented (70 – 60 dB, 80 – 70 dB, etc).
**Results – Significant Differences:** Personality Traits -- Ecstasy users scored higher on experience seeking sub-scale of the SSS-V and non-planning impulsivity sub-scale of the Barratt Impulsiveness Scale.

Dipole Source Model of Evoked Potential Recording -- N1 / P2 component varied by intensity and only marginally by drug use across all intensities (ecstasy users, cannabis users and non-users). There was a significant interaction between stimulus intensity and drug use. N1 / P2 differed between ecstasy users and cannabis users at 80 dB, and ecstasy users N1 / P2 in ecstasy users differed from cannabis users and non-user controls at 90 dB, though members of all 3 groups had similar AEPs with a 70 dB tone. Only ecstasy users showed increasing amplitude of tangential dipolar activity with increasing tone intensity, while amplitude of dipolar activity was not dependent on tone intensity in cannabis users or in non-user controls.

**Results – No Differences Found:** Personality Traits -- Ecstasy users, cannabis users and non-users did not score differently on these Barratt Impulsiveness Scale scale scores: Global, motor, or cognitive impulsivity. Ecstasy users, cannabis users and non-user controls did not score differently on these SSS-V scales: Global, disinhibition, boredom susceptibility or thrill and adventure seeking.

Relationships between Personality Traits and Evoked Potentials -- There were no correlations between scores on either psychometric scale (SSS-V or Barratt Impulsiveness Scale) and dependency of tangential dipoles on stimulus intensity (loudness).

**Dipole Source Model of Evoked Potential Recording** -- There were no differences in latency for N1 / P2 across groups (ecstasy users, cannabis users and non-users), though there was a marginal tendency for shorter latency with increasing intensity appearing across all groups. There were no differences between ecstasy users, cannabis users and non-users in radial source of N1 / P2 component. AEP did not differ by hemisphere, so responses of hemispheres combined. Ecstasy users, cannabis users and non-user controls had similar N1 / P2 components when tone was 70 dB, but N1 / P2 differed in ecstasy users at higher tone intensities.

Relationships between Drug Use Parameters and Dipole Source Evoked Potential Recording – There were no significant correlations between frequency, duration or intensity of ecstasy use and extent of dependence of tangential dipole activity on ascending stimulus intensity. Frequency, duration or intensity of cannabis use was also not correlated with the extent of dependence of tangential dipole activity on stimulus intensity in ecstasy users.

**Overall Effects:** Auditory evoked potentials (AEPs) were compared across ecstasy users, cannabis users and non-user controls, with AEPs studied through dipole source analysis. In ecstasy users, tangential dipole source activity varied with loudness (intensity) of the tone presented. Intensity of tone did not change tangential dipole source activity in cannabis users or in non-users. All 3 groups had similar global scores on measures of sensation seeking and impulsivity, 2 traits associated in past research with reduced serotonergic activity. However, ecstasy users had higher scores than members of the other 2 groups on specific sub-scales of both measures of sensation seeking and impulsivity. Ecstasy users had higher scores on scales that assessed non-planning impulsivity and experience-seeking (but not thrill-seeking or prone-ness to boredom). There were no correlations between impulsivity and sensation-seeking scores and differences in the extent of dependence of dipole source activity on stimulus intensity. None of the drug use parameters tested were associated with the dependence of dipole source activity on stimulus intensity for ecstasy users, with frequency, duration and intensity of use all examined. The authors’ specific hypothesis is confirmed; regular ecstasy use is related to changes in the N1 / P2 component of auditory evoked potentials, producing changes that are associated with reduced serotonergic activity. These changes are also separable from the effects of cannabis use, as cannabis use did not produce the same changes in dipole source activity.

**Comments:** This paper is a companion paper to that of Gouzoulis-Mayfrank et al, 2000, since both papers rely on the same sample of ecstasy users, cannabis users, and non-user controls. That paper found ecstasy users performing worse on tests of memory and general intelligence, and on some tests of executive function, while this paper found differences in AEP. The authors state that measures of the tangential dipole allow for the separation the primary sensory cortex, which receives dense serotonergic innervation,
from the secondary sensory cortex, which receives less serotonergic innervation. However, unlike differences in performance on tests of cognitive function, the authors did not find a relationship between any parameter of drug use and across-group differences in AEP component. This is either an indication that changes in AEP are highly sensitive to ecstasy use (at 25 occasions of use or above) or that these changes arise from another unmeasured drug use parameter. It is surprising to find that in this study, the two drug using groups did not differ from non-user controls on measures of sensation-seeking, and that ecstasy users only differ from members of the other 2 groups on sub-scales of these measures. This finding is especially notable considering that impulsivity and sensation-seeking, like changes in AEP, are associated with reduced serotonergic function. While ecstasy users did have slightly fewer years of education than cannabis users or non-user controls, this difference was not statistically significant.


Purpose: Neuropsychological, including mood, personality, cognitive function: to investigate the effects of ecstasy use on cognitive and serotonergic function and to control for a wide array of confounding variables by selecting all participants from the same sub-culture and by using analyses of covariance to control the effects of one or more confounding factor.

Design: Non-experimental (retrospective) 3-group between subjects (across groups) design comparing heavy ecstasy users and moderate ecstasy users with matched non-user controls. Drug use (ecstasy use or no ecstasy use) and extent of use (moderate ecstasy use or heavy ecstasy use) served as between-subjects factors.

D-Fenfluramine Challenge – Double-blind cross-over design, with all subjects receiving 1 placebo infusion and 1 d-fenfluramine infusion occurring at least 5 days apart, and with drug use and extent of use serving as between-subjects factors. All subjects completed measures of psychopathology and tests of cognitive function and all underwent d-fenfluramine challenge.

Subjects: 21 heavy ecstasy users, 21 moderate ecstasy users and 20 non-ecstasy users residing in the Netherlands, with subjects recruited from amongst the dance event community by advertisements.

Matching: On gender and age; moderate and heavy ecstasy users matched on use of other drugs.

Criteria for Inclusion, Heavy Ecstasy Users – Having used ecstasy on 48 or more occasions in last 2 years prior to study. Moderate Ecstasy Users – Having used ecstasy on 12-48 occasions in the last 2 years prior to study. Non-users – No past or current use of ecstasy. All Groups – Being male, aged 18-28, absence of current daily alcohol use > 3 units, current regular use of cocaine (> once a month) or amphetamine (> once a week or more often than ecstasy). No current use of opiates or prescription drugs. No history of major psychiatric disorder in last year, including history of alcohol or substance abuse. Abstinence from any psychoactive drugs, including all illicit drugs, for 1 week prior to last study day, with compliance verified through urinary drug screen performed on both study days.

Drug Use Parameters – Moderate ecstasy users took an average of 169 ± 252 tablets over a lifetime on an average of 73 ± 68 occasions; heavy users took an average of 741 ± 678 tablets over a lifetime on an average of 230 ± 170 occasions. (Ranges not provided in either case). Average dose per use was 2 ± 1.1 tablets for moderate users and 3.1 ± 1.1 tablets for heavy users (ranges not provided). Average duration of use, in months, for moderate ecstasy users = 52.8 ± 28.8 months, and for heavy ecstasy users = 54 ± 21.6 months (ranges not provided). Frequency information is not provided, but using other drug use parameters, frequency of use can be estimated at .5 – 3 occasions per month for moderate ecstasy users and at 3 – 5 times per month for heavy ecstasy users. Time from last use of ecstasy to psychometric study day, in days was 15.7 ± 9.5 days for moderate ecstasy users and 9.0 ± 7.5 days for heavy ecstasy users,
and time from last use to d-fenfluramine challenge was 28.1 ± 8.8 days for moderate users and 19 ± 8.6 days for heavy users. **Other Drugs** – Cannabis, average lifetime consumption in number of joints, moderate users = 1890 ± 2620 joints, heavy users = 1850 ± 2700, non-users – 379 ± 1190. Cannabis use in 3 months before study, moderate ecstasy users: 3 / 21 never used, 8 / 21 used 1 per wk, 10 used > 1 per wk. Heavy ecstasy users, 7 / 21 never used, 7 / 21 used 1 per wk and 7 / 21 used > 1 per wk. Non-users, 14 / 20 never used, 2 / 20 1 per wk and 4 / 20 used > 1 per week. Amphetamine, in last year – Moderate users, 10 / 21 never used, 8 / 21 used once per month or less, 3 used few times per month, 0 used more often. Heavy users, 0 never used, 8 / 21 used once per month or less, 8 used few times per month, 5 / 21 used 1 per wk. Non-users, 19 / 20 never used, 1 / 20 used once per month or less, and none used more often. Cocaine, 1 per month or less: moderate users, 14 / 21, heavy users, 14 / 21, non-users, 0 / 20.

**Group Demographics and Matched Variables** – Heavy ecstasy users, moderate ecstasy users and non-users were matched on gender and age, and both ecstasy using groups approximately matched on drug use. **Gender**, as M / F ratio: Heavy ecstasy users, 21 / 0: moderate ecstasy users, 21 / 0: non-users, 20 / 0. **Age**. Average age for moderate ecstasy users = 22.1 ± 2.3 (range not provided): average age for heavy ecstasy users = 21.7 ± 2.8: average age for non-users = 20.6 ± 2.2. **Other variables** – Education level, as coded and in approximate years, where 1 = lower general or vocational, 2 = intermediate, 3 = at least pre-university. For moderate users, 3 / 21 at level 1 (approx. 10 years), 7 / 21 at level 2 (approx. 12 years) and 11 / 21 at Level 3 (approx. 14 years). Heavy ecstasy users, 7 / 21 = Level 1 (approx. 10 years), 5 / 21 = Level 2 (approx. 12 years) and 9 / 21 = Level 3 (approx. 14 years). Non users, 1 / 20 = Level 1 (approx. 10 years), 6 / 20 = Level 2 (approx. 12 years) and 13 / 20 = Level 3 (approx. 14 years). On average, heavy ecstasy users had 11.5 years education (2.1), moderate users had 13 years education (2.4) and non-users had 13.5 years (2.6). **Weight**, in kg – Moderate users, 74.9 ± 8.4 kg, heavy users = 71.5 ± 10.7 kg, non-users = 73.8 ± 11.1 kg. **Average Number of Raves Attended** – Moderate users = 33.5 ± 25.2, heavy users = 47 ± 31.8, non-users = 32.5 ± 24.9. **ADHD Diagnosis Before Age 15** – Average number of criteria for attention deficit disorder and for hyperactivity, moderate users = 2.5 ± 2.4 (AD), 3 ± 2.5 (HD), heavy ecstasy users = 2.9 ± 2.8 (AD), 3.3 ± 2.2 (HD), non-users, 1.7 ± 1.9 (AD), 3 ± 2.5 (HD).

**Measures**: Psychopathology, Mood – Psychiatric diagnoses, including ADHD, assessed via psychiatric interview. Depressed mood and symptoms of depression measured via BDI, and state and trait anxiety measured via STAI. All measures administered 1 week before d-fenfluramine challenge.

**Impulsivity and Hostility** – Impulsivity was measured via Barratt Impulsiveness Scale. Sensation seeking measured via Temperament and Character Inventory (TCI), similar to the TPQ in containing harm avoidance and novelty seeking. Aggression and hostility measured via BDHI. Subjects completed all measures on study day 1 week before d-fenfluramine challenge.

**Tests of Cognitive Function** – All tasks selected from a computerized battery of neuropsychological measures (FePsy). **Tests of RT** – Auditory and visual. **Tests of Information Processing** – Visual search involving matching to sample with grid patterns and adapted form of WCS, learn sorting rules through trial and error. **Memory** – Computerized Corsi Blocks (Watch sequence of flashing blocks and reproduce pattern, with increasingly complex patterns. Span and “supraspan” scored. **Tests of Working Memory** – View 6 words or figures, then view new list of 6 with one previously presented word, and select previously presented word, with serially presented and simultaneously presented words or figures (4 tests altogether, possibly form of “Sternberg task). Both correct responses and reaction time scored.

**Neuroendocrine Response to d-Fenfluramine** – Plasma prolactin and cortisol measured after infusion of 30 mg d-fenfluramine or placebo. Challenge performed after overnight fast and glucose drink, and hormones sampled in blood drawn hourly (1, 2, 3, 4, 5, 6, and 7 h post-infusion). No description of assays used for hormones, but concentration of d-fenfluramine and nor-dexfenfluramine measured via liquid-gas chromatography with mass selective detection.

**Analysis**: Psychopathology, Mood – Initial across-group comparisons made by performing Student’s t-tests (for heavy ecstasy users, moderate ecstasy users and non-users). Subsequent analyses examining the impact of additional effects on each measure used ANCOVAs with the confounding variable serving as covariate. Potential confounding variables included: use of alcohol per day, cannabis use (lifelong and
frequency of use in last 3 months), time since last use of ecstasy, BDI score (for measures other than BDI), STAI anxiety score, retrospective ADHD diagnosis and educational level.

Impulsivity and Hostility – Psychopathology, Mood – Initial across-group comparisons made by performing Student’s t-tests (for heavy ecstasy users, moderate ecstasy users and non-users). Subsequent analyses examining the impact of additional effects used ANCOVAs with confounding variables serving as covariates. Potential confounding variables included: use of alcohol per day, cannabis use (lifelong and frequency of use in last 3 months), time since last use of ecstasy, BDI score, STAI anxiety score, retrospective ADHD diagnosis and educational level.

Tests of Cognitive Function – Initial across-group comparisons made by performing Student’s t-tests (for heavy ecstasy users, moderate ecstasy users and non-users). Subsequent analyses examining the impact of additional effects used ANCOVAs with confounding variables serving as covariates. Potential confounding variables included: use of alcohol per day, cannabis use (lifelong and frequency of use in last 3 months), time since last use of ecstasy, BDI score, STAI anxiety score, retrospective ADHD diagnosis and educational level.

Neuroendocrine Response to d-Fenfluramine Challenge – Difference scores calculated for plasma cortisol and plasma prolactin by subtracting time-corrected area under curve (AUEC) at placebo from AUEC after d-fenfluramine. Across-group comparisons made via 2-tailed Student’s t-tests. Subsequent analyses examining the impact of additional effects used ANCOVAs with confounding variables serving as covariates. Potential confounding variables included: body weight, use of alcohol per day, cannabis use (lifelong and frequency of use in last 3 months), time since last use of ecstasy, AUC for dextfenfluramine, TCI scores on all 3 sub-scales (harm avoidance, reward dependence and novelty seeking), BDI score, STAI anxiety score, retrospective ADHD diagnosis and educational level.

Relationships between Neuroendocrine Response to d-Fenfluramine and Tests of Cognitive Function – Unspecified correlational or ANCOVA analyses performed to investigate any associations between neuroendocrine response to d-fenfluramine and scores on tests of cognitive function.

Results – Significant Differences: Psychopathology and Mood – Heavy ecstasy users had higher BDI and STAI scores than moderate ecstasy users and non-users, but significant differences disappear in analyses with other variables as covariates.

Tests of Cognitive Function – Reaction time, longest in heavy users, shortest in non-users (heavy ecstasy users > moderate ecstasy users > non-users). However, differences reduced after accounting for education level and BDI score. Span measured through computerized Corsi blocks test was shorter in ecstasy users when compared with non-users, with no significant differences in performance of heavy and moderate ecstasy users (heavy ecstasy users, moderate ecstasy users < non-users). Heavy and moderate ecstasy users both recognized fewer words on serially presented list than did non-users. Heavy ecstasy users recalled fewer words simultaneously presented than moderate ecstasy users or non-users; (heavy ecstasy users < moderate ecstasy users, non-users); moderate ecstasy users recognized fewer simultaneously presented words, but the difference was not significant. Heavy and moderate ecstasy users recalled fewer serially presented figures, heavy ecstasy users, moderate ecstasy users < non-users). (Heavy users did recall fewer figures than moderate users but the difference was not significant). Non-users also recalled more simultaneously presented figures than heavy ecstasy users or moderate ecstasy users; differences between recall of heavy and moderate users were not significant. (Heavy ecstasy users, moderate ecstasy users < non-users).

Neuroendocrine Response to d-Fenfluramine – Heavy ecstasy users had higher nor-dexfenfluramine AUCs than moderate ecstasy users, with moderate ecstasy users possessing lowest AUC and heavy users highest nor-dexfenfluramine AUC. (Differences between non-users and either group of ecstasy users not significant). Cortisol – Both heavy and moderate ecstasy users had lower plasma cortisol (difference score between fenfluramine and placebo AUEC), heavy ecstasy users, moderate ecstasy users < non-users), indicating blunted cortisol response after d-fenfluramine for both groups of ecstasy users. Analyses with other variables as covariates did not change differences in cortisol or prolactin response in ecstasy users and response in non-users.

Page 360 of 367
Correlation, Neuroendocrine Response to d-Fenfluramine and Tests of Cognitive Function – Amount of cortisol released after d-fenfluramine infusion correlated with memory span scores, apparently indicating that greater cortisol release after d-fenfluramine was related to greater memory span scores.

**Results – No Differences Found:**

- **Psychopathology, Mood** – When other (unspecified) variables used as covariates, heavy ecstasy users no longer had higher BDI or STAI scores than moderate users or non-users. Signs of ADHD were the same in all 3 groups.
- **Impulsivity and Hostility** – Members of all 3 groups had similar scores on the TCL, the BDHI and the Barratt Impulsiveness Scale. Ecstasy users had higher novelty seeking scores than non-users, but the difference was not significant.
- **Tests of Cognitive Function** – Heavy and moderate ecstasy users did not differ in span on computerized Corsi blocks, though both performed less well than did non-users. All 3 groups (heavy ecstasy users, moderate ecstasy users and non-users) scored similarly on the visual match to sample task (test of test of information processing). All 3 groups (heavy ecstasy users, moderate ecstasy users and non-users) scored similarly on the computerized WCS-like task.

**Neuroendocrine Response to d-Fenfluramine** – AUC for plasma d-fenfluramine did not differ across groups (heavy ecstasy users, moderate ecstasy users and non-users had similar d-fenfluramine AUC). While prolactin release after d-fenfluramine was highest in the non-user group and lowest in heavy ecstasy users, the differences between groups were not statistically significant.

**Relationships between Neuroendocrine Response to d-Fenfluramine and Tests of Cognitive Function** – Cortisol release after d-fenfluramine was not associated with RT, general information processing or classification (these analyses unreported, so perhaps not performed). No relationships reported between prolactin release after d-fenfluramine and any test of cognitive function.

**Overall Effects:** Heavy ecstasy users, moderate ecstasy users and non-users all drawn from the Dutch dance event scene scored similarly on tests of impulsivity and hostility. Ecstasy users had slightly higher scores on novelty seeking, but their scores were not significantly different from non-users. While heavy ecstasy users scored higher on the BDI and the STAI than moderate ecstasy users and non-users, differences in these measures disappeared when controlling for the effects of other variables. RT seemed to increase with ecstasy use, (compared across all 3 groups), but differences in RT were reduced when BDI scores and education level were controlled for. Both groups of ecstasy users did not perform as well on verbal and visual memory, including a test of spatial sequential memory (Corsi blocks). However, all 3 groups performed similarly on a test of information processing (visual search) and a classification task (executive function). While both heavy and moderate ecstasy users showed blunted cortisol release after d-fenfluramine, differences in prolactin release after d-fenfluramine (while present) were not significant. Controlling for the potentially confounding effects of other variables did not change across-group differences in prolactin and cortisol release. Cortisol release after d-fenfluramine was positively associated with memory span score, with greater release of cortisol usually indicating higher memory span score.

**Comments:** This paper is one of several papers that divides ecstasy users into a “heavy user” group and a “moderate user” group, and compares both to a non-user control group sampled from the same sub-culture. Extent of use in this paper is not defined by commutative exposure (either as number of occasions or tablets) but as number of tablets consumed within a specified period, so that the two groups are divided on frequency of use more than cumulative use. Hence this paper may not be strictly equivalent to other papers if differences in the impact of specific drug use parameters exist. While this study may benefit from using an all-male sample drawn from the same sub-culture, the multitude of comparisons performed by the authors may have introduced both Type I errors (false positives, from sheer number of comparisons) and Type II errors (false negatives, arising from number of analyses of covariance performed). It is notable that while extent of ecstasy use seems to be associated with performance in some areas (some tests of verbal and visual memory), simply using ecstasy seems to affect other areas of cognitive function measured (span on Corsi blocks, cortisol response to d-fenfluramine).
Wareing et al. (2000). Working memory deficits in current and previous users of MDMA (“Ecstasy”).


Purpose: Mood, cognitive function: To investigate whether changes in mood (affect) or cognitive function seen after ecstasy use are no longer present after continued abstinence from ecstasy use, or whether they remain after continued abstinence. Specific hypotheses tested – That both current and previous ecstasy users would not perform as well on a test of executive function (letter generation task) than would non-users; that current ecstasy users, former ecstasy users and non-users would differ in arousal (direction unspecified) and that ecstasy users would exhibit higher levels of anxiety than non-users.

Design: Non-experimental (retrospective) 3-group between-subjects (across groups) design comparing current ecstasy users and previous ecstasy users with non-user controls on psychometric measures and tests of cognitive function, with drug use (ecstasy use versus non-use) and time of use (current versus previous ecstasy use) as between-subjects variables. All subjects completed measures of anxiety, arousal and tests of cognitive function.

Subjects: 10 current ecstasy users, 10 previous ecstasy users and 10 non-users residing in England and recruited via “snowball technique” (direct contact with researchers and word of mouth through friends).

Matching – On gender, age and education.

Criteria for Inclusion, Ecstasy Users – Having regularly used ecstasy up 7 days prior to study day.

Previous Ecstasy Users – Abstinence from ecstasy for at least six months prior to study date and having regularly used ecstasy before abstinence. Non-users – No past or current use of any illicit drug, including ecstasy. All Groups – No other inclusionary or exclusionary criteria reported. All ecstasy users reported abstention from ecstasy for at least 7 days prior to study day, but it is unclear whether this was a requirement for study participation.

Drug Use Parameters – No information reported for lifetime use of ecstasy, either in occasions or tablets. Calculating from figures provided, current ecstasy users had taken ecstasy on an average of approximately 414.92 ± 138.644 occasions over a lifetime, (approximately 1348.49 tablets) and previous users had taken ecstasy on an average of approximately 376.74 ± 87.395 occasions (approximately 1280.92 tablets). The average dose per use, in tablets, was 3.25 ± .86 for current users and 3.4 ± 1.6 tablets for previous users. Frequency of ecstasy use was, on average, approximately 8.43 ± 3.33 times per month (101 ± 40.05 days a year) for current users and 8.05 ± 6.07 times per month for previous ecstasy users (96.6 ± 72.83 days per year). Duration of use was, on average, 49.2 ± 16.44 months for current users and 46.8 ± 14.4 months for previous users. Time since last use, in days, was (on average) 8.2 ± 5.75 days for current users and 323.25 ± 130.05 days for previous users. Other Drugs – Percentage of current and previous ecstasy users who had taken each drug: amphetamines, 70% current users, 60% previous users, cocaine, 0% current users, 10% previous users, LSD, 30% current users, 60% previous users, marijuana, 70% current users, 60% previous users. Non-users did not report using any of these drugs.

Group Demographics and Matched Variables – Current ecstasy users, previous ecstasy users and non-ecstasy users matched on gender, age and education. Current and previous ecstasy users approximately matched on use of other drugs. Gender, Actual numbers not reported, but authors state “each group had equal numbers of males and females,” meaning either that each group had a 5 / 5 gender ratio or that each group contained the same (but unequal) number of men to women (6 / 4, for example). Age. Average age of current ecstasy users = 22.2 ± 2.2: average age of previous ecstasy users = 22.6 ± 2.22: average age of non-users = 22.6 ± 2.12 (ranges not provided). Education Level, in years – Current users average education level = 12.2 ± 1.03: average education level of previous ecstasy users = 12.6 ± .84: average education of non-users = 12.3 ± .67. Other Variables – On average, current users rated own health (on
scale of 1 = very good to 5 = very poor), 2.8 ± 0.92, previous ecstasy users rated own health as 2.5 ± 0.85 and non-users rated own health as 1.7 ± 0.48.

**Measures:** State Anxiety and Arousal – Author-devised measures (previously used with normal healthy humans), specifically tailored to measure anxiety and arousal in experimental setting. Central Executive Function – Measured via consonant-generating task (Generate random string of consonants, without repeating sequence or alphabetic sequence, at set rate of 4, 2 or 1 seconds per letter. Scores were redundancy (frequency of each letter produced), number of letters produced per set and number of vowel intrusions.

Information Processing Speed – Measured via visual search / match to sample task (indicate whether 2 rows of letters are “same” or “different,” with rows growing increasingly longer), with scores for total number of rows classified and number classified correctly.

**Measures of Memory** – Measured via visual memory task (not described) and word span.

Measures of Cognitive Function, Other – Brook’s spatial matrix task (not described, either visual search or match to sample) and verbal fluency (not described, either estimated verbal IQ or crystallized intelligence (if vocabulary) or executive function (if word generation-FAS).

**Analyses:** State Anxiety and Arousal – Analysis not specifically stated: highly likely that either each measure was examined via 1-way ANOVA, with drug use (current ecstasy user, previous ecstasy user or non-user) as between-subjects factor or both were analyzed together via MANOVA, with drug use as a between-subjects factor and each score as dependent variable. Post-hoc comparisons were made via Tukey’s test (stated in paper).

Tests of Cognitive Function – Analysis specified only for test of central executive function and information processing speed, but probably used to analyze other measures as well. Tests of executive function measured via MANOVA with drug use (current ecstasy user, previous ecstasy user and non-user) as between-group variable and scale scores as dependent variables.

**Additional Analyses** – The effects of other variables on performance on tests of central executive function and information processing speed were examined via ANCOVA. Covariates included were: health self-rating, anxiety score, arousal score and use of LSD, marijuana and amphetamines (dummy coded, 1 if used, 0 if did not use), with each covariate entered separately. ANCOVAs applied to both information processing speed scores (number of rows classified, percentage correct) and to all 3 consonant production scores (number of letters generated, percentage redundant and vowel intrusions).

**Results – Significant Differences:** State Anxiety and Arousal – Current ecstasy users were more anxious than non-users; previous ecstasy users were more anxious than non-users and less anxious than current ecstasy users, but the difference between all 3 groups significant. Previous ecstasy users experienced greater arousal than current ecstasy users (non-users experienced an intermediate level of arousal, differences not significant).

Test of central executive function – Non-users had fewer vowel intrusions than either current or previous ecstasy users at all levels of production (4 s, 2 s and 1 s) (current ecstasy users ≥ previous ecstasy users > non-users). Non-users had a lower percentage of redundant letters and produced a greater number of words during the 1 s condition, with non-users < current ecstasy users ≤ previous ecstasy users).

Tests of Information Processing Speed – Non-users had a greater percentage of correct responses than either current or previous ecstasy users, but only at highest level of difficulty (longest rows).

**Additional Analyses** – Differences between ecstasy users and non-users on information processing speed scores and for letter production and percent redundant in consonant generation task regained after controlling for self-reported health rating, anxiety, arousal and use of LSD, marijuana and amphetamine. Group differences in arousal were still significant after controlling for the factors listed above.

**Results – No Differences Found:** Test of central executive function – While non-users had a lower percentage of redundant letters and produced more letters than either group of ecstasy users in the 4 s and 2 s conditions, these differences were not significant. Previous ecstasy users had a lower percentage of redundant letters than did current ecstasy users, but these differences were not statistically significant.
Information Processing Speed – Current ecstasy users, previous ecstasy users and non-users classified similar numbers of rows at all levels of difficulty and had a similar percentage of correct responses for all but the highest level of difficulty.

Measures of Memory – There were no differences between the 3 groups (current ecstasy users, previous ecstasy users or non-users) on scores on the visual memory task or the word span task.

Measures of Cognitive Function, Other – Current ecstasy users, previous ecstasy users and non-users all had similar scores on Brook’s spatial matrix task and in verbal fluency.

Additional Analyses – Group differences in vowel intrusions were no longer significant after controlling for all of the following factors: self-reported health score, anxiety, arousal, use of LSD, marijuana and amphetamines. Group differences in state anxiety were also reduced to below significance after controlling for all the factors listed above (excepting anxiety).

Overall Effects: Both previous and current ecstasy users did not perform as well as non-users on a consonant production task, described as a test of central executive function. However, differences between ecstasy users and non-users were only statistically significant when people were asked to generate 1 consonant per second. Current and previous ecstasy users had a higher rate of vowel intrusions across all rates of consonant generation (4 s, 2 s and 1 s rates). Non-users, current ecstasy users and previous ecstasy users had similar scores on a test of information processing speed. While all 3 groups were also equally accurate under conditions of low and intermediate difficulty, both current and previous ecstasy users were less accurate under condition of highest difficulty. Non-users, current ecstasy users and previous ecstasy users scored similarly on tests of verbal memory, visual memory, verbal fluency and visual search or matching to sample. Current ecstasy users reported the highest levels of state anxiety, previous ecstasy users an intermediate level of anxiety and non-users the lowest level of anxiety, though authors indicated that members of all 3 groups scored lower on anxiety than expected from previously established norms with healthy adults. Current ecstasy users reported the lowest level of arousal, non-users reported an intermediate level of arousal and previous users reported the highest level of arousal. Some of the group differences in vowel intrusion may have been due in part to differences in self-rated health, anxiety, arousal or extent of drug use (LSD, marijuana and amphetamine), since performing an analysis of covariance with these factors reduced group differences in vowel intrusion. Performing an analysis of covariance that includes self-reported health rating, arousal, LSD, marijuana and amphetamine use also reduced group differences in state anxiety. The authors’ first hypothesis was partially confirmed: current and previous ecstasy users did not perform as well as non-users on a test of executive function, but this was only true for the fastest rate of letter generation and for vowel intrusions at all rates of generation. While the authors’ second hypothesis was confirmed (current ecstasy users, previous ecstasy users and non-users differed on levels of state anxiety and arousal), the hypothesis was non-directional and hence easily confirmed by any form of group differences.

Comments: This paper is notable for its attempt to pinpoint the longevity of changes in affect and decrements in cognitive function seen after regular ecstasy use. The author also attempted to control for other potential confounding variables, such as use of other drugs, state arousal, and anxiety. The findings suggest that group differences in anxiety and increase in vowel intrusions in ecstasy users performing the letter generation task might both be due in part to factors other than ecstasy use. It is possible that the authors tried to perform too many analyses with a small number of subjects (10 per cell), especially in the series of ANCOVAs meant to detect the effects of potentially confounding variables. Though the authors do not highlight the point, it is surprising that they were unable to find group differences in visual or verbal memory. The sample size is small and caution should be used when generalizing from this study to the population at large.


Purpose: Cognitive function (Memory): To investigate whether continued ecstasy (MDMA) use produces progressive memory impairment over time in recreational users.

Design: Non-experimental (prospective but uncontrolled) 1-group within-subject design comparing drug-free ecstasy users at baseline and 1 year after baseline. All subjects completed measures of intelligence (WAIS-III Vocabulary and Block Design) and memory (RBMT) at baseline and again 12 months after baseline.

Subjects: 15 ecstasy users residing in the Toronto (Ontario, Canada) area, recruited via word-of-mouth and self-referred. Matching – Within-subjects design, so no comparison groups were employed. Criteria for Inclusion – Selection criteria for ecstasy use unspecified, but statistics on number of times ecstasy used suggests all subjects had to have used ecstasy at least once. No past or current major medical or psychiatric illnesses as assessed through medical history and psychiatric interview, and no history of migraine, eating disorders or dyslexia. Fluent English-speaking individual. Absence of positive drug screen for illicit or prescription psychoactive drugs and absence of alcohol dependence. At least 7 nights of 7-9 hours sleep, and abstinence from ecstasy for at least 2 weeks prior to study day, with compliance verified via urinary drug screen conducted at unspecified date (presumably on study day).

Drug Use Parameters - Ecstasy Use-At Baseline – Ecstasy users had taken ecstasy on an average of 19 occasions over a lifetime (1-55 occasions), taking an average of 1.2 tablets (117 mg) per occasion (.5-2.5 tablets). Average frequency of ecstasy use was 2.4 times per month (0-8 times per month), and duration of use was, on average, 18.4 months (1-60 months). Average time since last use, in days, was 42 days (14-168 days). Average monthly intake, in milligrams (calculated by multiplying usual dose by frequency of use) was reported at 280 mg (approximately 2.8 tablets) (50-2000 mg, or .5-20 tablets).

Ecstasy Use-Follow Up (12 months later) – Ecstasy users had taken ecstasy on an average of 55 occasions over a lifetime (3-225 occasions), taking an average of 1.75 tablets (175 mg) per occasion (.5-3 tablets). Average frequency of ecstasy use was reported at 2.4 times per month (0-15 times per month), and duration of use was, on average, 30.4 months (13-72 months). Average time since last use, in days, was 28 days (14-252 days). Average monthly intake, in milligrams (calculated by multiplying usual dose by frequency of use) was reported at 420 mg (approximately 4.2 tablets) (50-4500 mg, or .5-45 tablets).

Use of Other Drugs – 7/15 had used amphetamines at baseline, and 9 / 15 had used amphetamines at follow-up. 8 / 15 ecstasy users had used cocaine at baseline and 10 / 15 had used cocaine at follow-up. 1 / 15 had used a benzodiazepine at baseline, and 1 / 15 had used a benzodiazepine at follow-up. 5 / 15 had used a sedative hypnotic at baseline and 5 / 15 had used a sedative hypnotic at follow-up. 8 / 15 had used LSD or other hallucinogens at baseline and 10 / 15 had used LSD or other hallucinogens at follow-up. 14 / 15 had used cannabis at baseline and 15 / 15 (all subjects) had used cannabis at follow-up. 1 / 15 had used solvents or inhalants at baseline and 1 / 15 had used solvents / inhalants at follow-up. 6 / 15 had used opiates at baseline and 7 / 15 had used opiates at follow-up. 5 / 15 had used PCP or related drugs at baseline and 6 / 15 had used PCP or related drugs at follow-up. 14 / 15 had used alcohol at baseline and 14 / 15 had used alcohol at follow-up. 14 / 15 had used nicotine at baseline and 14 / 15 had used nicotine at follow-up.

Group Demographics and Matched Variables – No control groups participated in this study, so there are no matched variables. Gender, as M / F ratio – 12 / 3. Age – Ecstasy users were aged 17-31, and the modal age was 24.1. Education – On average, ecstasy users had received 14 years of education.

Measures: Measures of Intelligence – the Vocabulary and the Block Design tests from the WAIS-III. Vocabulary is a measure of verbal IQ, and block design is a measure of non-verbal (performance) IQ. Tests of Memory – The complete Rivermead Behavioral Memory Test battery. The RBMT contains tests of retrospective and prospective memory. Tests of Retrospective Memory – First and Second Name (Recall for name of person in photograph immediately after presentation and after delay), Pictures (Name objects in 10 pictures and select targets from set of 10 after filled delay), Story (Listen to and recall story immediately after presentation and again after delay) Faces (Select 5 target faces from set of 10, with filled delay between presentation and recall), Route (Retrace route within room immediately after presentation and again after delay). Tests of Prospective Memory – Belonging (Remember to ask for
The authors attempted to reduce the effects of erratic sleep patterns on performance by testing subjects only after subjects reported getting 7 to 9 hours sleep a night for at least 7 nights in a row. Analyses: Tests of Intelligence and Tests of Memory – A paired Student’s t-test was performed on the Vocabulary, Block Design and RBMT sub-test scores, with scores compared across administrations (at baseline and 12 months after baseline), with time of administration as a within-subjects factor, with t-tests compared using Cohen’s d.

Relationships between Cognitive Function and Drug Use Parameters – Change scores were calculated for each measure (follow-up – baseline) and each change score was correlated with drug use parameters (number of times used, frequency of use, duration of use, average dose per use and time since last use).

Results - Significant Differences Found: Tests of Memory – Overall RBMT significantly declined from baseline to follow up. Performance on each of the RBMT sub-tests either remained stable or declined across administration. Performance on Story-Immediate and Story-Delayed significantly declined from baseline to follow-up.

Relationships between Cognitive Function and Drug Use Parameters – Performance on the WAIS-Vocabulary declined with increasing frequency of ecstasy use (significant negative correlation between Vocabulary change score and frequency of use). Performance on the First and Second name RBMT sub-test was inversely correlated with total number of times ecstasy used, with lower scores on the First and Second Name task associated with increased number of occasions where ecstasy was used. Poorer immediate recall of Route was associated with a longer duration of ecstasy use (significant negative correlation between Route score and duration of use).

Results - No Significant Differences: Tests of Intelligence – There were no differences between performance at baseline and performance at follow-up for WAIS-III Vocabulary or WAIS-Block Design tests.

Tests of Memory – Though overall RBMT score declined from baseline to follow-up, individual test scores for the following tests were not significantly lower at follow-up when compared to baseline: First-Second Name, Belonging, Appointment, Pictures, Faces, Route-Immediate, Route-Delayed, or Message.

Relationship between Cognitive Function and Drug Use Parameters – Time elapsed since last use of ecstasy was not correlated with changes in performance on any test. There were no correlations between change scores for Block Design, Belonging, Appointment, Pictures, Story-Immediate, Story-Delayed, Faces, Route-Delayed or Message and any of the drug-use parameters measured (lifetime use, frequency of use, duration of use, days since last use).

Overall Effects: While performance on 2 selected measures of intelligence did not change after a year of continued ecstasy self-administration, level of performance on a measure of memory at follow-up had declined from the level measured at baseline. Ecstasy users had a lower total score on the RBMT at follow-up and their scores on all sub-tests of the RBMT either remained stable or declined from baseline to follow-up. When compared with performance at baseline, immediate and delayed recall for a short story declined at follow-up. However, there were no significant changes in performance from baseline to follow-up in any of the tests of prospective memory (such as remembering to request a borrowed belonging) or for either immediate or delayed recall of faces or pictures. Frequency of ecstasy use was related to changes in performance on WAIS-Vocabulary, with more frequent ecstasy use associated with poorer Vocabulary scores. Performance on First and Second Name was related to number of times ecstasy was used in a lifetime, with a greater number of exposures associated with poorer performance on First and Second Name. Immediate, but not delayed, recall for a route presented by the experimenter was inversely related to duration of ecstasy use, with longer duration of use associated with poorer immediate recall of the route.

Comments: To date, this is the first longitudinal study of the effects of continued ecstasy use on any one cognitive function. While the authors did not enroll participants in a controlled schedule of ecstasy or MDMA administration, they did assess memory after a year of unrestricted self-administration of ecstasy. The authors attempted to reduce the effects of erratic sleep patterns on performance by testing subjects only after subjects reported getting 7 to 9 hours sleep a night for at least 7 nights in a row. The within-
subjects design also allowed for some control of the effects of other drugs on performance, since drug use patterns remained fairly similar from baseline to follow-up. However, little is known about drug use parameters for other drugs, so it is possible that volume or frequency of other drugs used increased over time. Since duration, frequency and degree of ecstasy use were still chosen by the subjects themselves, the relationship between these drug use parameters and subsequent changes in performance on tests of memory or intelligence might be related to one or more pre-existing factors that might control level of ecstasy consumption and changes in test performance. This paper may be the first step toward conducting more prospective studies on the effects of ecstasy on cognitive performance.