

Research into the effects of MDMA in humans and in nonhuman animals continues to take place. None of the published reports appearing between December, 2008 and November, 2009 require a change in risk/benefit analysis in relation to trials with MDMA in a clinical setting. Two reports lend support to the existence of hypothesized therapeutic effects of MDMA. This review covers clinical trials of MDMA administration in humans, a naturalistic study of the effects of ecstasy (material represented as containing MDMA) and studies of ecstasy users.

1.0 Clinical Trials

Ten clinical trials of MDMA were published in the review period, including investigations into the behavioral effects, pharmacology and pharmacokinetics of MDMA, either alone or in combination with other intoxicants.

1.1 Studies Relating to Potentially Therapeutic Effects

Dumont and colleagues reported elevated blood oxytocin after administering 100 mg MDMA versus placebo in 12 men and 3 women (average age = 21.1 years) in a randomized, double-blind crossover study, with this large elevation in oxytocin peaking at 1.5 hours post-drug and returning to baseline 4 hours later (Dumont et al. 2009c). They found increased self-reported prosocial feelings (friendliness and gregariousness) in people with greater elevations of oxytocin, a hormone involved in physiological and social processes, including lactation and parturition, affiliation, bonding and trust (Bartz and Hollander 2006; Kosfeld et al. 2005). Bedi and colleagues used functional magnetic resonance imaging (fMRI) to assess brain activity after placebo, 0.75 and 1.5 mg/kg MDMA in seven men and two women (average age = 24 years) when viewing angry, fearful (frightened) and happy faces. Both doses of MDMA in this randomized, double-blind placebo-controlled study reduced amygdalar activity in response to angry faces, especially in the left amygdala, but only 1.5 mg/kg produced a significant reduction in amygdalar activity. (Bedi et al. 2009). It is notable that lower left amygdalar activity after 1.5 mg/kg MDMA was reported in a previous imaging study that did not involve viewing facial expressions (Gamma et al. 2000). Ventral striatal response to happy faces was greater after both doses of MDMA than placebo, though significant differences were only observed after the lower dose. Neither dose affected brain activity in response to fearful faces. Bedi and colleagues also assessed mood with Profile of Mood State (POMS) and subjective effects with visual analog scales, reporting increased self-reported sociability in both measures after both doses of MDMA. Taken together, both the studies above support changes in emotional or attentional response to others' emotional expressions and prosocial orientation that may help people build a stronger therapeutic alliance or confront emotionally upsetting memories or thoughts during psychotherapy.

1.2 Pharmacokinetics

Using periodic urinary sampling and verifying these methods with plasma sampling, Perfetti and colleagues sought to detect specific MDMA metabolites in eleven men and four women after 1.5 mg/kg MDMA (range 70-100 mg), and detecting four known metabolites and thioether conjugates (at 0.002%) (Perfetti et al. 2009), hypothesized to be neurotoxic in rodent and in vitro models (Jones et al. 2004). Slight variations in metabolite recovery were associated with genetic variations in functionality of the metabolic enzymes CYP2D6 and catechol-O-methyltransferase (COMT). Two studies conducted by Mueller and colleagues compared MDMA metabolism in adult male squirrel monkeys and humans (seven men and two women between the ages of 18-24 years), finding nonlinear pharmacokinetics in both species (Mueller et al. 2009a; Mueller et al. 2009b). These comparative studies demonstrate that MDMA produced similar plasma drug levels in both species, though with monkeys exhibiting a shorter half-life. As with previous studies in monkeys (Mechan et al. 2006) and rodents (Baumann et al. 2007; Baumann et al. 2009), this research indicates that non-human animal studies have consistently overestimated human equivalent doses. Barnes and colleagues examined detection of MDMA metabolites in sweat in ten men and five women given placebo, 1 and 1.6 mg/kg MDMA (Barnes et al. 2009).

1.3 Other Clinical Trials

Dumont and colleagues conducted randomized, double-blind crossover studies in two separate samples of 16 individuals to compare the effects of 100 mg MDMA alone and in combination with ethanol, publishing three reports on the combined drug effects of MDMA and ethanol (“alcohol”) (Dumont et al. 2008; Dumont et al. 2009b) and cannabis (Dumont et al. 2009a). The study comparing MDMA with cannabis enrolled 12 men and four women, average age 26.4 years, and the study of ethanol and MDMA enrolled nine men and seven women, average age 22.1 years. The effects reported are consonant with previous reports of acute physiological and psychological effects alone, and include increased cardiovascular effects and changes in mood and energy. In a functional magnetic imaging (fMRI) study in nine men and three women (average age 23.3 years), Ramaekers and colleagues assessed acute effects of MDMA on brain activity during a visual response inhibition task after administering 75 mg MDMA (Ramaekers et al. 2008). They reported that MDMA altered brain activity in the inferior parietal lobules and thalamus when people performed different components of the task, and that MDMA acutely impaired prospective recall (tracking trial numbers in order to know when to correctly inhibit response on a specific trial), and failure to inhibit responses correlated with plasma MDMA.

1.4 Adverse Events

In the study of the combined effects of MDMA and cannabis, one subject “felt unwell” without any corroborating physiological changes 30 minutes after MDMA alone, and 60 minutes after MDMA and cannabis, one participant experienced heart rate greater than 180 bpm for longer than 55 seconds after MDMA and cannabis, and another reported experiencing transient, mild hallucinations after MDMA and cannabis. Both these participants were excluded from further participation. As they describe either

psychological distress or cardiovascular effects, these adverse events are either expected effects of MDMA or may relate to the combination of MDMA and cannabis. One participant in the fMRI study stopped taking part in the study ten minutes after entering the scanner, presumably due to distress produced by the combination of the drug and scanner.

2.0 Naturalistic Study

A naturalistic study assessed and compared mood and cognitive function in 16 regular ecstasy users who chose to use ecstasy during the first study night and 16 regular ecstasy users who chose not to do so (Pirone and Morgan 2009), assessing participants on the night of use, one day later and four days later. Using ecstasy was associated with increased positive mood on the night it was used and increased negative mood the day after use that returned to baseline four days after use. The researchers failed to detect sub-acute effects of ecstasy use on immediate or delayed memory or decision-making tasks. Self-reported sleep quality on the night of use was related to performance on immediate and delayed memory tasks. Decision making, assessed via gambling task, was poorer at baseline and one day after ecstasy use, but performance was the same four days afterward.

3.0 Studies of Ecstasy Users

Nine reports compared people reporting regular use of ecstasy with controls reporting no ecstasy use. Seven studies were retrospective comparisons (Boland et al. 2009; Carhart-Harris et al. 2009; Cowan et al. 2009; Karageorgiou et al. 2009; McCann et al. 2009; Raj et al. 2009; Selvaraj et al. 2009), and one study reported on the presence of self-reported electric shock-like sensations in some ecstasy users (Boland et al. 2009). Two prospective studies in the same or nearly similar samples were published as well (Schilt et al. 2009a; Schilt et al. 2009b). Retrospective studies examined brain structure and function, cognition and self-reported symptoms through a variety of means, and included measuring markers of potential brain injury (Cowan et al. 2009), measuring estimated serotonin transporter sites (Selvaraj et al. 2009), functional MRI (Karageorgiou et al. 2009; Raj et al. 2009), assessing sleep architecture with electroencephalography (Carhart-Harris et al. 2009), assessing cognitive function after sleep deprivation (McCann et al. 2009), or examining somatic complaints in a subset of ecstasy users (Boland et al. 2009). It should be noted that the same research team performed three of the four imaging studies (Cowan et al. 2009; Karageorgiou et al. 2009; Raj et al. 2009). The two prospective studies examined behavioral impulsivity in a sample of people expressing an interest in taking ecstasy prior to and again after some had self-administered the drug (Schilt et al. 2009a) and the impact of genetic variations in MDMA metabolism on memory in a similar sample before and after ecstasy use (Schilt et al. 2009b). Given that retrospective studies compare individuals reporting repeated use of a substance of unknown identity, and that most are polydrug users, findings from these studies can best be considered as marking the upper limits of risk estimation for clinical trials of MDMA.

Findings included failure to find group differences in serotonin transporter levels (Selvaraj et al. 2009), failing to detect any impact of acute tryptophan depletion on sleep in male ecstasy users (Carhart-Harris et al. 2009), detecting group differences relating to cannabis use, but not ecstasy use, in a marker of brain injury or repair associated with cannabis use (Cowan et al. 2009), detecting group differences attributed to ecstasy use in some areas of brain activity or cognitive function, but not others (Raj et al. 2009), and detecting differential effects of sleep deprivation on cognitive function of ecstasy users versus non-users (McCann et al. 2009). Previous reports have also reached a similar array of findings, including both detecting and failing to detect long-term effects of ecstasy use. In the first prospective study, Schilt and colleagues reported that greater impulsivity at baseline predicted later ecstasy use in women but not men (Schilt et al. 2009a). In their second prospective study, they reported a trend for a smaller retest (or learning) effect on a verbal memory task in participants who chose to use ecstasy after low to moderate use, particularly those with two of three variations in the catechol-O-methyl-transferase (COMT) gene (Schilt et al. 2009b). It is notable that owing to the prospective study design, participants were not matched for genotype.

None of the reports appearing in the literature between December 2008 and November 2009 change estimated risk/benefits ratio for MDMA.

4.0 References

- Barnes AJ, De Martinis BS, Gorelick DA, Goodwin RS, Kolbrich EA, Huestis MA (2009) Disposition of MDMA and metabolites in human sweat following controlled MDMA administration. *Clin Chem* 55: 454-62
- Bartz JA, Hollander E (2006) The neuroscience of affiliation: forging links between basic and clinical research on neuropeptides and social behavior. *Horm Behav* 50: 518-28
- Baumann MH, Wang X, Rothman RB (2007) 3,4-Methylenedioxymethamphetamine (MDMA) neurotoxicity in rats: a reappraisal of past and present findings. *Psychopharmacology (Berl)* 189: 407-24
- Baumann MH, Zolkowska D, Kim I, Scheidweiler KB, Rothman RB, Huestis MA (2009) Effects of dose and route of administration on pharmacokinetics of (+ or -)-3,4-methylenedioxymethamphetamine in the rat. *Drug Metab Dispos* 37: 2163-70
- Bedi G, Phan KL, Angstadt M, de Wit H (2009) Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology (Berl)*
- Boland B, Mitcheson L, Wolff K (2009) Lhermitte's sign, Electric shock sensations and high dose ecstasy consumption: preliminary findings. *J Psychopharmacol*
- Carhart-Harris RL, Nutt DJ, Munafò MR, Christmas DM, Wilson SJ (2009) Equivalent effects of acute tryptophan depletion on REM sleep in ecstasy users and controls. *Psychopharmacology (Berl)* 206: 187-96
- Cowan RL, Joers JM, Dietrich MS (2009) N-acetylaspartate (NAA) correlates inversely with cannabis use in a frontal language processing region of neocortex in MDMA (Ecstasy) polydrug users: a 3 T magnetic resonance spectroscopy study. *Pharmacol Biochem Behav* 92: 105-10

- Dumont G, Kramers C, Sweep F, Touw D, van Hasselt J, de Kam M, van Gerven J, Buitelaar J, Verkes R (2009a) Cannabis Coadministration Potentiates the Effects of "Ecstasy" on Heart Rate and Temperature in Humans. *Clin Pharmacol Ther*
- Dumont G, Kramers C, Sweep F, Willemsen J, Touw D, Schoemaker R, van Gerven J, Buitelaar J, Verkes R (2008) Ethanol co-administration moderates 3,4-methylenedioxymethamphetamine effects on human physiology. *J Psychopharmacol*
- Dumont G, Schoemaker R, Touw D, Sweep F, Buitelaar J, van Gerven J, Verkes R (2009b) Acute psychomotor effects of MDMA and ethanol (co-) administration over time in healthy volunteers. *J Psychopharmacol*
- Dumont GJ, Sweep FC, van der Steen R, Hermsen R, Donders AR, Touw DJ, van Gerven JM, Buitelaar JK, Verkes RJ (2009c) Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci* 4: 359-66
- Gamma A, Buck A, Berthold T, Liechti ME, Vollenweider FX (2000) 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [¹⁸F]-PET in healthy humans. *Neuropsychopharmacology* 23: 388-95
- Jones DC, Lau SS, Monks TJ (2004) Thioether metabolites of 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine inhibit human serotonin transporter (hSERT) function and simultaneously stimulate dopamine uptake into hSERT-expressing SK-N-MC cells. *J Pharmacol Exp Ther* 311: 298-306
- Karageorgiou J, Dietrich MS, Charboneau EJ, Woodward ND, Blackford JU, Salomon RM, Cowan RL (2009) Prior MDMA (Ecstasy) use is associated with increased basal ganglia-thalamocortical circuit activation during motor task performance in humans: an fMRI study. *Neuroimage* 46: 817-26
- Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E (2005) Oxytocin increases trust in humans. *Nature* 435: 673-6
- McCann UD, Wilson MJ, Sgambati FP, Ricaurte GA (2009) Sleep deprivation differentially impairs cognitive performance in abstinent methylenedioxymethamphetamine ("ecstasy") users. *J Neurosci* 29: 14050-6
- Mechan A, Yuan J, Hatzidimitriou G, Irvine RJ, McCann UD, Ricaurte GA (2006) Pharmacokinetic profile of single and repeated oral doses of MDMA in squirrel monkeys: relationship to lasting effects on brain serotonin neurons. *Neuropsychopharmacology* 31: 339-50
- Mueller M, Kolbrich-Spargo EA, Peters FT, Huestis MA, Ricaurte GA, Maurer HH (2009a) Hydrolysis of 3,4-methylenedioxymethamphetamine (MDMA) metabolite conjugates in human, squirrel monkey, and rat plasma. *Anal Bioanal Chem* 393: 1607-17
- Mueller M, Kolbrich EA, Peters FT, Maurer HH, McCann UD, Huestis MA, Ricaurte GA (2009b) Direct comparison of (+/-) 3,4-methylenedioxymethamphetamine ("ecstasy") disposition and metabolism in squirrel monkeys and humans. *Ther Drug Monit* 31: 367-73
- Perfetti X, O'Mathuna B, Pizarro N, Cuyas E, Khymenets O, Almeida B, Pellegrini M, Pichini S, Monks TS, Lau SS, Farre M, Pascual JA, Joglar J, de La Torre R

- (2009) Neurotoxic Thioether Adducts of Mdma Identified in Human Urine after Ecstasy Ingestion. Drug Metab Dispos
- Pirona A, Morgan M (2009) An investigation of the subacute effects of ecstasy on neuropsychological performance, sleep and mood in regular ecstasy users. J Psychopharmacol
- Raj V, Liang H, Woodward N, Bauernfeind A, Lee J, Dietrich M, Park S, Cowan R (2009) MDMA (ecstasy) use is associated with reduced BOLD signal change during semantic recognition in abstinent human polydrug users: a preliminary fMRI study. J Psychopharmacol
- Ramaekers JG, Kuypers KP, Wingen M, Heinecke A, Formisano E (2008) Involvement of Inferior Parietal Lobules in Prospective Memory Impairment during Acute MDMA (Ecstasy) Intoxication: An Event-Related fMRI Study. Neuropsychopharmacology
- Schilt T, Goudriaan AE, Koeter MW, van den Brink W, Schmand B (2009a) Decision making as a predictor of first ecstasy use: a prospective study. Psychopharmacology (Berl) 203: 519-27
- Schilt T, Koeter MW, de Win MM, Zinkstok JR, van Amelsvoort TA, Schmand B, den Brink W (2009b) The effect of Ecstasy on memory is moderated by a functional polymorphism in the catechol-O-methyltransferase (COMT) gene. Eur Neuropsychopharmacol 19: 116-24
- Selvaraj S, Hoshi R, Bhagwagar Z, Murthy NV, Hinz R, Cowen P, Curran HV, Grasby P (2009) Brain serotonin transporter binding in former users of MDMA ('ecstasy'). Br J Psychiatry 194: 355-9