New MDMA Research at the 65th Annual Meeting of the College on Problems of Drug Dependence (CPDD) – June 14-19, 2003, Sheraton Bal Harbour, Miami, Florida

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If you've ever been to LA and you picture it your mind, you just need to add some New York and Latin American accents and you've got Miami, Florida. As a fog-addled denizen of the San Francisco Bay Area, fond as I am of hot coffee and democracy, it took a science conference to bring me to the Sunshine State. And what a conference. The annual meeting of the College on Problems of Drug Dependence is *the* conference for seeing and showing results relating to research on illicit drug use. And this year's conference was rich with preliminary results from studies of MDMA. Choosing which of the many MDMA presentations I should summarize in this limited space was difficult. Here are just a few of the many interesting studies.

M. Tancer of Wayne State University in Detroit presented data from the first few volunteers in an ongoing study of the effects of ambient temperature on people on MDMA. Healthy volunteers were given 2.0 mg/kg MDMA (about 140 mg, probably similar to one-and-a-half or two ecstasy pills) or placebo. So far, it looks like you get similar small body temperature increases from taking 2.0 mg/MDMA in a cold (18° C, or 64° F) room as in a warmer (30° C/86° F) room. Assuming subsequent volunteers show the same pattern, this suggests moderate doses of MDMA do not produce the difficulty regulating body temperature seen in several studies of rats were given MDMA. One possible explanation is that humans are less vulnerable to body temperature changes than rats because humans can remove any fur we are wearing, can sweat, and have high surface-to-volume ratios. However, it is also possible that the dose of MDMA was too low to derange body temperature aside from a slight rise due to vasoconstriction. In a rat study, Dafters (1994) found that 2.5 mg/kg MDMA produced an apparent similar rise in temperature in either warm (29° C/84° F) or cold (11° C/52° F) settings. Higher doses of 5.0 or 7.5 mg/kg were needed to make the animals become cold in the cold setting or hot in the normal setting. The importance of all this research is that increased body temperature can strain the body, possibly increasing risk of toxicity. Many deaths and serious adverse events in ecstasy users involve high (> 38° C/100° F) body temperature and we don't really know how much these cases are due to putative risk factors like too much dancing and too little water. So far, Tancer's ongoing study seems likely to confirm that moderate doses of MDMA do not impair regulation of body temperature in most people and that humans are not more sensitive than rats to this drug effect.

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laborators from the French Monitoring Centre on Drugs and Drug Abuse described results from a large French drug analysis program called SINTES (Système National d'Identification des Toxiques et Substances). The program obtains samples from both social/health workers and law enforcement and analyzes them with GC/MS and HPLC techniques. Of 1369 samples obtained from social/health workers, 97% were thought by submitters to contain MDMA. In reality, 83% contained MDMA and 5% contained amphetamines or MDMA-like compounds. There was wide variability in doses with only 2% of MDMA pills containing more than 100 mg MDMA. Average dose per pill appeared to be decreasing over time. Samples contained 74 =B1 18 mg MDMA in 2000, 63 =B1 14 mg MDMA in 2001, and 58 =B1 13 mg MDMA in 2002. If this trend is true in other European countries, it may have important implications for understanding studies of ecstasy users, who often seem to be taking more tablets than appeared common several years ago. More information of the SINTES program can be found on their website: http://www.ofdt.fr/BDD/sintes.

R.V. Irvine from the University of Adelaide, Australia presented preliminary data from an ongoing study measuring MDMA concentrations, biological changes, and physical changes in 24 ecstasy users before, during, and/or after a rave. Blood samples taken after the rave showed plasma concentrations of MDMA that were often around 0.3 mg/L MDMA. However, several participants had plasma concentrations that were above 0.75 mg/L MDMA. Previously, levels this high have only been documented in emergency medicine settings. These high drug levels are even more impressive when one considers they were seen the morning after the rave and that peak plasma concentrations may have been approximately twice as high. Heart rate and blood pressure were elevated in the morning, although not to a degree that would be inherently dangerous in a healthy individual. MDMA plasma concentrations were significantly correlated with body temperature (measured using the tympanic membrane in the ear), which was at or above 38ºC in two participants during morning measurements. Obviously, exercise may have contributed to all these physiological changes. These data suggest that at least some experienced users can tolerate high MDMA concentrations without clinically significant changes in physiology and that other factors such as drug combinations, behavioral or environmental conditions may be important in precipitating the acute adverse event seen in some users.

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R. de la Torre of the Institut Municipal d'Investigación Médica in Barcelona gave a comprehensive overview of the work he and his colleagues at the Universitat Autonoma de Barcelona have been conducting on the human pharmacology of MDMA. Recent studies have explored the effects of giving two doses of 100 mg MDMA, either four or twenty-four hours apart. Even though people notice fewer effects from the second dose than the first, the second dose is less metabolized than the first. As a result, MDMA exposures (measured as the area under the drug concentration vs. time curve) are about 20 to 30% higher after the second 100 mg MDMA dose than you would expect based on the first. There is less formation of at least one metabolite, 4-hydroxy-3-methoxy-methamphetamine,

which suggests that liver enzymes were inhibited by the first MDMA dose. Previous studies (e.g. Delaforge et al. 1999) using liver tissue have indicated that MDMA inhibits an enzyme called CYP2D6 (which is short for "cytochrome P450 isozyme 2D6"). De la Torre's presentation suggests this inhibition of CPY2D6 lasts more than 24 hrs after MDMA, which means people may have altered metabolism of some drugs (such as codeine) the day after MDMA. Because CYP2D6 is inhibited after MDMA, the enzyme appears less important in MDMA metabolism than researchers once thought. People with low CYP2D6 activity (about 10% of Caucasians are like this due to genetics) thus no longer seem likely to be at significantly increased risk of acute adverse events after MDMA (see also: Gilhooly & Daly 2002; O'Donohoe et al. 1998; Schwab et al. 1999). (How CYP2D6 activity influences risks of chronic toxicity remains difficult to assess.)

E. Tella of the Drug Enforcement Administration had a poster presentation summarizing his agency's concerns with the research chemicals AMT (alpha-methyl-tryptamine), 5-MeO-DIPT (5-methoxy-dipropyltryptamine) and the combination of BZP (benzylpiperazine) and TFMPP (3-trifluoromethylphenylpiperazine). He indicated that, in addition to emergency department visits and deaths, drug seizures are an important indicator the agency uses in assessing which research chemicals are significant problems. Because the agency generally seizes compounds in the course of fighting trafficking of scheduled drugs (like MDMA), this suggests that unscheduled compounds are more likely to become scheduled if unscrupulous people sell them as "ecstasy".

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All in all it was an interesting conference. Of course, like most conferences, the real action was the informal schmoozing in the halls. I heard about a lot of interesting findings and rumors. I hope that some of these data actually get presented at next year's conference. ■

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