Continuing Review: Literature Review 2 December 2008
Protocol # 63,384

Seven clinical trials with MDMA studies appeared in peer-reviewed journals since the last review of the literature (Bouso et al. 2008; Dumont et al. 2008; Hasler et al. 2008; Kolbrich et al. 2008a; b; Kuypers et al. 2008; O'Mathuna et al. 2008) The majority of these human studies replicated and extended previously reported findings. None of these studies has generated data that changes our risk/benefit calculations.

In the study with the greatest relevance to the investigation under review, Bouso and colleagues reported findings from six women rape survivors with PTSD who received up to 75 mg MDMA in a therapeutic setting as part of a MAPS-sponsored study that was halted in 2002 due to political considerations (Bouso et al. 2008). Though they did not perform statistical analyses, the researchers observed a greater reduction in anxiety and symptomatic improvement after MDMA than after placebo, and concluded that MDMA in doses up to 75 mg could be safely administered to people with PTSD.

Hasler and colleagues reported that co-administering the 5HT1A antagonist and beta blocker pindolol along with MDMA to eight men changed very few subjective effects aside from reducing feelings of "dreaminess" and reduced positively experienced derealization (pleasant feelings of being "in a dream") (Hasler et al. 2008). In two separate studies, Kolbrich and colleagues examined the subjective effects and pharmacokinetics of 1 and 1.6 mg/kg MDMA (Kolbrich et al. 2008a; b). Kolbrich and colleagues reported results comparable to those in previous reports for the subjective and physiological effects of MDMA in six men and two women, though with some differences, as less self-reported impaired ability to concentrate (Kolbrich et al. 2008a). Subjective effects from 1.6 mg/kg lasted longer than from 1 mg/kg. They indicated that there was only a slight correlation between self-reported subjective effects and plasma MDMA values (Kolbrich et al. 2008). In a study in ten men and seven women, the same research team confirmed that MDMA has nonlinear pharmacokinetics (Kolbrich et al. 2008b), findings first reported by de la Torre et al. in an all-male sample (de la Torre et al. 2000). They reported MDMA half-life to be seven to eight hours, a value similar to that reported in prior research (de la Torre et al. 2004). They also reported gender differences in peak plasma MDMA and metabolites, with higher peak MDMA and MDA and lower HMMA in women than in men.

O'Mathuna and colleagues studied the ability of 1.5 mg/kg (approximately 105 mg) MDMA to inhibit the metabolic enzyme P450 CYP2D6 in 15 men by assessing changes in metabolism of dextromethorphan and examined the effects of MDMA on caffeine metabolism to assess the effects of MDMA on another enzyme, CYP1A2 (O'Mathuna et al. 2008). MDMA did not alter caffeine metabolism, but the researchers reported that the MDMA-altered ratio of dextromethorphan to its metabolite dextorphan suggest that MDMA substantiallyinhibits CYP2D6 function, with an enzyme recovery half-life up to 46 hours. Kuypers and Ramaekers published their second study on the effects of an initial dose of 75 mg MDMA given in the evening and followed four hours later by 50 mg MDMA (Kuypers et al. 2008), assessing effects on mood and acute impairment of spatial

and verbal memory assessed over the night in seven men and seven women. They found that nocturnally administered MDMA had similar effects on mood and memory to diurnally administered MDMA (Kuypers and Ramaekers 2005; 2007), and that sleep deprivation contributed independently to reduced spatial memory. Participants in all studies tolerated administration of doses of up to 150 mg MDMA.

Dumont and colleagues compared the effects of 100 mg MDMA, a blood alcohol level (BAC) of 6% and both combined on attention, decision-making and memory in eight men and six women (Dumont et al. 2008), reporting findings similar but not identical to previous investigations of MDMA and ethanol (Hernandez-Lopez et al. 2002; Ramaekers and Kuypers 2006). They found that MDMA and ethanol independently contributed to acute memory impairment, while each substance interfered with the effects of the other on one attention task.

Parrott and colleagues conducted a naturalistic (quasi-experimental) study comparing activity, body temperature and salivary cortisol in eight men and four women attending a nightclub at a time when they took ecstasy and a time when they did not (Parrott et al. 2008). They found a non-significant increase in body temperature and a significant increase in salivary cortisol that is far larger than recorded in clinical trials (see for example Harris et al. 2002; Mas et al. 1999). Participants experienced more hot or cold flushes after MDMA that were unrelated to changes in body temperature.

Twenty-two retrospective or longitudinal reports described findings from retrospective studies in ecstasy users, with nearly every study presenting results that have appeared elsewhere before. In most cases, participants reported an average cumulative use greater than 20 times. Twelve studies assessed cognitive function (Bedi and Redman 2008a; b; Clark et al. 2008; de Sola Llopis et al. 2008; de Sola et al. 2008; Fisk and Montgomery 2008; Hanson et al. 2008; Indlekofer et al. 2008; McCann et al. 2008; Moeller et al. 2007; Montgomery and Fisk 2008; Schilt et al. 2008), five assessed psychological well-being (Bedi et al. 2008; Craig et al. 2008; Falck et al. 2008; Loxton et al. 2008; Soar et al. 2008), and four examined brain structure or function with imaging or with evoked response potentials (ERP), a type of averaged electroencephalography (de Sola et al. 2008; de Win et al. 2008b; McCann et al. 2008; Moeller et al. 2007). As has continued to be the case, the relationship between ecstasy use and impaired cognitive function is stronger than that between ecstasy use and long-term changes in psychological function. Four of seven studies found impaired memory or working memory in ecstasy users (Fisk and Montgomery 2008; Indlekofer et al. 2008; Montgomery and Fisk 2008; Schilt et al. 2008), two studies found group differences that were either non-significant or had a small effect size (Bedi and Redman 2008a; McCann et al. 2008), and a third found that while ecstasy users did less well than non-drug users, their performance was not significantly different from that of cannabis users (de Sola et al. 2008). Bedi and Redman also reported that polydrug users who did and did not use ecstasy reported more memory failures than non-drug user controls. Performance on objective tests of memory was only sometimes related to self-reported memory, with self-reported memory assessment adding little predictive value in detecting actual memory impairment (Bedi and Redman 2008b). Researchers reported findings supporting and failing to support differences in executive

function and impulsivity (Clark et al. 2008; de Sola Llopis et al. 2008; Fisk and Montgomery 2008; Hanson et al. 2008; Loxton et al. 2008; Montgomery and Fisk 2008; Schilt et al. 2008). For instance, Clark and colleagues found cannabis and not ecstasy users gathered less information before making a decision, yet lifetime and average weekly dose of ecstasy were inversely (negatively) related to updating from information gathered (Clark et al. 2008). In contrast, a study comparing ecstasy users to people reporting no illicit drug use found ecstasy users took longer to gravitate toward an advantageous decision (Moeller et al. 2007). Researchers continue to report findings supporting a role for polysubstance use as playing a role in differences between ecstasy users and controls (Bedi and Redman 2008a; de Sola et al. 2008; Hanson et al. 2008).

All four studies of psychological well-being or psychological problems in ecstasy users found that polysubstance use in general or use of one or more other substances was associated with impaired psychological well-being (Bedi et al. 2008; Craig et al. 2008; Falck et al. 2008; Soar et al. 2008). One team found a stronger association between ecstasy use and depression symptoms in people reporting over 50 uses, but no such association in anyone reporting more moderate use (Falck et al. 2008). Polydrug use and not ecstasy use was associated with anxiety and depression in another sample (Bedi et al. 2008). A third study supports at least one pre-existing factor, less parental warmth, as leading to increased psychological problems in ecstasy users (Craig et al. 2008). The fourth detected an association between several substances, including ecstasy use, and self-reported psychological problems (Soar et al. 2008).

Two studies using imaging to estimate numbers of serotonin reuptake (SERT) sites reported that when compared with non-ecstasy users, ecstasy users reporting an average lifetime dose between 95 and 322 occasions had fewer SERT sites (de Win et al. 2008b; McCann et al. 2008), but that the two groups did not differ with respect to estimated numbers of dopamine sites (McCann et al. 2008). One of the two reports also used magnetic resonance spectroscopy (MRS) to detect chemical markers of neuronal injury and failed to find any in the same sample with numbers of SERT sites (de Win et al. 2008b). McCann and colleagues reported an association between lower levels of estimated SERT sites in specific frontal and parietal areas and poorer verbal memory performance in ecstasy users and controls, but also found that group differences in cognitive function, while present, were not statistically significant (McCann et al. 2008). A study using diffusion tensor imaging with fractional anisotropy (DFI with FA) to assess indications of neuronal injury failed to find differences in FA for ecstasy users and controls, but detected a difference in (smaller lambda1) in regions of the corpus collosum (Moeller et al. 2007). An assessment of a form of the P3 auditory ERP in ecstasy users, cannabis users and people without any illicit drug use found no group differences in P3 amplitude, yet detected an association between lifetime cannabis use and more rapid P3 appearance (de Sola et al. 2008).

A neuroendocrine challenge with citalopram failed to find any signs of blunted cortisol or prolactin in ecstasy users when compared to cannabis users or controls reporting no illicit drug use (Allott et al. 2008). Current ecstasy users reported worse sleep quality than non-ecstasy users on an online survey, and while the difference between self-reported sleep

quality in former users and non-ecstasy users was in the same direction, it was not statistically significant (Carhart-Harris et al. 2008). Pooling data from their previous studies, Montgomery and colleagues found no effect of self-reported fatigue on working tests of working memory, though ecstasy users reported greater tiredness at the start of testing (Montgomery et al. 2007). A study in ecstasy users, cannabis users and people without a history of illict drug use did not find any group differences in signal-averaged electrocardiography (Kanneganti et al. 2008).

One prospective study examined the brains of people before and after they used an average of six ecstasy tablets as compared to people who did not use ecstasy during the same 12 to 36 month interval (de Win et al. 2008a). The study used multiple methods of assessment, including single photon emission spectography (SPECT) to image serotonin transporter sites, MRS, and DFI with FA to detect indications of neuronal injury or repair. De Win and colleagues failed to find reduced serotonin uptake sites or markers of neuronal injury after ecstasy use, but found reduced fractional anisotropy in the thalamus that was within the normal range for the population but statistically significant. The researchers did not correct for number of tests, increasing the possibility of this being a chance finding. These findings are also interesting when contrasted with those of Moeller and colleagues described above.

There were approximately 60 studies of MDMA in vitro or in animals, most either examining one or more pharmacological mechanism of action of MDMA or addressing one or more hypothesized mechanism of action for MDMA neurotoxicity after multiple or high doses of MDMA. Nearly two years after the initial publication first suggesting that the interspecies scaling formula for computing human-equivalent doses of MDMA over-estimated dose equivalence (Mechan et al. 2006), a second study by the same research team confirmed this in squirrel monkeys (Mueller et al. 2008), strongly suggesting that most studies of MDMA neurotoxicity in nonhuman primates employed inappropriately high doses of MDMA. As well, researchers studying effects of MDMA on tactile receptors in rats also confirmed nonlinear pharmacokinetics in this species, finding that a dose of 3 mg/kg was closer to human dose equivalence (Starr et al. 2008).

Other studies that may have import on assessment of the literature or that report new findings are described below, though their import to humans remains uncertain. A series of experiments in rats attempting to control for metabolism, body temperature, and degree of oxidative stress in rats found that sustained elevations in body temperature and MDMA metabolism independently played roles in reducing brain serotonin (Goni-Allo et al. 2008). A study in monkeys using pretreatment with serotonin and norepinephrine uptake inhibitors suggests that norepinephrine release or reuptake may be at least partially involved in producing acute impairments in spatial learning (Verrico et al. 2008). Increased activity after injections of 1 mg/kg followed an hour later by 3 mg/kg MDMA in rats was associated with increases in brain serotonin and dopamine as measured by within-brain microdialysis (Baumann et al. 2008), and a study in mice reported possible involvement of 5HT2B receptors in MDMA-related increased activity (Doly et al. 2008). When compared with MDMA alone, the addition of levo-thyroxine in monkeys significantly increased elevation in body temperature in monkeys, but did not

make MDMA more appealing (Banks et al. 2008). Replicating findings from another rat strain (Koenig et al. 2005), Fonsart et al reported a higher LD50 for MDMA in male versus female Sprague-Dawley rats and found differences in MDMA metabolism, including greater plasma MDMA in female rats (Fonsart et al. 2008). Another study examining rats seven days after one or 20 daily doses of MDMA reported lower testosterone levels (Dickerson et al. 2008). One study reported cardiac tissue damage after fairly high dose regimen of 9 mg/kg injected on four consecutive days (Shenouda et al. 2008).

None of the publications appearing in the literature between December 2007 and November 2008 change the risk/benefit ratio for receiving MDMA in a therapeutic setting and for participating in this study. MDMA continues to be safely administered in a clinical research context. Evidence for long-term effects of ecstasy remains, but studies also suggest that risk of exposure to MDMA within a research or medical setting is low.

There will be no more drug administration in this study, with the only further participation being a long-term follow-up questionnaire.

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