MAPS' MDMA Investigator's Brochure
Update #2
A Review of Research in Humans and Non-Human Animals

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A Review of Original Research and Quantitative Reviews of MDMA

Introduction

The pharmacology and effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") continue to be a topic of interest for medical and neuroscience researchers. Approximately 130 original research studies and one quantitative (meta-analytic) review of the nature and effects of MDMA have been published since the completion MAPS' second yearly review of the literature (Jerome and Baggott 2003). Published reports include trials of MDMA in humans, studies of Ecstasy users, studies in non-human animals (mostly rodents and non-human primates) and in vitro studies. The current review covers nearly all English-language original research papers appearing between January 2003 and late February to early March, 2004. As was the case with the earlier update, this review is chiefly concerned with studies relevant to estimating risks to human participants in trials of MDMA. This review does not cover studies of Ecstasy user demographics and studies in non-human animals relating to drug discrimination or pharmacology when it does not directly inform risk estimation in humans. Other recent reviews have tackled the pharmacological and neuropharmacological literature in non-human animals, either specifically (Cole and Sumnall 2003B) or in the context of a general review (Green et al 2003B), and those wishing to read more about pharmacology, acute behavioral effects of MDMA in rodents, or drug-discrimination studies may turn to these reviews. While most papers covered in this review were published between 2003 and 2004, I reviewed some papers that fell outside this time period. Exceptions to the March, 2004 cut-off date were made for clinical trials (Farre et al. 2004) and a few studies in Ecstasy users (Halpern et al. 2004; McCardle et al. 2004). In a very small percentage of papers, nearly all of them case reports, only the abstract could be located at the time of writing the review. Many of the research reports reviewed appeared in a single issue of Psychopharmacology specifically devoted to MDMA. While the issue appeared in print in 2004, a large number of papers were electronically published before then.

Nearly all studies were located through the use of the PubMed database maintained by the National Institute of Health. This is a searchable database containing citations and abstracts of papers appearing in a large number of scientific journals. In some cases, researchers sent their work upon request, and in other cases, researchers informed me of the existence of specific papers.

The first comprehensive literature review commissioned by MAPS was completed in August, 2001, (Baggott et al. 2001), and focused on research that might inform human trials with MDMA. This literature review, also referred to as the "Investigator's Brochure," or IB, covered all clinical trials of MDMA, a summary of early use by psychotherapists, retrospective studies of the effects of Ecstasy (material purported to contain MDMA), research investigating MDMA neurotoxicity in non-human animals and in humans, and an examination of case reports of adverse events in Ecstasy users. This review did not cover behavioral research on the acute effects of MDMA in non-human animals.

An examination of all information available at the time of completion led us to conclude that human participants faced minimal risk in clinical trials of MDMA given at doses in the range of 125 mg. No serious adverse events had been reported during any of the trials conducted, and both drug-naïve and experienced participants tolerated MDMA at doses ranging from 16.6 mg (0.25 mg/kg in Grob et al., Unpublished) to 204 mg (2.5 mg/kg, Grob et al. Unpublished).

The second review of the literature covered the period after August 2001 to early 2003, and was completed in January, 2003 (Jerome and Baggott 2003). Unlike the initial review, the second yearly review only covered clinical trials, studies in Ecstasy users, and studies of neurotoxicity and toxicity in vitro and in non-human animals. It did not review studies of Ecstasy user demographics or case reports of adverse events. Clinical trials published in this period included investigations using doses that ranged from approximately 35 mg (0.5 mg/kg, Harris et al. 2002) to 171 mg (2 mg/kg, on average approximately 145 mg, Tancer et al. 2003, in press at the time of completion). Conclusions concerning the safety of clinical trials with MDMA remained the same, with two exceptions. When the second review was completed, it was apparent that the association between Ecstasy use and impaired psychological well-being, (such as increased dysphoria, psychological complaints, aggressiveness), while still present, might be due at least in part to factors other than Ecstasy use. Possible causes of the association included pre-existing conditions (Lieb et al. 2002) and polysubstance abuse itself (Daumann et al. 2001). Second of all, a study reporting dopamine toxicity in non-human primates raised concerns that MDMA might possess dopamine toxicity (Ricaurte et al. 2002). The 2002 update to the IB concluded that the methodological flaws in the study finding dopamine toxicity, along with the absence of any detectable dopamine toxicity in Ecstasy users (see Mithoefer et al. 2003), led us to conclude that the risk of dopamine toxicity from MDMA in humans was minimal. Human trials of MDMA published in this period continued to be free of serious adverse events, and MDMA was well-tolerated by volunteers in these studies. After examining research appearing in 2002, we concluded that MDMA still possessed some risks to human participants in clinical trials, but that these risks were minimal.

The third review of the MDMA literature is identical to the review written in 2002 in its inclusion of clinical trials of MDMA, studies in Ecstasy users, and toxicity studies in non-human animals. New avenues of research and novel findings include a study of the subjective, physiological and neuroendocrine effects of an initial dose of MDMA followed a day later by a second dose of MDMA, studies that found former Ecstasy users had lower scores on some measures of memory than current Ecstasy users, polysubstance using or cannabis-using controls, the retraction of the study claiming to have found dopamine toxicity in non-human primates, and a report on the effects of 18 months of MDMA self-administration in rhesus monkeys. Studies published in 2003 and 2004 cast further doubt on the link between Ecstasy use and decline in psychological well-being, with a number of studies either failing to find the association or finding an equally strong or stronger association between decline in psychological well-being and other factors, such as polydrug or cannabis use. Researchers continue to find that Ecstasy users have subtle but detectable impairments in memory and cognitive function, with recent studies

finding effects on visual working memory as well as verbal memory. However, recent studies also raise issues about the nature of this link between Ecstasy use and deficits in cognitive function. There is no longer any evidence for dopamine toxicity after MDMA in any species outside the mouse. The original research and a quantitative review published in 2003 have not caused us to re-evaluate our original assessment of risk to human participants in clinical trials of MDMA. There are still some potential risks involved in clinical trials of MDMA, and they are still minimal. As noted in previous documents, reliance on studies in people who repeatedly used Ecstasy has produced a cautious assessment of risk, given that Ecstasy users represent people who have taken MDMA (and other drugs) frequently and repeatedly in sub-optimal conditions, such as warm, crowded dance clubs.

During the past year and a quarter, researchers in the Netherlands, Spain and the US reported findings from clinical trials of MDMA in humans, and a team of researchers in Switzerland presented findings of their investigations into the long-term effects of 1.5 to 1.7 mg MDMA in MDMA-naïve humans. Researchers assessed the effects of doses ranging from 1 mg/kg (52.3 mg in one subject in Tancer and Johanson 2003) to 2 mg/kg (171 mg in another subject in Tancer and Johanson 2003), with most studies administering doses ranging from 100 to approximately 120 mg. New findings include assessments of the subjective, physiological and pharmacological effects of two repeated doses of MDMA (Farre et al. 2004), at a cumulative dose of 200 mg (or 100 mg per day), evidence for serotonin release in the immunological effects of MDMA (Pacifici et al. 2004), and evidence that skills involved in driving motor vehicles are impaired acutely after MDMA (Lamers et al. 2003). No serious adverse events were reported during these clinical trials, and MDMA was well tolerated in all studies. None of the research teams reported the occurrence of any serious adverse events. It also appears that a second, and equal, dose of MDMA given a day after an initial dose is well-tolerated by human participants and did not provoke any adverse events.

The long-term effects of administering more than one dose of MDMA per session have not yet been studied in humans. It is possible that some long-term effects require a threshold dose, and that risks increase by some degree with increasing dose. However, it should also be noted that even some Ecstasy users who reported taking doses similar to or greater than 187 mg did not exhibit detectable signs of reduced cognitive function when former Ecstasy users reporting similar dosing patterns did show some impairments (Curran et al. 2003; Thomasius et al. 2003).

Studies in Ecstasy users continued to investigate psychological well-being, cognitive function, brain structure and function, and other domains thought to be associated with the serotonin system or relating to previously detected differences in Ecstasy users. Researchers in Australia, Germany, Italy, the Netherlands, Spain, the UK and the US examined various samples of mostly young people reporting Ecstasy use, comparing them with one or more groups of controls who reported no Ecstasy use. Recent studies continued to find an association between repeated Ecstasy use and reduced psychological well-being. However, continuing the trend seen in 2002, a large number of studies also reported findings that suggest that polydrug use, cannabis use, or pre-existing conditions

associated with drug use may explain at least part and perhaps most of the decline in psychological well-being in Ecstasy users. In contrast, researchers continued to find that Ecstasy users had impairments in memory, executive function (planning and decision making), and information processing. It appears that one or more parameters of Ecstasy use, such as lifetime consumption and average dose per use, may be related to some of these impairments. However, an examination of the findings also suggests that cognitive function in Ecstasy users may be influenced by factors other than those related to Ecstasy use. One new development in studies of cognitive function in Ecstasy users is a pair of reports that detected impaired cognitive function in former Ecstasy users, but not in current users (Curran et al. 2003; Thomasius et al. 2003). These findings are open to a number of interpretations, but do not support simple claims of permanent long-term effects appearing in all users, or of transient effects that dissipate with abstinence. Another new development is findings of impaired visual working memory in Ecstasy users, even without any decline in verbal working memory. As well, several studies have only detected impaired cognition in people reporting Ecstasy use above a specific level (usually lifetime consumption equal to or greater than 50 to 80 occasions or tablets). The only data presented on the long-term effects of MDMA after human clinical trials failed to detect any differences in markers of serotonin function or in cognitive function. One recent report (Buchert et al. 2003) may indicate that earlier studies of serotonin function in Ecstasy users (McCann et al. 1998) overestimated degree of reduced serotonin transporter sites, and that these reductions in serotonin transporter sites disappear with abstinence from MDMA. After considering recent study findings, it appears that human volunteers in clinical trials face very little risk of decline in psychological well-being afterwards, while the original estimates of minimal risk to serotonin or cognitive function remain much the same.

A large number of in vitro and non-human animal studies published in 2003 further investigated MDMA neurotoxicity, its mechanisms, and ways to reduce it. This included the one report in rats of damage to serotonin neurons (Schmued et al. 2003), with the damage associated with a combination of hyperthermia and high dose (20 or 40 mg/kg). In contrast, a study in mice did not detect cell death in substantia nigra or striatum (mice are subject to dopamine toxicity after MDMA), though it did find signs of oxidative stress (Fornai et al. 2004). Other studies examined various treatments that attenuated or eliminated brain serotonin reduction in rats or dopamine reduction in mice; these included lower ambient temperature, stress, and THC, the active ingredient in cannabis.

A number of new developments in this research area also appeared during this period. Several papers raise questions about the relevance and generalizability of neurotoxicity studies in nonhuman animals. Research finding that blood S-(+)-MDMA in monkeys given 10 mg/kg of this enantiomer (form) of the drug was ten times higher than MDMA levels in humans given typical active doses (Bowyer et al. 2003) casts doubt on the accuracy of interspecies scaling as a means of calculating dose equivalents across species. A study of self-administered MDMA in monkeys found no signs of damage to axons, non-significant reductions in serotonin, and no reductions in dopamine after 18 months of self-administration, though monkeys seemed to lose interest in self-administering MDMA over time. However, most significant among new developments

was the retraction of the report finding dopamine toxicity after repeated MDMA administration in non-human primates. The findings were retracted after the authors discovered that all but one animal in this study had received methamphetamine, not MDMA, and that subsequent attempts to replicate this study failed to find dopamine toxicity. Dopamine toxicity was not detected even after giving monkeys up to cumulative doses of 25.8 mg/kg intragastric and 12 mg/kg injected in a six hour period (Ricaurte 2004). In vitro and non-human animal studies in 2003 are likely to keep alive controversies over MDMA neurotoxicity. None of the findings alter original estimations of risk in humans given fully active doses of MDMA in "room temperature" (normothermic) settings.

Other areas of MDMA toxicity in non-human animals included studies of effects on liver and heart valve cells and a number of investigations of the mechanisms and effects of MDMA-induced hyperthermia. Among these findings is the publication of data previously only supplied to institutional review boards indicating that MDMA, like fenfluramine, is an agonist at the newly discovered 5HT2B cell and triggers growth in heart valve cells (Setola et al. 2003). However, its actions at 5HT2B receptors and on heart valve cells are far weaker than those of fenfluramine or fenfluramine metabolites, and these effects are unlikely to be significant when MDMA is administered intermittently rather than on a chronic basis. To date, there are still no reported cases of heart valve disease in Ecstasy users. Research into the mechanisms of MDMA-associated hyperthermia suggest that non-shivering heat, associated in part with action of uncoupling proteins, may be involved in raising body temperature after MDMA (Sprague et al. 2003; Mills et al. 2003). Since high doses were used in these studies (40 to 50 mg/kg), it is unclear whether non-shivering heat is involved at lower doses or has relevance either for hyperthermia in Ecstasy users or in slight increases in body temperature sometimes seen in clinical trials of MDMA.

Neither the previous nor the current review of the literature includes an examination of adverse events in Ecstasy users. However, a survey of case reports published in 2002 and 2003 have only located two new conditions appearing in Ecstasy users, a case of gingivitis in an adolescent who stored an Ecstasy tablet between his upper lip and gum (Brazier et al. 2003), and serous chorioretinopathy, a transient eye condition associated with use of sympathomimetic drugs, including Ecstasy (Michael 2003), with the condition resolving after discontinuation of use. All other case reports described adverse events already known to be associated with Ecstasy use, and include hyperthermia (Ben-Abraham et al. 2003; Greene et al. 2003; Finsterer et al. 2003) cerebrovascular (Auer et al. 2002; Yin et al. 2003) and cardiac (Lai et al. 2003; Madhok et al. 2003) events, hyponatremia (Cabellero et al. 2002; Kwon et al. 2003, Sue et al. 2003; Traub et al. 2002) liver problems (Cabellero et al. 2002), and urinary retention (Delgado et al. 2004; Inman et al. 2003). There was one case of pneumomediastinum (a pulmonary condition that might also be associated with inhaled drugs, such as cannabis) (Badaoui et al. 2002), a case of kidney problems that may have been associated with hyponatremia (Kwon et al. 2003), a vehicular accident (Weinbroum et al. 2003), and catatonia (Masi et al. 2002). One report described a series of deaths after coadministration of Ecstasy with the MAOI inhibitor moclobemide in (Vuori et al. 2003). A case series of seven adverse events

occurring at the same nightclub on the same evening found that severe adverse events (specifically hyperthermia) were dose dependent (Greene et al. 2003). Case reports cannot be used as a gauge of frequency of occurrence in the general population of Ecstasy users, since it is likely that unusual or serious events are more likely to be reported, but examining case reports can provide information on the possibility of events that might occur. Some of these events may be partially setting-dependent. For instance, the combination of sweating from strenuous exercise without replacing electrolytes and the injunction to drink plenty of water may increase the likelihood of hyponatremia in Ecstasy users. In addition, these events are relatively rare (Baggott 2002; Henry and Rella 2001; Gore 1999), probably affecting a fraction of 1% of the Ecstasy using population. To date, none of these serious adverse events have occurred in trials with MDMA. Carefully screening prospective participants for contraindicating conditions, providing electrolyte-containing beverages, and monitoring cardiovascular function and body temperature during MDMA administration should further reduce the likelihood of these events occurring within the context of a controlled trial.

Two cases of Parkinson's disease or parkinsonism were reported in former Ecstasy users (Kuniyoshi and Jankovic 2003; O'Suilleabhain and Giller 2003). However, an editorial commenting on these cases (Kish 2003) noted that there is no evidence of dopamine toxicity after Ecstasy use in humans or any other species besides mice. In one case, there was a family history of early-onset Parkinson's disease (Kuniyoshi and Jankovic 2003), and in another (O'Suilleabhain and Giller 2003), the case was insensitive to L-DOPA treatment. Given these criticisms, and the lack of dopamine toxicity detected in Ecstasy users and in a post-mortem study of the brain of an Ecstasy user (Kish et al. 2000; Reneman et al. 2002A; Semple et al. 1999), it seems very unlikely that a direct link exists between repeated Ecstasy use and movement disorders (Jerome et al. 2004; Kish et al. 2003; Sumnall et al. 2004).

Concluding Remarks

While there is still a great deal about MDMA and its effects that remain poorly understood, knowledge concerning the pharmacology and effects of MDMA has grown over the last five years and continues to grow. With a few exceptions, most findings reported in 2003 confirm or elaborate on previously reported research findings. It still seems that MDMA shares some effects with stimulants and other effects with hallucinogens acting on 5HT2A receptors in humans, but there continues to be evidence hinting at a unique profile of subjective effects that have led some to place it in a novel drug class, the "entactogens." An additional dose of 100 mg MDMA given 24 hours after an initial dose of 100 mg produced even greater changes in some subjective and physiological effects, yet the increase in strength was less than what was estimated on the basis of participants' plasma MDMA levels, suggesting some tolerance to specific MDMA effects. Acute immunological changes are associated with serotonin release. Ecstasy users continue to be impaired in specific areas of cognitive function, with lifetime Ecstasy consumption and abstinence from use, or effects related to these drug use parameters, may both influence effects on cognitive function. Specifically, heavy Ecstasy users (people reporting a lifetime consumption of 50 or more tablets, or on 50 or

more occasions) were more likely to exhibit these impairments than moderate users (those with a lifetime consumption of fewer than 50 occasions or tablets), and former users were more likely to exhibit impairments than current users. Though one research team detected harm to serotonin neurons in rats, most studies continue to find lower levels of serotonin or signs of harm to axons only. Concerns about detrimental effects to dopamine cells turned out to be unfounded. Studies continue to suggest some developmental toxicity, though it must be noted that these studies employ high and repeated doses of MDMA. None of the studies reported so far suggest that clinical trials of MDMA present a high risk to human participants screened for contraindicating conditions and monitored for adverse events after drug administration.

Note

Abstracts of papers reviewed in this document can be located on PubMed (www.ncbi.nlm.nih.gov/entrez) or through MAPS' bibliography of the MDMA literature (www.maps.org/wwwpb), and copies of many papers may be viewed through www.maps.org/wwwpb.

Clinical Trials

Introduction

Since 1986, MDMA has been administered to over 230 people in uncontrolled and controlled clinical or laboratory settings, with data from previous studies reviewed in the IB and the 2002 update to the IB. Past research has investigated physiological (for example Lester et al. 2000; Mas et al. 1999), subjective (for example Cami et al. 2000; Vollenweider et al. 1998), neuroendocrine (for example Grob et al. 1996; Harris et al. 2002), immunological (for example, Pacifici et al. 2002; Pacifici et al. 2000), and long-term effects (for example, Vollenweider et al. 2000) of MDMA. In addition, researchers published one imaging (Gamma et al. 2000A) and one EEG (Frei et al. 2001) study. MDMA was tolerated in samples familiar and unfamiliar with the effects of Ecstasy, and no serious adverse events were reported in these studies. Most studies reached similar conclusions about the effects of MDMA in humans, finding that MDMA shared effects in common with some psychostimulants and some hallucinogens, and some unique features supporting the placement of MDMA in a novel drug class, the entactogens (see Nichols and Oberlender 1990). Previous reviews demonstrated the importance of serotonin release on producing acute subjective and physiological effects, but also found roles for dopamine and the serotonin 5HT2A receptor. To date, data published or presented from clinical trials located in 2003 do not contradict previously reported findings, though some studies address new areas of research. More detailed coverage of past research can be found in the IB (Baggott et al. 2001) and the 2002 update to the IB (Jerome and Baggott 2003).

Human trials of MDMA were performed in Spain, the US and the Netherlands. Six research papers have appeared in the last year (Farre et al. 2004; Lamers et al. 2004; Pacifici et al. 2004; Pichini et al. 2003; Pizarro et al. 2003; Tancer and Johanson 2003), and two teams presented data at conferences (Tancer et al. 2003; Ludewig et al. 2003). Earlier research conducted by five of six teams appeared in the original Investigator's Brochure, and the research from all six teams was reviewed in the 2002 update of the IB. In three of six cases, recently published reports draw on the same samples represented in previously published reports (Lamers et al. 2004; Pichini et al 2003; Pizarro et al. 2003). In a fourth case, data from a manuscript now published but previously in press was presented to institutional review boards, though it did not appear in the publicly available review (Tancer and Johanson 2003). The conference presentation by Ludwig and colleagues drew on a sample that was similar, but not identical, to a sample described in previous presentations (e.g. Vollenweider et al. 2001; 2000).

Preliminary data from a study from a study of MDMA-assisted therapy in people with posttraumatic stress disorder (PTSD) was presented to institutional review boards in the 2002 update of the IB. This study remains inactive, as described below. However, another study of MDMA-assisted therapy in people with PTSD has commenced.

Four of six published reports investigated physiological effects of MDMA (Farre et al. 2004; Lamers et al. 2004; Pacifici et al. 2004; Tancer and Johanson 2003), and three

reports investigated subjective effects or effects on psychomotor tasks and cognition (Farre et al. 2004; Lamers et al 2004; Tancer and Johanson 2003). One report specifically investigated rewarding effects (Tancer and Johanson 2003), and another report investigated possible causes of immunological effects (Pacifici et al. 2004). Two reports investigated MDMA pharmacology and deposition in biological fluids (Pizarro et al. 2003; Pichini et al. 2003). Finally, one report described the effects of an initial dose of 100 mg MDMA followed by a second 100 mg dose given 24 hours after the initial dose (Farre et al. 2004).

Conference presentations included preliminary findings from research on MDMA effects on body temperature (Tancer et al. 2003, Presentation at the 65th Conference of the College on Problems of Drug Dependence), and preliminary findings from a study of cognitive performance in MDMA-naïve individuals one month after receiving MDMA (Ludewig et al. 2003, presented at the 58th Annual conference of the Society for Biological Psychiatry). All studies described above used randomized, double-blind, placebo-controlled designs, and all save one study relied on a within-subjects design. (The study performed by Pacifici and colleagues was incompletely crossed, and did not have a placebo-no paroxetine condition).

To date, one trial of MDMA-assisted psychotherapy was begun in Spain, and a second trial of MDMA-assisted therapy has commenced in the US. The MAPS-sponsored trial of MDMA in women with posttraumatic stress disorder (PTSD) arising from sexual assault is still inactive due to political pressure from the Madrid Anti-Drug Agency, despite receiving permission from the Spanish Ministry of Health (Doblin 2003). Preliminary findings from this study were provided to institutional review boards in the most recent update to the IB, with no serious adverse events, and no signs of worsening symptoms, occurring in participants enrolled in this study. Volunteers in the study underway in the US will undergo two experimental sessions where they will receive 125 mg MDMA or placebo, as well as up to ten non-drug assisted therapy sessions. Twelve of 20 participants will receive MDMA, and eight will receive placebo. To date, two subjects have undergone experimental psychotherapy sessions, and though it is not known whether MDMA or placebo was administered during the sessions, no serious adverse events have been reported so far (Mithoefer 2004).

Group demographics and characteristics of volunteers taking part in all studies published or presented in 2003 were similar to those reported in previous research studies. These included absence of any major physical or mental illnesses, as established through physical examination and psychiatric interviews, and having no substance abuse disorders save those for nicotine and MDMA, when relevant. All published reports restricted enrollment to people reporting past use of Ecstasy, though one conference presentation examined an MDMA-naïve sample. Four of six studies enrolled male participants only (Farre et al. 2004; Pacifici et al. 2004; Pichini et al. 2003; Pizarro et al. 2003), whereas two studies (Lamers et al. 2004; Tancer and Johanson 2003) and both conference presentations (Ludewig et al. 2003; Tancer et al. 2003) enrolled both men and women. The Spanish team typed all volunteers for CYP2D6 function (enzyme involved in MDMA metabolism), while the other research teams did not type volunteers for

variance in CYP2D6 function. As noted in the IB and the 2002 update to the IB, metabolism of MDMA involves several enzymes, and it appears that being an extensive CYP2D6 metabolizer may be less important than initially believed.

Doses of MDMA employed in all recently published studies ranged from 52.3 mg (approximately 1 mg/kg for one subject in Tancer and Johanson 2003) to 171.8 mg (2 mg/kg for a subject in Tancer and Johanson 2003). Other doses included 1 mg/kg across other subjects in Tancer and Johanson 2003, 75 mg (Lamers et al. 2004), 100 mg (Farre et al. 2003; Pacifici et al. 2004; Pichini et al. 2003; Pizarro et al. 2003), approximately 103 and 119 mg MDMA (1.5 and 1.7 mg/kg MDMA (Ludewig et al. 2003), and other 2 mg/kg doses in Tancer and Johanson 2003. One study administered two successive 100 mg doses, with one dose given a day after the first dose (Farre et al. 2004), so participants in this study received a cumulative dose of 200 mg over 48 hours. All doses were well-tolerated by study volunteers and no adverse events were reported during the course of any of the published reports.

Reports continued to find that MDMA has sympathomimetic effects (Farre et al. 2004; Tancer and Johanson 2003), and confirmed its immunosuppressant and anti-inflammatory actions (Pacifici et al. 2004) initially described in the IB. Current research also confirmed previous reports of the stimulant-like and hallucinogen-like subjective effects of MDMA, including elevation in both positive and negative mood (Farre et al. 2004; Pacifici et al. 2004; Tancer and Johanson 2003), and slight perceptual alterations. MDMA-induced elevation in cortisol and prolactin were also confirmed (Farre et al. 2004; Pacifici et al. 2004; Tancer and Johanson 2003). One study makes direct comparisons between MDMA, the psychostimulant d-amphetamine and the serotonin releaser and 5HT2C agonist mCPP (Tancer and Johanson 2003), finding that MDMA shares features with each of the other compounds. Another study investigated the relationship between serotonin release and the immunological effects of MDMA via pretreatment with the serotonin uptake inhibitor paroxetine (Pacifici et al. 2004), demonstrating a role for serotonin release in the immunological effects of MDMA (Pacifici et al. 2004). Thus these studies elaborated on or sought to clarify findings noted in previous reports (e.g. Pacifici et al. 2002; Pacifici et al. 2000).

Novel findings include a profile of MDMA effects on skills and tasks related to driving a motor vehicle (Lamers et al. 2004), an assessment of the reward value of MDMA (Tancer and Johanson 2003), the first description of tolerance to some subjective, physiological and neuroendocrine effects of MDMA after a second dose given 24 hours after the first dose (Farre et al. 2004), preliminary findings of lack of long-term effects on cognitive function (Ludewig et al. 2003, Presented at 58th Conference for Biological Psychiatry) and preliminary findings of slightly elevated body temperature in both a cold and a warm room (Tancer et al, presentation at 65th Conference of the College on Problems of Drug Dependence). The profile of MDMA effects related to driving found psychomotor skills such as visual tracking and reaction time improved after 75 mg MDMA, little changes in tasks involving executive function such as word fluency, and impairment in tasks involving time estimation for moving objects (Lamers et al. 2004). A measure of reward value relying on choices made between the test drug and receiving or giving up money

found that MDMA had high reward value in a sample reporting previous use of Ecstasy (Tancer and Johanson 2003). However, none of the newly reported findings or presentations of preliminary findings call into question any of the conclusions reached in the IB concerning the effects or safety of MDMA.

In conclusion, research presented or reported in 2003 employed similar designs and doses of MDMA to those used in previous studies, and administering MDMA in controlled settings continues to produce no adverse events. Volunteer characteristics are similar to those in previous reports, and in several cases data has been gathered from samples featured in previous reports. None of the newly reported findings differ significantly or are in conflict with earlier findings reported either in the IB or in the 2002 update of the IB.

Physiological Effects

None of the recent publications or presentations described surprising findings concerning the physiological effects of MDMA in humans. All research teams assessing cardiovascular changes found elevated blood pressure and heart rate or pulse, and those assessing changes in body temperature continued to report slight elevations in body temperature (Farre et al. 2004; Tancer and Johanson 2003). Tancer and Johanson measured blood pressure, heart rate and body temperature after 1 and 2 mg/kg doses of MDMA (approximately 70 and 150 mg) in 12 volunteers found that peak changes in these variables appeared no later than 2 hours after drug administration (Tancer and Johanson 2003), suggesting that the likelihood of adverse events declines after this point in time. The recent findings described do not differ significantly from previous research presented in the IB and the 2002 update to the IB (see for example Grob et al. 1996; Lester et al 2000; Liechti and Vollenweider 2001; Mas et al. 1999; Tancer and Johanson 2001).

2 mg/kg MDMA elevated systolic and diastolic blood pressure above values seen after placebo (Tancer and Johanson 2003). Peak elevation in systolic and diastolic BP appeared 1 hour after drug administration.

2 mg/kg MDMA also elevated heart rate significantly above values reported after placebo, with the greatest increase in heart rate seen at 20 BPM above normal, an increase similar to that seen during moderate exercise (Tancer and Johanson 2003). Peak increase in heart rate was seen 1 h post-drug. This study reported that when compared to d-amphetamine and mCPP, MDMA produced the greatest increases in blood pressure and heart rate. However, values for MDMA were still very similar to those seen for the other compounds studied.

A second dose of 100 mg MDMA given a day after an initial 100 mg dose elevated blood pressure and heart rate, doing so to a greater degree than seen after the initial dose (Farre et al. 2004). However, plasma MDMA levels after this dose are similar to values association with the slightly higher dose of 125 mg. Given the higher plasma MDMA levels after the second dose, cardiovascular changes are actually somewhat lower than

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expected, suggesting tolerance to these effects. A greater number of subjects had peak SBP above 140 mmHg after the second administration than after the first. In contrast, the increase in heart rate seen after the second dose of MDMA was only slightly greater than that seen after the first dose, and the second dose of MDMA, like the first, failed to significantly increase body temperature.

Only two published reports assessed body temperature after MDMA (Farre et al. 2004; Tancer and Johanson 2003). Farre and colleagues assessed temperature after an initial dose of 100 mg MDMA, and a subsequent dose of the same amount given 24 hours after the first dose, finding no significant increases in body temperature after either dose (Farre et al. 2004). Tancer and colleagues assessed changes in body temperature after 2 mg/kg MDMA, finding a slight elevation in body temperature that was comparatively lesser than that produced by 20 mg d-amphetamine. Peak elevation in body temperature was seen 2 hours after drug administration. At no time did the increase in body temperature exceed 1 degree Celsius.

Tancer and colleagues also presented preliminary findings concerning the role ambient temperature might play in changes in body temperature after 2 mg/kg MDMA at the 2003 CPDD conference (Tancer et al, 2003, Presentation at 58th Conference of the College on Problems of Drug Dependence). Ambient temperature did not appear to alter the slight increase in body temperature after 2 mg/kg MDMA, with subjects in a cold room (18 degrees C or 64 degrees F) exhibiting the same increase as subjects in a warm (30 degrees C, or 86 F) room. Though data was only collected from a very small sample of four volunteers, the findings suggest that humans are less sensitive than other species to the thermoregulatory effects of MDMA. It is also possible that significant changes in thermoregulation only occur after higher doses. None of the data presented or published so far contradicts previously reported conclusions in the IB and or data reported at the 2002 update to the IB, with all reports indicating that MDMA is sympathomimetic and produces a slight increase in body temperature.

Subjective Effects and Side Effects

Only two recent publications explicitly assessed the subjective effects of MDMA (Farre et al. 2004; Tancer and Johanson 2003), though another report mentions subjective effects (Pacifici et al. 2004). Tancer and Johanson assessed subjective effects via several instruments, including the Addiction Research Center Inventory (ARCI), the Profile of Mood States (POMS), the Hallucinogen Rating Scale (HRS), visual analog scales (VAS), and an end of session questionnaire. Farre and colleagues used a Spanish version of the ARCI and the same visual analog scales employed in earlier studies performed by the same team (Cami et al. 2000; Hernandez-Lopez et al. 2002).

MDMA increased positive and negative mood (Farre et al. 2004; Tancer and Johanson 2003). Tancer and Johanson reported that peak negative mood 1 h post-drug, and peak positive mood 2 h post-drug. MDMA also increased feelings of energy, and unlike a previous reports (Cami et al. 2000), it did not increase sedation (ARCI "PCAG") (Farre et al. 2004; Tancer and Johanson 2003). Volunteers in one study reported increases in

feeling social and stimulated, and decreased feelings of hunger (Tancer and Johanson 2003), and volunteers in the other study noted changes in perception, euphoria and stimulation (Farre et al. 2004). When compared with 20 mg d-amphetamine and 0.75 mg/kg mCPP, 2 mg/kg MDMA increased talkativeness, positive mood and feeling high (Tancer and Johanson 2003). MDMA produced increased scores on five of the six scales of the HRS, including scales measuring changes in affect, perception, cognition and somatic experience, though it is notable that these changes also appeared after mCPP. A second dose of MDMA produced slightly more stimulation, slightly less sedation, and apparently increased perceptual alterations, but again not to the degree expected from examining plasma MDMA levels, leading Farre and colleagues to suggest that their results indicate tolerance to specific MDMA effects. Volunteers in both studies had previous experience with Ecstasy, and so it is possible that some of the subjective effects reported in this study may arise from their expectations. However, one of the two studies was a randomized, double-blind comparison of two doses of three different substances, somewhat reducing the chance that responses were guided by previous knowledge of Ecstasy effects. As well, changes in subjective effects were similar to those reported in drug-naïve samples (see Liechti et al. 2001; Vollenweider et al. 1998).

When Tancer and Johanson asked volunteers in this study to guess what drug they had received during each session, apparently both MDMA and mCPP were identified as either hallucinogens or MDMA-like drugs (empathogens, an alternative term for entactogens). In contrast, d-amphetamine was correctly identified more often than it was mistaken for a hallucinogen or an MDMA-like drug. This somewhat surprising finding suggests that MDMA may share more features with a serotonin releaser that does not produce euphoria or stimulation than it shares with a psychostimulant.

When subjective effects were analyzed across time (Tancer and Johanson 2003), peak effects for elevated positive mood, such as POMS “Elation” and “positive mood” and ARCI MBG and BG (scales for euphoria and stimulant-like effects), and visual analog measures for Social, appeared 2 hours post-drug, whereas elevation in negative mood (such as POMS Anxiety, ARCI LSD (scale for anxiety and unpleasant or unusual somatic effects) appeared 1 hour post-drug, at a time coinciding with most peak physiological effects, raising the possibility that the peak in positive mood and related effects occurs at a different time from the peak in negative mood-related effects.

In their report, Pacifici and colleagues noted that three days of paroxetine pretreatment attenuated euphoria in people receiving 100 mg MDMA. This report does not describe how subjective effects are assessed, nor does it give any further detail on subjective effects of MDMA, but the findings are comparable to effects of a single pretreatment with the serotonin uptake inhibitor citalopram (Liechti et al. 2000A), and support the importance of serotonin release in producing the subjective effects associated with MDMA.

Tancer and Johanson (2003) sought to assess the reward value of MDMA through using the Multiple Choice Procedure (MCP) in12 MDMA-experienced people. At the end of each session, volunteers responded to a series of twenty choices between the drug they

had received and receiving or giving up a specific amount of money. The point at which a volunteer chooses to receive or give up money rather than receive the test drug is considered an indicator of reward value. The MCP was administered for placebo and both doses of all three comparison drugs (1 and 2 mg/kg MDMA, 0.5 and 0.75 mg/kg mCPP, and 10 and 20 mg d-amphetamine). Only 2 mg/kg MDMA and 20 mg amphetamine attained significantly higher reward value than placebo, with volunteers assigning the highest reward value to 2 mg/kg MDMA. These findings are comparable to previous findings that MDMA has some abuse potential (e.g. Cottler et al. 2001; Jansen 1999; Topp et al. 1999; Von Sydow et al. 2002). However, it should also be noted that a review of trials performed on samples of mostly MDMA-naïve volunteers who received 1.5 to 1.7 mg/kg MDMA (Liechti et al. 2001) failed to find any interest in self-administering MDMA outside of a laboratory setting.

None of the studies published in 2003 formally assessed occurrence of side effects, though one paper noted that it was difficult to collect saliva from subjects after MDMA administration, (Pichini et al. 2003), and another noted that people felt less hungry after MDMA (Tancer and Johanson 2003). The profile of somatic effects (both unwanted and "neutral" or non-valenced) is well-established, with detailed information found in the IB. Researchers have not described any new side effects occurring in volunteers enrolled in their studies.

Published findings in 2003 did not employ any volunteers with major mental disorders. However, data from an unpublished and currently halted study of MDMA-assisted psychotherapy in women with PTSD arising from a sexual assault was presented in the 2002 update to the IB (Bouso 2003, personal communication). The women taking part in this study were not worse off after the study, and some showed signs of improvement.

Taken together, the findings reported in these studies are consonant with those reported in the IB (see Cami et al. 2000; Grob et al. 1996; Vollenweider et al. 1998) and the 2002 update of the IB (see Harris et al. 2002; Hernandez-Lopez et al. 2002; Liechti and Vollenweider 2001; Tancer and Johanson 2001). Previous research has indicated that MDMA produces stimulant-like and hallucinogen-like effects, with inconclusive but suggestive findings concerning unique pharmacological effects. Current research findings are in agreement with those from previous studies. Some of the findings from Tancer and Johanson could be interpreted as offering support for unique pharmacological effects including increased sociality and friendliness after MDMA, as hypothesized to occur in "entactogens" like MDMA.

Subjective effects after a second dose of MDMA were generally greater than those reported after an initial dose (Farre et al. 2004). However, the increase in strength of effects is less than expected from plasma MDMA levels, suggesting tolerance to some effects when a second dose is given 24 hours after an initial dose. This study did not describe effects appearing after two more closely-spaced doses, though the same team has conducted immunological studies of two doses of 100 mg given four hours apart (Pacifici et al. 2001).

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Psychomotor and Cognitive Function

Previous controlled and uncontrolled studies have formally or informally examined MDMA effects on psychomotor and cognitive processes (Cami et al. 2000; Downing 1985; Frei et al. 2001; Gamma et al. 2000A; Vollenweider et al. 1998). As discussed in the IB, MDMA failed to alter performance on most tasks, such as simple reaction time tasks or Stroop performance (Cami et al. 2000; Gamma et al. 2000A; Vollenweider et al. 1998), but did alter digit-symbol substitution performance (Cami et al. 2000) and decision making (Downing 1986).

Spurred on by this research, and by reviews and reports of traffic accidents and difficulty driving after Ecstasy use, researchers in the Netherlands decided to study the effects of 75 mg MDMA on tasks and skills related to driving a motor vehicle in eight men and four women previously experienced with Ecstasy (Lamers et al. 2004). Ethanol (0.5 g/kg) and placebo served as comparison substances. Surprisingly, MDMA failed to alter and sometimes even improved volunteers' performance on some tasks. Participants given 75 mg MDMA performed a word fluency task (generate words meeting specific criteria during a given interval) and a computerized Tower of London task at levels similar to those seen after placebo. MDMA did not affect eye-hand tracking, and it improved psychomotor speed compared to placebo, with responses were faster after MDMA than after placebo. However, MDMA did interfere with volunteers' ability to estimate the time it took for an object to move from one place to another when the object was hidden from view. It is possible that alteration in time perception, noted in previous studies, (Vollenweider et al. 1998) might make it more difficult to estimate amount of time needed for a hidden object to pass from one point to another.

The findings of Lamers and colleagues clarify and elaborate on previous findings concerning the acute effects of MDMA. Though these new findings may appear to be in conflict with some earlier reports and reviews of impaired driving or driving-related abilities after MDMA (i.e. Logan et al. 2001), differential effects on specific tasks has already been suggested (Cami et al. 2000). Even if MDMA does improve some driving-related skills, such as psychomotor speed, it still appears that MDMA might impair other driving-related skills, such as time estimation for moving objects.

It should be noted that the same team of researchers tested driving related skills more directly through a driving simulator in a quasi-experiment conducted in a sample of 15 men and five women (Brookhuis et al. 2004) one hour after they had self-administered Ecstasy tablets, and again after having attended a club or party and taken Ecstasy and other drugs, with the second driving simulation task performed four to five hours after the first simulated drive. Simulated drives post-drug were compared to presumably drug-free performances by the same sample. Brookhuis and colleagues found that self-administration of Ecstasy was associated with impaired driving skills, including a greater acceptance of narrow gaps between simulated vehicles, and impairments were greater when Ecstasy was combined with other substances. Incidence of (simulated) crashes increased after Ecstasy when compared with presumably drug-free performance, and increased again after returning from a dance event or party. A control group of 13 people

with no history of Ecstasy use showed slightly less risky driving during a presumably drug-free session, indicating that impaired performance and increased crashing might be associated with repeated use of Ecstasy, or with pre-existing factors associated with drug use, such as risk-taking. However, findings of impaired driving acutely after Ecstasy self-administration, and especially after the coadministration of Ecstasy and other drugs, are consonant with previous reports of erratic driving after the use of Ecstasy alone or with other drugs (Logan et al. 2001).

Performance on a simple reaction time (RT) task and the digit-symbol substitution task (DSST) was assessed in volunteers after an initial dose of 100 mg MDMA, and after a second dose given 24 hours later (Farre et al. 2004). This study also measured the changes in extra-ocular muscles that can lead to convergent squint (esophoria) and divergent squint (exophoria). Results reported were similar to those first reported by Cami and colleagues, that of unimpaired reaction time, slightly impaired DSST performance, and significant esophoria, both after the initial dose and after the second dose of MDMA. The second dose of MDMA did not produce greater esophoria than the initial dose.

Neuroendocrine Effects

Three studies evaluated stress hormone release after MDMA (Farre et al. 2004; Pacifici et al. 2004; Tancer and Johanson 2003). In line with previous research, (Grob et al. 1996l; Harris et al. 2002; Mas et al. 1999; Vollenweider et al. 1998), these studies found that MDMA elevated levels of the stress hormones cortisol and prolactin.

A study in twelve men found that 100 mg MDMA increased levels of plasma cortisol and prolactin, with levels of both hormones peaking 4 to 5 hours post-drug (Pacifici et al. 2004). The same study reported that pre-treatment with the serotonin uptake inhibitor paroxetine reduced cortisol and prolactin levels after MDMA. Another study found that 2 mg/kg MDMA produced significant increases in salivary cortisol when compared with placebo (Tancer and Johanson 2003). The researchers detected peak hormone levels 3 and 2 hours post drug in a sample of 12 volunteers that contained both men and women (Tancer and Johanson 2003). Findings from both studies are in agreement with previous reports of increased cortisol and prolactin after similar doses of MDMA (Grob et al. 1996; Harris et al. 2002; Mas et al. 1999; Vollenweider et al. 1998). Finally, a third study found increased levels of prolactin and cortisol in nine men after an initial dose of 100 mg MDMA, and again after an additional 100 mg administered a day later (Farre et al. 2004). Cortisol levels after the second dose of MDMA were even greater than cortisol after the first dose, but prolactin release after the second dose of MDMA was no greater than prolactin levels seen after the first dose. These somewhat divergent findings suggest that MDMA-related changes in prolactin are reduced after repeated dosing. Cortisol is not similarly affected. This data also suggests that the effects of MDMA on these two hormones differ on at least one aspect or process.

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Immunological Effects

To date, Pacifici and colleagues are the only team of researchers studying the immunological effects of MDMA in humans (Pacifici et al. 2004; Pacifici et al 2002; Pacifici et al. 2001; Pacifici et al. 2000). They have found generally immunosuppressive and anti-inflammatory effects that last for about one to two days (Pacifici et al. 2000; 2001). All subjects in these studies have been men reporting some previous experience with Ecstasy.

Pacifici and colleagues continue to elaborate on their initial findings. In their most recent publication (Pacifici et al. 2004), they investigated the role played by serotonin release in the effects of MDMA on the immune system. Volunteers received a daily dose of 20 mg paroxetine for three days prior to receiving 100 mg MDMA. Paroxetine pretreatment attenuated many of the immunological effects of MDMA, such as reduced numbers of CD4 cells, increased numbers of NK cells and reduced production of the pro-inflammatory cytokine IL-2. Paroxetine pretreatment completely prevented MDMA from dampening lymphocyte proliferation after encountering a potential antigen, and strongly inhibited an increase in the anti-inflammatory and immunosuppressive cytokine IL-10. Overall, findings suggest that at least some of the immunological changes produced by MDMA, are the direct or indirect result of serotonin release. However, other neurotransmitter systems, such as norepinephrine and dopamine, may be more strongly involved in other immunological changes, such as reductions in CD4 cells and increases in NK cells. Paroxetine pretreatment also halved MDMA-associated increases in cortisol and prolactin release, suggesting that some of the immunological changes may be related to changes in neuroendocrine function.

Research findings are in agreement with earlier studies performed by Pacifici and colleagues. While it offers a possible and partial explanation for the immunological effects of MDMA, it does not alter our understanding of these effects. A pair of immunologists who reviewed the effects of drugs acting on serotonin and dopamine (like cocaine and MDMA) proposed other explanations for the immunological effects of these drugs as well, noting that some immune cells sport serotonin and dopamine receptors (Gordon and Barnes 2003). All studies conducted by Pacifici and colleagues have been restricted to men, but to date, there is no reason to expect different results in women. The immunological effects of MDMA are transient and are comparable to the effects of consuming four to five alcoholic drinks. Nevertheless, caution may be appropriate when administering MDMA to people with suppressed immune systems.

Pharmacology

To date, pharmacological studies of MDMA have either consisted of investigations into the roles played by specific neurotransmitters in the physiological and subjective effects of MDMA (see Vollenweider 2001 for a review and summary) or examinations of MDMA metabolism. Researchers have detected several MDMA metabolites, including the major metabolite HMMA, and the less abundant metabolites HMA and MDA (De la

Torre et al. 2000; Navarro et al. 2001). Researchers have sought to detect MDMA and metabolites in blood, urine, sweat and saliva.

Results from current pharmacological studies are similar to those reported in previous studies, with very few novel findings reported. Four studies, all performed by a team of researchers in Spain, examined MDMA metabolism in at least two separate samples of male Ecstasy user volunteers. Two of four reports focused on drug detection, or detection of drug enantiomers (different versions of the same molecule) (Pizarro et al. 2003; Pichini et al. 2003). One report examined immunological changes after MDMA given alone, and after three days of pretreatment with the serotonin uptake inhibitor paroxetine (Pacifici et al. 2004), and one report examined the physiological, subjective, cognitive, neuroendocrine and pharmacokinetic effects of two doses of 100 mg MDMA given 24 hours apart (Farre et al. 2004).

Plasma and urine collected from one man given 100 mg MDMA was used to devise a means of measuring enantiomers of MDMA, and enantiomers of the metabolites MDA, HMMA, and HMA with gas chromatography-mass spectrometry (GC-MS) (Pizarro et al. 2003). The detection method was successful, and the authors detected both R-(-) and S-(+) enantiomers of MDMA and metabolites. The R/S ratio of MDMA was opposite that of MDA in blood and urine, but the R/S ratio for HMMA remained close to 1 (meaning, there was little difference in amount of each enantiomer) in urine and blood. Pizarro and colleagues interpreted these findings as evidence that enzymes other than CYP2D6 are involved in the metabolism of MDMA. The study was not constructed to assess the involvement of specific enzymes in MDMA metabolism, but the IB and update to the IB refer to other papers suggesting roles for COMT, CYP1A2, CYP3A4, and other enzymes. There is little support for the contention that functional differences in CYP2D6 explain adverse reactions after MDMA (see IB, Kreth 2000; Schwab et al. 1999).

Pichini and colleagues employed a commercially available immunoluminescent assay (DrugWipe), sweat collection, and the use of gas chromatography with mass spectrometry (GC-MS) to detect MDMA and metabolites in sweat after 100 mg MDMA in a sample of 9 men reporting previous Ecstasy use (Pichini et al. 2003). The researchers also compared their results with results from an earlier study of theirs assessing MDMA and metabolites in blood and saliva (Navarro et al. 2001). MDMA was found in the sweat of most subjects, with MDMA first detected 1.5 hours after administration, though it was only detected 4 hours post-administration in two of nine participants. The authors found wide intra-subject variability in levels of MDMA detected in sweat, noting that subjects with higher concentrations of MDMA in sweat also had the highest concentrations of blood and salivary MDMA. All volunteers enrolled in this study were extensive CYP2D6 metabolizers, so differences in MDMA concentration were unrelated to CYP2D6 function. Surprisingly, Pichini and colleagues were unable to detect HMMA in sweat, despite its greater abundance than HMA or MDA in blood or urine.

The investigation assessing the role of serotonin release in the immunological effects of MDMA (100 mg) briefly discusses alterations in MDMA metabolism presumably caused

by three days' pretreatment with 20 mg paroxetine, an SSRI and CYP2D6 inhibitor (Pacifici et al. 2004). Paroxetine pretreatment increased plasma concentrations of MDMA (20% Cmax) and 30% increase in AUC). Paroxetine pretreatment increased levels of unmetabolized MDMA in blood. While these findings are provided in relation to possible causes of immunological effects, the authors note that higher MDMA levels would not intensify or increase dose-dependent effects of the drug, because paroxetine prevents the serotonin transporter from binding to MDMA, thereby preventing serotonin release.

When compared with an initial dose of 100 mg MDMA, a subsequent dose of the same amount given 24 hours later produced a 77% increase in plasma MDMA levels, a higher area under curve (AUC), a measure of drug concentration, and a lower elimination constant (Farre et al. 2004). Farre and colleagues state that plasma MDMA levels seen after the second dose were equivalent to those previously associated with 125 mg MDMA (Mas et al. 1999). Urinary levels of MDMA were also higher after the second dose of MDMA. MDMA levels after the second dose were higher than expected when summing any remaining MDMA from the first dose with that of the second dose, a finding supporting non-linear pharmacokinetics. Extrapolating from these findings, trials using repeated "booster" doses of MDMA should take into account the effects of non-linear pharmacokinetics, including greater levels of MDMA than might be expected from summing remaining levels with the next dose. Making the second dose lower than the first dose may reduce the risk of unexpected increases in physiological effects of two closely spaced doses of MDMA. It should be noted that therapists using booster doses administered them 2 to 4 hours after the initial dose (Greer and Tolbert 1998; Metzner and Adamson 2001) rather than a day after the first dose.

Though these studies clarify and elaborate on earlier areas of interest in the study of MDMA pharmacology, to date no recent publication presents findings that contradict earlier findings reported in the IB or the update to the IB. While great variability across subjects in detection of MDMA in sweat is notable, all subjects in this study tolerated the same dose of MDMA (Pichini et al. 2003). Volunteers also tolerated two successive doses of 100 mg MDMA (Farre et al. 2004). The significance of failing to detect the major metabolite HMMA in sweat remain unclear, and do not relate to findings relating to subjective or physiological effects.

Potential Long Term Effects

As was the case in 2002, there are still no published prospective studies of potential long-term effects of known doses of MDMA in humans. Data from previous published and unpublished reports of assessments of Ecstasy users made after MDMA administration may be found in the IB (Chang et al. 2000; Grob et al., In Preparation). A team of researchers in Switzerland have presented data concerning the effects of MDMA in drug-naïve volunteers at conferences, as noted in the IB and the 2092 update to the IB, but has not yet been published. So far, data from these presentations and reports has found transient changes in cerebral blood flow, no changes in serotonin transporter site density,

and no changes in cognitive performance two weeks to a month after 1.5 to 2.5 mg/kg MDMA (Grob et al., unpublished; Vollenweider et al. 2000).

While studies comparing Ecstasy users to polydrug users and non-drug users have often found changes in serotonin transporter site density or changes in cognitive function, these studies cannot be used as the basis of estimating risk of long-term effects in clinical studies, as has been stated in the IB and the 2002 update to the IB. These studies are retrospective, raising the possibility that one or more pre-existing or coexisting factors may explain differences in these measures. Studies examining mood, cognitive function and brain serotonin in Ecstasy users are addressed in the next section.

The Swiss research team responsible for earlier conference presentations referred to in previous reviews presented more data gathered from a sample of 15 MDMA-naïve men and women given up to 1.7 mg/kg MDMA (approximately 119 mg) (Ludewig et al. 2003, Data Presented at 58th conference of the Society for Biological Psychiatry). The researchers assessed cognitive ability and mood before and after administering two doses of MDMA (Ludewig et al. 2003). The researchers assessed visual and working memory with the CANTAB test battery, and they assessed mood with psychological ratings. The researchers found no changes in CANTAB scores after MDMA administration, and they failed to find any increase in anxiety or depression. Like previous evaluations performed by the same team, these findings fail to detect any long-term effects after one to two doses of MDMA in a controlled setting.

Conclusion

Six published reports and two conference presentations of human clinical trials of MDMA appeared between January 2003 and early (up to mid-April) 2004. Researchers administered doses similar to those proposed for use in MDMA-assisted therapy. One study examined the effects of two repeated doses of MDMA, though each dose was given 24 hours apart, and not 2 to 4 hours apart. None of the findings reported contradict previous research discussed in the IB or the 2002 update to the IB, and no adverse events have occurred during the course of these studies. Recent reports extend and clarify knowledge of the subjective effects, immunological effects, metabolism, and possible long-term effects of MDMA, but none of these findings alter the initial safety assessment of 125 mg MDMA given in controlled settings. Little data exists concerning the administration of a second dose two hours after an initial dose, but a previous report (?Pacifici et al. 2001) has administered a second dose four hours after an initial dose without producing any serious adverse events. It appears that MDMA is well tolerated, produces few adverse events, and can be safety administered in human trials in controlled settings.

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Studies in Ecstasy Users

Introduction

A large portion of investigations into the long-term effects of MDMA in humans consist of retrospective studies of Ecstasy users. With the exception of the conference presentations described in the previous section, studies of the long-term psychological and cognitive effects of MDMA consist exclusively of retrospective studies of samples of Ecstasy users, usually compared with one or more samples of individuals who have not used Ecstasy. The term "Ecstasy users" refers here to individuals who self-administer material sold illicitly and purported to contain MDMA. Because examinations of tablet contents suggest that up to 40% of tablets sold as Ecstasy contain substances in addition to or instead of MDMA, this term is preferable when referring to this material (Cole et al. 2003; Baggott et al. 2000), even if at least a slim majority of tablet contents are MDMA or a related compound such as MDEA (MDE) or MDA. As noted in the IB and in the previous section, studies in Ecstasy users offer a conservative estimate of the upper limits of risk for participating in human trials of MDMA.

Areas of investigation include studies of serotonin function and measures believed to be directly tied to serotonin function in humans, measures of mood or psychological well-being, and measures of cognitive function. In 2003, researchers in Europe and the US published studies in all of the areas listed above. In most cases, authors of recent publications have already published studies in Ecstasy users, though this is not true in all cases (for example McCardle et al. 2004; Hanson and Luciana 2004; Roiser and Sahakian 2003).

Issues and methodological flaws common to retrospective studies in Ecstasy users have been discussed in detail in the IB, as well as in other reviews (Baggott 2002; Cole and Sumnall 2003A; Green et al. 2003B), and so they will not be discussed here. However, note that volunteers in studies of Ecstasy users have already decided to self-administer Ecstasy, and that the behavioral and psychological antecedents of this choice may distinguish Ecstasy users, especially regular or heavy users, and people who decide not to self-administer the drug.

While most studies of people who have self-administered Ecstasy are evaluations of long-term effects, some recent publications examined acute or sub-acute effects in samples of Ecstasy users, presumably because it is easier to perform these studies than to obtain permission and carry out human trials of MDMA. While these studies lack control over the dose and presence of MDMA, some (e.g. Brookhuis et al. 2003) collected and assessed pill content from subjects.

This section will first review retrospective and naturalistic studies investigating acute and sub-acute effects of Ecstasy. Then, studies assessing psychological well-being and cognitive function in Ecstasy users will be reviewed, followed by a discussion of the relevance of study findings to assessments of serotonin function. Finally, the review will address assessments of other domains and functions, such as response to auditory startle

and pre-pulse inhibition (PPI), with most of these processes believed to serve as markers for one or more aspect of serotonin function.

Subjective and Physiological Effects of Ecstasy; Naturalistic and Retrospective studies

Most researchers wishing to understand the acute and sub-acute effects of MDMA in humans have relied on human trials of MDMA, as described in the previous section. However, some have assessed drug effects after the self-administration of Ecstasy (Brookhuis et al. 2004; Curran et al. 2004; Oliveri and Calvo 2003; O'Regan et al. 2004; Verheyden et al. 2003A). Since Ecstasy pill content was not always assessed in these studies and measures were not as specific or detailed as they were in clinical trials, these studies may offer less reliable evaluations of MDMA effects. However, a few recent studies are unusual either in their focus on specific acute effects, such as skills used in driving a car (Brookhuis et al. 2004), specific sub-acute effects, such as pain tolerance (O'Regan et al. 2004), or because they used on-site testing in a common setting for Ecstasy use (Curran et al. 2004). In addition, one study featured an unusually large sample for a study of sub-acute effects (Verheyden et al. 2003A).

Physiological and subjective effects seen after self-administration of Ecstasy were similar to effects appearing in clinical trials. In an evaluation of skills related to driving a motor vehicle (Brookhuis et al. 2004), 20 volunteers exhibited elevated heart rate after self-administering at least one tablet of Ecstasy (average dosage from tablets tested = 59 ± 22 mg) (Brookhuis et al. 2004), and heart rate was even more elevated when volunteers were assessed again, usually after self-administering more Ecstasy, either alone or in combination with other substances. Brookhuis and colleagues found that most tablets supplied by participants contained MDMA, though a few contained the related compound MDE, or the psychostimulant amphetamine. Both after Ecstasy alone and after consuming multiple substances, volunteers reported changes in perception, and the Brookhuis and colleagues noted that volunteers were more talkative after self-administration of Ecstasy alone or along with other drugs. As discussed in the previous section, Ecstasy use reduced driving skills, making drivers more accepting of small gaps between cars in a driving simulator, and increasing the likelihood of a (simulated) crash (Brookhuis et al. 2004). Combining Ecstasy with other substances and spending several hours in a club or dance event produced more serious impairments in performance on the driving simulator than Ecstasy alone.

In a study conducted on-site at a club setting, Curran and colleagues found that pulse was elevated in a sample of 29 Ecstasy users who had self-administered Ecstasy just previous to assessment (Curran et al. 2004). Volunteers who had taken Ecstasy in this setting reported increased positive mood, including increased contentment and alertness, and increased negative mood, including increased anxiety, when compared with people at the same club setting with no history of Ecstasy use and who had not taken Ecstasy on that night (Curran et al. 2004).

The study described above (Curran et al. 2004), and a study employing semi-structured interviews of 428 of 466 Ecstasy users (Verheyden et al. 2003A) assessed self-reported

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sub-acute effects. Volunteers in the first study completed psychometric measures four days after Ecstasy use, and interviewees in the second survey described effects they experienced 24 to 48 hours after use, with average time since last use not reported. Both studies were performed by the same research team, though interviews were carried out by BBC staff for a planned broadcast program (Verheyden et al. 2003A). Volunteers in both studies were restricted to providing responses from a list generated by the investigator or interviewer, and they did not provide their own list of sub-acute effects. Unfortunately, both investigations failed to assess Ecstasy tablets used by study volunteers, and interviews asked volunteers to describe sub-acute effects in general rather than referring to a specific (as in most recent) instance of Ecstasy use. Nevertheless, study findings correspond to reports of sub-acute effects given in clinical trials (for example Harris et al. 2002; Liechti et al. 2000A; Liechti et al. 2001B; Liechti and Vollenweider 2001; Liechti and Vollenweider 2000A; Vollenweider et al. 1998) and previous retrospective surveys (for example Davison and Parrott 1998; Liester et al. 1992; Solowij and Hall 1992) discussed in greater detail in the IB. Effects appearing 24 to 48 hours post-drug and reported in the study of 428 Ecstasy users included increased anxiety (41.1%), fatigue (40.2%), continued loss of appetite (34.6%), insomnia (34.1%) continued jaw clenching or tight jaw (28.6%), feeling calm (25.7%), continued perception of increased heart beat (14.3%) and increased feelings of warmth toward others (11.9%), with no other effects reported by more than 10% of the sample (Verheyden et al. 2003A). In the study examining Ecstasy use on-site (Curran et al. 2004), 29 Ecstasy users reported experiencing an increase in depressed mood, feeling more discontented and irritable, increased state aggressiveness or anger, and increased trouble sleeping four days after Ecstasy self-administration (Curran et al. 2003). Study volunteers reported that all of these effects were resolved seven days after use. The sub-acute effects reported by people taking part in these studies are similar to those listed in clinical trials of MDMA and in retrospective studies, as can be seen in the IB.

In addition to studies of self-reported sub-acute effects of Ecstasy, two studies (Oliveri and Calvo 2003; O'Regan et al. 2004) assessed specific responses or differences in brain activity at a time when people in clinical trials report experiencing residual effects (e.g. Vollenweider et al. 1998; Liechti et al. 2000A). The investigators performing these studies apparently selected specific responses or processes on the basis of their alleged relationship to serotonin function in humans, but without specifying whether the intent was to assess transient changes in serotonin function or long-term effects on serotonin function.

In one study, researchers measured time elapsed before the removal of the dominant hand from an icy water bath (the cold pressor test) in a sample of 15 male Ecstasy users reporting a lifetime consumption of between 200 and 300 tablets, and 10 male non-Ecstasy users (O'Regan et al. 2004), with the cold pressor test considered a measure of pain tolerance. Ecstasy users and non-users were assessed mid-week, after attending a club or dance event, with Ecstasy users assessed three to four days after their most recent use of Ecstasy. The investigators did not assess Ecstasy tablet content, and volunteers did not undergo blood or urinary drug screening, so it is possible that some subjects had not taken MDMA, and that time since last use was either longer or shorter than reported.

Nevertheless, time until hand removal was shorter for Ecstasy users than for non-users, indicating greater sensitivity to cold-related pain, suggesting that decreased or changed pain tolerance is a possible sub-acute effect of MDMA. Since the researchers failed to perform an assessment at baseline or at a time when volunteers are unlikely to be experiencing sub-acute effects, the duration of this effect after Ecstasy use, or its relationship to regular Ecstasy use (rather than as a residual effect) remain unclear. Since the relationship between pain produced by the cold pressor test and other types of pain is not known, it is unclear whether this finding will generalize to chronic or cancer-related pain. However, Ecstasy users surveyed in previous reports listed somatic complaints, such as muscle aches and back pain, as occurring on the days following Ecstasy use (Cohen 1995; Peroutka et al. 1988). Regardless of whether reduced pain tolerance is a reliable measure of changes in serotonin availability, this study provides preliminary evidence that changed or reduced pain tolerance may be a sub-acute effect of Ecstasy use. To date, no clinical trials of MDMA have assessed pain perception immediately after MDMA or a day later. Curiously, some anecdotal reports of the therapeutic use of MDMA suggest a transient reduction in at least certain forms of chronic pain after MDMA or Ecstasy in a therapeutic context (Greer and Tolbert 1998; Holland 2001; Stevens 2000; Stevens 1999; Stevens 1997). Hence the net effect of MDMA on pain perception remains unclear but may be dependent upon the type of pain assessed and the time of assessment.

Oliveri and colleagues assessed visual cortical excitability in 10 Ecstasy users, most of them men, and 10 approximately gender-matched non-drug user controls (Oliveri and Calvo 2003). The researchers assessed Ecstasy users three days after they reported Ecstasy use. Subjects underwent transcranial magnetic stimulation (TMS) to induce phosphenes (perception of discrete dots or blobs of light in a darkened space), and recorded how much stimulation was needed to produce phosphenes in each volunteer. The investigators interspersed real TMS with "sham" TMS to prevent volunteers from knowing when stimulation was occurring. This study found that less stimulation was needed to produce phosphenes for Ecstasy users than to produce them in non-Ecstasy using controls. Hence changes resulting in a lower threshold for phosphenes generation, such as increased cortical excitability, may also be a sub-acute effect of Ecstasy. Oliveri and colleagues also reported that greater frequency of Ecstasy use was associated with a lower TMS threshold for producing phosphenes, and frequency of Ecstasy use was also related to likelihood of experiencing hallucinations (apparently during the course of the TMS session). Since Ecstasy users also reported use of cannabis, hallucinogens and other drugs, and because the study used a retrospective design, greater cortical excitability might also be associated with a pre-existing factor, or with concurrent use of other drugs. The significance of these research findings to clinical trials with MDMA remain unclear.

Only one study, an analysis of interviews with 417 of 466 Ecstasy users, examined self-reported long-term effects of Ecstasy use (Verheyden et al. 2003A). More than 25% of the sample reported experiencing tolerance to the effects of Ecstasy (needing to take more), decreased concentration, depressed mood and feelings of openness toward others. It is difficult to evaluate the significance of these self-reported long-term effects, largely

because they may be related to pre-existing conditions or the effects of polysubstance abuse. However, people reported experiencing both positive and negative long-term effects of Ecstasy use. The most common reasons listed for abstinence from Ecstasy use or reduction in use reported in a sample of 259 users was financial cost or perceived toll on the body, and the most common reasons for continuing or increasing Ecstasy use given by 82 interviewees were that Ecstasy use was part of an individual's lifestyle, and tolerance to the effects of Ecstasy.

Mood and Psychological Well-Being

On the basis of an assumed relationship between mood or psychological well-being and serotonin, researchers have sought to establish an association between repeated Ecstasy use and negative mood or psychological complaints. Studies published prior to July 2001 offered only mixed support for this relationship, with some studies reporting more psychological problems in Ecstasy users (i.e. Parrott and Lasky 1998; Gamma et al. 2000B; Gerra et al. 1998), while others failed to find an association, even when impaired cognitive function was detected in the same sample (i.e. Verkes et al 2000). By the end of 2002, a number of reports indicated that the association between Ecstasy use and negative mood states might be partly, if not mostly, due to other factors, such as concurrent cannabis use, polydrug use, or pre-existing conditions that may have led to Ecstasy use (i.e. Daumann et al. 2001; Lieb et al. 2002; Morgan et al. 2002).

While many studies appearing between 2003 and early 2004 found an association between Ecstasy use and psychological complaints or problems, a majority of these studies also lend strong support to one or more additional or alternative explanations for this association, including pre-existing conditions, substance use or abuse, and cannabis use. On the basis of an examination of previous and recent research, it appears increasingly unlikely that Ecstasy use directly produces a decline in psychological well-being. However, it remains possible that one or parameter of Ecstasy use may still play a role in this association.

Eleven studies assessed depressed mood or depression in Ecstasy users and controls (Alting von Geusau et al. 2004; Curran et al. 2004; 2003; Daumann et al. 2003A; Daumann et al. 2003B: de Win et al. 2004; Gerra et al. 2003; Halpern et al. 2004; Hanson and Luciana 2004; McCardle et al. 2004; Roiser et al. 2004; Thomasius et al. 2003). One study assessed anxious mood only (Dafters et al. 2004), and two studies assessed current mood state, either through the Profile of Mood States or through other means (McCardle et al. 2004; Jacobsen et al. 2004). Eight studies examined incidence of mood disorders or self-reported psychiatric symptoms (Alting van Geusau et al. 2004; Curran et al. 2003; Daumann et al. 2004; Halpern et al. 2004; Hanson and Luciana 2004; McCardle et al. 2004; Roiser and Sahakian 2004; Thomasius et al. 2003). Non-Ecstasy using controls in these studies included polydrug users (Curran et al. 2004; de Win et al. 2004; Roiser and Sahakian 2004; Thomasius et al. 2003), cannabis users (Curran et al. 2003; Dafters et al. 2004; Daumann et al. 2004; Jacobsen et al. 2004; McCardle et al. 2004) and drug-naïve or nearly drug-naïve individuals (Alting von Geusau et al. 2004; de Win et al. 2004; Hanson and Luciana 2004; Thomasius et al. 2003). One study used an Affective

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(emotion-related) Go/No Go task to measure affective bias (Roiser and Sahakian 2004), defined as the tendency to give more attention to items associated with a specific emotion or affect (for instance, greater attention to sad or unpleasant over happy or pleasant words or faces). A sixth study examined an all-male sample of former Ecstasy users only (last use = 1205 days), and included assessments of mood, self-reported negative mood states, impulsivity, and reasons for continued abstinence from Ecstasy (Verheyden et al. 2003B). A significant number of the studies listed above were either equally or primarily interested in neurocognitive changes (Alting von Geusau et al. 2003; Curran et al. 2003; Dafters et al. 2004; Halpern et al. 2004; Hanson and Luciana 2004; Jacobsen et al. 2004; McCardle et al. 2004; Thomasius et al. 2003), with only a few reports wholly focused on psychological well-being (Daumann et al. 2004; de Win et al. 2003; Roiser and Sahakian 2003).

While five of seven studies reported that Ecstasy users had significantly lower Beck Depression Inventory (BDI) scores than controls, two studies failed to find this relationship, or found only qualified support for it. Twenty-six age and gender matched Ecstasy users reporting use on an average of 64.9 ± 122.9 occasions had significantly higher BDI scores than 26 drug-naïve controls (Hanson and Luciana. 2004), though scores were not indicative of clinical depression. Former heavy Ecstasy users with a lifetime consumption of 268 ± 614 tablets and self-reported abstinence for 870 ± 612 days had significantly higher BDI scores than polydrug user controls (de Win et al. 2004), but both moderate (lifetime consumption = 29 ± 18 tablets) and heavy (lifetime consumption = 530 ± 621) current Ecstasy users did not have higher BDI scores than polydrug using controls. It is notable that no statistically significant differences in prevalence of mood disorders, diagnosed through psychiatric interview, were detected in the same sample described above. While a higher number of Ecstasy users in this study (across all groups) had been diagnosed with a mood disorder, the episode predated Ecstasy use in half of these cases. Roiser and Sahakian (2004) found that both current (abstinent for = 75 ± 79 days) and former (abstinent for 1021 ± 1018 days) Ecstasy users had significantly higher BDI scores than drug-naïve controls, but that there was only a trend for former Ecstasy users to have higher scores than polydrug user controls. The study of mood effects before, during and after Ecstasy use (Curran et al. 2004) found that while Ecstasy users had higher BDI scores than polydrug users four days after a night of substance use (Curran et al. 2004), BDI scores in both groups were comparable seven days later. Ecstasy users in this sample also reported being more discontented than polydrug users four, but not seven, days after use. At baseline, 32 current and 32 former Ecstasy users (all male) reporting last use of Ecstasy at 39 and 873.6 days respectively, with estimated lifetime consumption of 527 and 1105 tablets, had similar BDI scores to gender-matched cannabis user controls when assessed in a study chiefly designed to test the effects of manipulating tryptophan availability in Ecstasy users (Curran et al. 2003). A study comparing 17 Ecstasy users (lifetime consumption not reported; range = 2 to over 30 times, median = 4 to 9 times) with 15 cannabis user controls found significantly higher BDI scores in Ecstasy users that the authors described as “approaching clinical significance,” though as described below, no differences in state mood were detected between the two groups (McCardle et al. 2004). Lastly, there were no significant differences in the BDI scores of 23 Ecstasy users reporting lifetime use on 60 occasions

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and 16 very light polydrug user controls (Halpern et al. 2004). A review of study findings published in 2003 continues to support an association between regular Ecstasy use and higher BDI scores, but it also appears that pre-existing conditions and polydrug use may explain some of this association.

By contrast, all four investigations that assessed psychological well-being with the SCL-90-R, a self-report measure of psychological complaints, either failed to find differences between Ecstasy users and controls, or reported mixed results. One study found that all scores on the SCL-90-R save those for depression were higher in 60 Ecstasy users (lifetime use of 271 tablets) when compared with cannabis users at first examination (Daumann et al. 2004), while another study found that when compared to non-drug user controls, the only elevated SCL90R in 30 current (last use = 23 ± 16.14 days) and 31 former (last use = 515 ± 495 days) Ecstasy users to be depression scores (Thomasius et al. 2003). Thomasius and colleagues also found that polydrug users shared higher global, anxiety, obsessive-compulsive and interpersonal sensitivity scores with current and former Ecstasy users. When 19 of 38 participants in the sample studied by Daumann and colleagues were assessed again 18 months later, the authors found that continuing cannabis use was more strongly related to presence of psychological complaints than continued use of Ecstasy (Daumann et al. 2004). Only men in another sample of Ecstasy users (lifetime Ecstasy consumption = 53.82 tablets) had higher SCL90 anxiety, interpersonal sensitivity and "insufficiency of thought" scores when compared with a same-gender sample of non-drug users (Alting von Geusau et al. 2004), while women (lifetime Ecstasy consumption = 38.78) did not differ from gender-matched controls. Lastly, SCL-90-R scores of 23 Ecstasy users reporting a lifetime of 60 episodes of Ecstasy use and very little use of other substances were similar to the scores of 16 non-drug using controls (Halpern et al. 2004).

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Table 1
Studies of Mood, Psychological Well-being and Psychological Complaints

Frequency	Lifetime Use*	Duration	Period of Abstinence	Number, (M:F)	Comparisons+	Depression	Anxiety	Hostility	Impulsiveness	Reference
1.96 (2.44)	53.82 (35.56)	27.36 (NA)	>= 14	12 (12: 0)	ND	No	Yes	No	NA	Alting Von Geusau al. 2004-Men
1.44 (1.2)	38.78 (14.95)	26.88	>= 14	9 (0: 9)	ND	No	No	No	NA	Alting von Geusau et al. 2004-women
3.5 (1.8)	527.8 (734.5)	51.6 (34.8)	39 (22.6)	32 (32: 0)	CU	NA	NA	Yes, but also PD	Yes (one scale)	Bond et al. 2004-Current
7 (4.3)	1105.85 (1923.03)	42 (31.2)	873.6 (655.2)	32 (32: 0)	CU	NA	NA	Yes, but also PD)	Yes	Bond et al. 2004-Former
3.5 (1.8)	527.8 (734.5)	51.6 (34.8)	39 (22.6)	32 (32: 0)	CU	No	No	No	No	Curran et al. 2003-current
7 (4.3)	1105.85 (1923.03)	42 (31.2)	873.6 (655.2)	32 (32: 0)	CU	No	No	No	No	Curran et al. 2003-former
2.35 (0.86)	207.87 (21.98)	32.64 (17.04)	>=3	29 (20: 9)	CU	Yes D4, No D7**	NA	Yes D4, No D7**	NA	Curran et al. 2004
NA	363.8 (532.7)	NA	>= 7	16 (7: 9)	ND, CU	NA	No	NA	No	Dafters et al. 2004-heavy
NA	20.21 (10.5)	NA	>= 7	19 (10: 9)	ND, CU	NA	No	NA	No	Dafters et al. 2004-light
3.1 (1.8)	271.3 (454.4)	56.6 (47.3)	218.3 (374.9)	60 (42: 18)	PD, Post	No	Yes	Yes	Yes, 1 scale	Daumann et al. 2004-Time 1
0.6 (1.2)	21.1 (38.46)	8.95 (2.11)	206.1 (431.9)	19 of 38; NR	PD, Pre	NA	No	No	No	Daumann et al. 2004-Time 2
NA	268 (614.3)	55.2 (31.2)	870 (612)	16 (8: 8)	PD	Yes, BDI only	No	NA	NA	De Win et al. 2004-former
NA	530 (621.1)	55.2 (25.2)	69 (72)	23 (12: 11)	PD	No	No	NA	NA	De Win et al. 2004-heavy
NA	28.6 (17.8)	49.2 (31.2)	108 (177)	15 (9: 6)	PD	No	No	NA	NA	De Win et al. 2004-moderate
8.6 (4.6)	58.9 (29.5)	20.5 (10)	21	15 (15:0)	ND	Yes	NA	Yes, not all	NA	Gerra et al. 2003
NR	NR (med <50)	NR	NR (med = 60	23 (8:15)	Light PD	No	No	No	Yes?	Halpern et al. 2004
2.3 (2.0)	64.9 (122.9)	27 (22.9)	10.9 (10.5)	26 (14: 12)	ND	Yes, BDI, SCID	Unclear, NA	NA	NA	Hanson and Luciana 2004

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Frequency	Lifetime Use*	Duration	Period of Abstinence	Number, (M:F)	Comparisons+	Depression	Anxiety	Hostility	Impulsiveness	Reference
1.86 (2.73)	259.4 (301.2)	28.86 (18.86)	341.9 (449.2)	23 (18: 5)	ND	NA	NA	NA	Not Corr'd PPI	Heekeren et al. 2004
NA	10 (1-25)	NA	NA, > 2?	6 (4: 2)	CU	No$	No$	NA	NA	Jacobsen et al. 2004
NA	NR (med = 4 to 9)	26.4	31.5	17 (13:04)	CU	Yes	No	No	NA	McCardle et al. 2004
NA	NA	NA	NA	15 (15:0)	PD	Yes, state mood	NA	NA	NA	O'Regan et al. 2004
Highest (4.4)	273.4 (411)	NA	75 (79)	30 (15:15)	PD, ND	Yes, ND only	NA	NA	NA	Roiser and Sahakian 2004-Current
Highest (9.9)	792.6 (1525.8)	NA	1021 (1018)	20 (10:10)	PD, ND	Yes, ND only	NA	NA	NA	Roiser and Sahakian 2004-Former
NA	767.87 (579.04)	54.52 (28.13)	515 (495)	31 (16:15)	PD, ND	Yes	Yes, ND only	No	NA	Thomasius et al. 2004-former
NA	817.1 (1133.86)	53.01 (32.45)	23 (16.14)	30 (15:15)	PD, ND	Yes	Yes, ND only	No	NA	Thomasius et al. 2004-current
7.73 (5.13)	approx .1146)	47.85 (29.73)	1290.8 (814.9)	66 (66:0)	None	Yes in MH	No	Yes in C group	No	Verheyden et al. 2003

*Use in tablets or occasions
+ CU = cannabis users: ND = Non-drug users: PD = Polydrug users.
MH = Abstinent due to mental health changes, C = Abstinent due to circumstances.
**D4 = Four days post-drug: D7 = A week (7 days) post-drug.
$ POMS administered, apparently not analyzed; Depression and anxiety scores lower in Ecstasy users).

Formal measures of psychiatric illness, including clinician or observer-scored scales, were performed in four studies (de Win et al. 2004; Gerra et al. 2003; Halpern et al. 2004; Hanson and Luciana 2004). A sample of fifteen men who had contacted a drug abuse center and who were verifiably abstinent from Ecstasy for three weeks (lifetime consumption = 58.9 tablets) had higher MMPI Depression scores than fifteen age and gender-matched non-users drawn from the community (Gerra et al. 2003). Since people seeking information or help for drug abuse or dependence are expected to be in poorer mental health than non-drug users who have not sought help, these findings may be due at least in part to the nature of the sample. De Win and colleauges evaluated current ecstasy users (divided into heavy and moderate users) reporting lifetime consumption of 28.6 and 530 tablets, respectively, former Ecstasy users with a lifetime consumption of 268 tablets, and polydrug user controls with the Composite International Diagnostic Interview (CIDI), and failed to find any significant differences in CIDI scores between groups (de Win et al. 2004). Hanson and Luciana assessed 26 Ecstasy users reporting a lifetime use of about 65 (64.9) tablets for psychiatric illnesses with the Structured

Clinical Interview for DSM-IV (SCID). The researchers attained diagnoses for eight participants. Most diagnoses were for unipolar depression, and all episodes occurred prior to the study, though it is unclear whether diagnoses predated onset of Ecstasy use. Hanson and Luciana also diagnosed four of the eight participants with additional anxiety disorders. However, it should be noted that 14 of the participants in this sample also received a DSM-IV diagnosis of MDMA-related substance abuse, as well as abuse or dependence disorders relating to other substances, while controls were excluded on the basis of diagnosis with substance abuse. A sample of 23 Ecstasy users and 16 very moderate polydrug user controls closely matched for low use of other drugs did not differ with respect to clinician-rated depression or anxiety as assessed through the Hamilton Depression Scale and Hamilton Anxiety Scale (Halpern et al. 2004). The 23 users had reported a lifetime use of 60 occasions. In addition, two Ecstasy users had to be excluded from the follow-up assessment in a combined cross sectional and longitudinal examination of psychological complaints in Ecstasy users and cannabis user controls (Daumann et al. 2004) because they had developed psychiatric symptoms. However, as previously described, these researchers also reported that cannabis use was more strongly tied to psychological problems than Ecstasy use. Research employing observer-scored and formal assessment of psychological well-being and presence of psychiatric illness seems to produce mixed results, with some studies reporting increased psychiatric diagnoses in Ecstasy users and controls, and some reporting no group differences.

Both studies assessing current mood state in Ecstasy users found that Ecstasy users' self-reported mood was similar to that of controls. A study comparing 17 Ecstasy users (lifetime consumption not reported; range = 2-over 30 times, median = 4 to 9 times) and 15 cannabis-user controls (McCardle et al. 2004) found that POMS scale scores were similar across both groups. Jacobsen and colleagues also failed to find any differences in POMS scale scores between a sample of six adolescent Ecstasy users reporting use of Ecstasy on ten occasions and six cannabis user controls.

One research team sought to assess presence of sad or negative mood through the Affective (mood related) Go/No Go procedure in current and former Ecstasy users, polydrug user and drug-naïve controls (Roiser and Sahakian 2004). Another study required Ecstasy users and drug-naïve controls to identify a previously shown face after viewing isolated features, varying the gender and mood expressed by the faces (Hanson and Luciana 2004). Both studies failed to find differences between Ecstasy users and controls, leading the authors to conclude that in fact Ecstasy users were not more attentive to or more likely to experience negative mood than controls. There was a trend for Ecstasy users to do less well than drug-naïve controls in recalling sad faces only (Hanson and Luciana 2004), and there was a trend for current Ecstasy users to show more rapid response to positive items in the Go/No Go procedure (Roiser and Sahakian 2004). However, there was also a trend for both current and former Ecstasy users to make fewer errors when first viewing sad items than either control group. Considering results from both studies, it seems regular Ecstasy use had little impact on the accessibility of either positive or negative moods, and trend-level findings are somewhat contradictory, suggesting greater accessibility for and recall of both positively and negatively valenced items.

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In a study of male abstinent Ecstasy users, volunteers reported abstaining either because of self-described psychological problems (such as anxiety, paranoia, or depressed mood), or because of changes in life circumstance, such as a decline in quality of Ecstasy, no longer enjoying the drug, or no longer clubbing (Verheyden et al. 2003B). Men who said they stopped using Ecstasy because of mental health problems were five years younger than those who said they stopped using Ecstasy because of changes in circumstances, and they also reported earlier onset of Ecstasy use. An analysis taking age into account found that those abstaining for mental health reasons had significantly higher BDI scores than those abstaining for circumstantial reasons, and respondents abstaining from Ecstasy for mental health reasons had higher anxiety on the Hospital Anxiety and Depression (HADS) scale. Those abstaining for circumstantial reasons had higher scores on a measure of anger (the Multidimensional Anger Inventory, or MAI). However, there were no significant differences between the two groups of former Ecstasy users on the HADS depression scale. The two groups of abstinent Ecstasy users were further distinguished by the number of Ecstasy use parameters associated with elevated scores on measures of depressed mood (BDI), anxiety (STAI) and anger (MAI), with many correlations found between parameters of Ecstasy use and these measures in the "mental health" abstainers, but not in the "circumstantial" abstainers. In fact, the only measure correlated with Ecstasy use parameters in the "circumstantial" abstainers (average dose per use, frequency of use and physical aggression) was also associated with duration of cocaine use in the same group. These findings could either be considered evidence for the existence of a sub-set of Ecstasy users sensitive to effects of Ecstasy use on mood, but it could also be considered a sign that at least some Ecstasy users take the drug to self-medicate in response to other psychological problems. .

A thorough examination of all the results described above does not provide a simple understanding of the nature and strength of the relationship between repeated Ecstasy use and reductions in psychological well-being, as indicated by increased signs of depression or anxiety. It appears that repeated Ecstasy use as at least sometimes associated with increased signs of depression. On the other hand, few studies found Ecstasy use to be associated with a psychiatric diagnosis, and Ecstasy users did not seem to have a greater number of psychological complaints than controls. Given the findings reported in the longitudinal study, as well as previous findings drawn from a study in a large representative sample (Lieb et al. 2002), it seems equally likely that pre-existing conditions may lead some individuals to decide to use Ecstasy.

A report chiefly focusing on neurocognitive performance in Ecstasy users and controls also assessed self-reported anxious mood in 19 light Ecstasy users (lifetime consumption of 20.21 ± 10.5 tablets), 16 heavy Ecstasy users (lifetime consumption = 363.8 ± 532.7 tablets), 15 cannabis users and 19 non-drug using controls (Dafters et al. 2004). The researchers failed to find differences in anxiety levels for any of the groups, suggesting that regular use of Ecstasy and cannabis did not lead to an increase in anxiety. In another study, seventeen Ecstasy users (lifetime consumption not reported; median = 4 to 9 occasions, range = 2 to over 30 occasions) were not more anxious than 15 cannabis user controls (McCardle et al. 2004), as assessed by POMS anxiety score.

Previous and current examinations of psychological well-being in Ecstasy users continue to offer inconclusive findings suggesting a complex relationship between Ecstasy use and observer-rated or self-reported psychological problems. Only a longitudinal study similar to that carried out by Lieb and colleagues using measures of mood state or psychological function prior to onset of drug use will be able to distinguish attempts to self-medicate from problems caused by drug use. Though it may be the case that some individuals are sensitive to a mood-reducing effect associated with regular Ecstasy or psychostimulant use (i.e. Verheyden et al. 2003B), the bulk of recent research indicates that regular Ecstasy use is not uniquely associated with any particular psychological complaint. Rather, there is an association between the tendency to use drugs (cannabis or polydrug use) and psychological complaints. It remains unclear whether pre-existing psychological problems lead to increased drug use, or whether drug use leads to psychological problems.

Several parameters of Ecstasy use were associated with elevated negative mood and psychiatric problems, including lifetime consumption (de Win et al. 2004, log transformed number of tablets; Roiser and Sahakian 2004), frequency (Roiser and Sahakian 2004), duration (Curran et al. 2004, on Day 7), (de Win et al. 2004), and average dose per use (Thomasius et al. 2003). Daumann and colleagues found that at baseline, age of onset of Ecstasy use was positively correlated with some increased SCL-90-R scores (obsessive-compulsive, interpersonal sensitivity, depression and paranoid ideation). This may be similar to findings of earlier onset of Ecstasy use in former users who abstained from further use because of mental health problems (Verheyden et al. 2003B). Analyses controlling for the effects of frequency of use failed to find a relationship between lifetime consumption, suggesting that frequency of use may mediate the relationship between lifetime consumption and elevated BDI scores. Thomasius and colleagues found that SCL-90-R scores for somatization, anxiety, paranoid ideation and depression scores were predicted by average dose per use (Thomasius et al. 2003). Given these associations, it is possible that one or more aspect of Ecstasy use, or other factors correlated with the ecstasy use parameters described above, may elevate risk of experiencing negative mood states or psychological problems. On the other hand, a consideration and comparison of previous and current reports suggests that drug-use variables are not always tightly linked with findings of psychological problems. For instance, lifetime Ecstasy consumption ranged from 49.6 tablets (Morgan 1998) to 270 tablets (Gamma et al. 2000B) in studies in the IB reporting at least one positive finding with respect to mood or psychological problems. Though minimal doses in current studies are lower (21.1 for Daumann et al 2004-Time 2), maximum doses can be considerably higher (1105 tablets, reported in Bond et al. 2003), and six of the ten groups reporting lifetime exposure are higher than the maximum lifetime exposure listed in the IB. Likewise, frequency of use and duration of use appear similar in both groups of studies. Time since last use is unlikely to be a factor, since former users were more likely than current ones to have higher depressed mood, anxiety or other psychological complaints (de Win et al. 2004; Roiser and Sahakian 2004). Taking all this information into account, it appears that differences in drug use cannot readily or uniquely explain differences in findings.

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However, all studies reviewed here that contain polydrug using or cannabis using controls save one also detected relationships between use parameters for one or more other drug and negative mood states or psychological problems, and the only report that failed to find this relationship either did not perform analyses to detect it or did not report findings of such analyses. This strongly supports a more general association between polysubstance abuse and depression, anxiety and other psychological problems. Substances associated with a decline in psychological health included cannabis (Daumann et al. 2004), amphetamine (Daumann et al. 2004, baseline; Thomasius et al. 2003), and amyl nitrate (Roiser and Sahakian) all were associated with one or more measure of depression or psychological problems. Curran and colleagues failed to find any differences when comparing Ecstasy users with cannabis user controls. Since these studies are all retrospective, it is difficult to tell whether reduced psychological well-being in study respondents arose as a result of repeated use of the substances listed above, or whether substance use is a mark of pre-existing conditions affecting mood and psychological well-being.

No relationship was found between serotonin transporter density, as measured imaging with the ligand Beta-CIT, and self-reported depression (de Win et al. 2004). Though criticism has been leveled at the accuracy of assessments made with Beta-CIT (Kish 2003; 2002), Thomasius and colleagues used a more reliable radioactive drug or ligand, McN5652, and they also failed to find a relationship between serotonin transporter density, which was slightly lower in current Ecstasy users, and depression or other negative mood states, found to be higher in both current and former Ecstasy users (Thomasius et al. 2003). Findings drawn from a study of 32 current and 32 former Ecstasy users (lifetime consumption of current and former, 527.8 and 1105.8 tablets, respectively) and cannabis-user controls (Curran et al. 2003) also fails to support a simple association between a presumed indicator of serotonin system function and decline in psychological well-being (Curran et al. 2003). This study found that current and former Ecstasy users were not more sensitive to the mood-altering effects of tryptophan depletion or augmentation than cannabis user controls. Hence even if regular Ecstasy use is associated with increased depression or anxiety, this increase cannot be considered an indirect marker for changes in the serotonin system.

Anger and Aggression

Researchers continue to assess Ecstasy users on aggressiveness, on the assumption that reduced serotonin levels will be associated with increased aggression.
Previous research on the relationship between repeated Ecstasy use and aggression reviewed in the 2002 update to the IB had proved inconclusive (see Daumann et al. 2001; Gerra et al. 2002; Gerra et al. 2001). Some researchers reported that Ecstasy users had transient elevations in self-reported aggression (Gerra et al. 2000), and that they responded more aggressively than non-drug using controls in an aggression-eliciting task (Gerra et al. 2002). On the other hand, a different research team reported that aggression in Ecstasy users was more strongly associated with cannabis use than with Ecstasy use (Gouzoulis-Mayfrank et al. 2002).

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From 2003 to early 2004, four studies published by the same team in England investigated aggression and anger in Ecstasy users (Bond et al. 2003; Curran et al. 2004; 2003; Verheyden et al. 2003A). Two studies focused on anger, self-reported aggression and cognitive biases related to anger or aggression in Ecstasy users (Curran et al 2004; Bond et al. 2003), and another study assessed anger in abstinent Ecstasy users (Verheyden et al. 2003A). Additionally, trait aggression was correlated with parameters of Ecstasy use in a study using the same sample studied by Bond and colleagues (Curran et al. 2003). One of these studies study compared male and female Ecstasy users with cannabis user controls (Curran et al. 2004), and investigated angry cognitive bias four days after Ecstasy use, with angry cognitive bias referring to an increase in attention to anger or aggression-related stimuli. Bond and colleagues examined angry cognitive bias in all-male samples of current Ecstasy users that had abstained from Ecstasy for at least three weeks, former Ecstasy users that had been abstinent for at least a year, and polydrug using controls (Bond et al. 2003).

Curran and colleagues (2004) reported that four days after Ecstasy use, 29 male and female Ecstasy users with a lifetime consumption of 207.9 tablets were quicker to recognize aggressive sentences than non-aggressive ones, but this difference was no longer apparent seven days after use. There were no increased attention to aggression-related material was seen in 32 cannabis user controls four days attending a club or dance event. It is possible that increased attention to anger or aggression is a sub-acute effect of Ecstasy use rather than a long-term effect. When Bond and colleagues used a similar measure (differing only in its reliance on stories instead of sentences) to assess cognitive bias for anger in all-male samples of Ecstasy users and cannabis-user controls, they failed to find any differences between 32 current Ecstasy users (lifetime consumption of 527.8 tablets, time since last use = 39 days), 32 former Ecstasy users (lifetime consumption = 1105.8 tablets, time since last use = 873.6 days) and 32 cannabis using controls (Bond et al. 2003). In their paper, Bond and colleagues stated that all three groups of men showed a bias for perceiving anger when their scores were compared with other samples, leading the researchers to conclude that substance use (and not Ecstasy use per se) was associated with readiness to perceive and attend to anger or aggression. Current and former Ecstasy users in this study had similar scores on one measure of anger (the Multidimensional Anger Inventory), though former Ecstasy users scored higher on specific scales of the Aggression Questionnaire (AQ), like the Hostility scale. All groups felt more sedated and less alert after tryptophan depletion and all groups produced more aggressive or angry story endings under tryptophan depletion, with current and former Ecstasy users no more or less sensitive to this indirect means of manipulating brain serotonin than controls. Curran and colleagues reported a negative association between time since last use and AQ hostility scales in what is liable to be the same sample of Ecstasy users and cannabis user controls (Curran et al. 2003), with decreasing Hostility scores associated with longer periods of abstinence from Ecstasy.

The same team of researchers also investigated mood and reasons for abstinence in a group of 66 male Ecstasy users with an estimated lifetime consumption of 1146 tablets (Verheyden et al. 2003A). The sample almost certainly includes individuals assessed in

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the second assessment of angry bias (Bond et al. 2003), since subjects were all screened for enrollment in this study. Men who abstained from Ecstasy due to changed life circumstances had higher AQ scores than men who abstained from Ecstasy use for mental health reasons. Former users abstaining for mental health reasons experienced anger for a longer period of time than those who abstained as a result of life circumstances. Without a control group, it cannot be said that either group had scores that differed from other populations. Instead, the findings point out differences among groups of former Ecstasy users, indicating that not all former users have the same levels of trait aggressiveness.

Following the program of research they began in 1998, Gerra and colleagues recently published more studies investigating degree of aggression and hostility in samples of male Ecstasy users seeking information or treatment from a drug abuse clinic. In a recent study examining neuroendocrine responses to stress in Ecstasy users, Gerra and colleagues reported that three weeks after abstinence from Ecstasy use verified through urinary drug screening, 15 men reporting lifetime Ecstasy use of 58.9 occasions had higher Direct Aggression and Guilt subscales on the Buss-Durkee Hostility Inventory (BDHI, Italian translation) than 15 gender-matched controls drawn from the community (Gerra et al. 2003). However, Ecstasy users' scores on the rest of the scale were not significantly different from those of controls.

Since the SCL90 and SCL90R have a Hostillity sub-scale, information on degree of aggression or hostility can also be gathered from the four research teams that employed the SCL90R in their studies (Alting von Geusau et al. 2004; Curran et al. 2003; Daumann et al. 2004; Thomasius et al. 2003). Three of four published reports found no differences in Hostility scores for Ecstasy users and controls (Alting von Geusau et al. 2004; Curran et al. 2003; Thomasius et al. 2003), while in one case, Ecstasy users had higher Hostility scores than non-drug users on initial examination, but not when assessed again at a follow-up performed 18 months later (Daumann et al. 2004). Instead, it appeared that cannabis use was more closely related to increases on the Hostility and all other SCL90R sub-scale scores. Interestingly, a study reporting higher anxiety in male, but not female, Ecstasy users did not find higher Hostility scores in male Ecstasy users (Alting von Geusau et al. 2004); as with all other measures of psychological well-being, female Ecstasy users and mostly drug-naïve controls did not differ on Hostility scores either. In addition to these studies, a study that assessed angry mood with the POMS failed to find differences in mood between 15 Ecstasy users (lifetime consumption not listed; median = 4 to 9 occasions) and 17 controls (McCardle et al. 2004).

Most of the recently reviewed studies failed to find evidence in support of an association between Ecstasy use and increased anger, aggression or hostility. It seems more likely that elevated aggression or anger is associated with one or more pre-existing factors, and these, in turn, may be related to substance use. Note that one study explicitly noting increased attention to anger-related stimuli in all drug using samples (Bond et al. 2003). However, four of the studies reviewed were performed by the same team (Bond et al. 2003; Curran et al. 2004; 2003; Verheyden et al. 2003A), and three of these studies used overlapping or identical samples (Bond et al. 2003; Curran et al. 2003; Verheyden et al.

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2003A). One of the other studies not performed by this group did find evidence for at least some increases in aggressiveness (Gerra et al. 2003). However, most of the studies using the SCL90R also did not find an increase in aggressiveness or anger in Ecstasy users. In conclusion, it seems that regular Ecstasy use is not very strongly associated with increased aggressiveness or anger, making it very unlikely that human volunteers in clinical trials of MDMA will experience long-term increases in anger or aggressiveness. However, taking findings reported in Currran et al. (2004) into consideration, it is possible that transient increases in attention to anger or aggression may be among the sub-acute effects experienced a few days after drug administration, perhaps akin to the irritability and anxiety listed by some participants in previous trials (see the IB; Liechti et al. 2001).

Impulsivity

To date, researchers seeking to detect personality differences in Ecstasy users have assessed self-reported and behavioral impulsivity, with some studies detecting differences in psychometrically assessed (Gerra et al. 1998; Morgan et al. 2002; Morgan 1998; Tuchtenhagen et al. 2000) and behaviorally assessed (Morgan 1998) impulsivity, while other studies failed to find differences in impulsivity (Fox et al. 2001A; Rodgers et al. 2000), and even decreased impulsivity (McCann et al. 1994). As discussed in the IB and in the 2002 update to the IB, the relationship between Ecstasy use and impulsivity is complex, especially since use of illicit drugs is a behavior that may already be indicative of novelty seeking and impulsivity.

Seven studies assessed impulsivity in Ecstasy users (Bond et al. 2003; Curran et al. 2003; Dafters et al. 2004; Daumann et al. 2004; Gouzoulis-Mayfrank et al. 2003; Thomasius et al. 2003; Verheyden et al. 2003A). Four studies employed the Baratt Impulsivity Scale, a psychometric measure (Bond et al. 2003; Curran et al. 2003; et al. 2003; Daumann et al. 2004; Verheyden et al. 2003A). The IVE (Impulsiveness, Empathy and Venturesomeness) questionnaire, another self-report measure, was also used (Dafters et al. 2004) and a another study employed a Go/No Go task used to assess attention, but also considered a measure of impulsivity (Gouzoulis-Mayfrank et al. 2003; Thomasius et al. 2003). Two reports describe data drawn from identical samples (Bond et al. 2003; Curran et al. 2003). Only three of seven studies detected greater impulsivity in Ecstasy users (Bond et al. 2003; Curran et al. 2003; Daumann et al. 2004), with two of three reporting findings form the same sample. It is somewhat surprising to find so few reports of elevated impulsivity in Ecstasy users, considering the number of previous publications reporting an association between regular Ecstasy use and impulsivity. Current Ecstasy users with a lifetime consumption of 527.8 tablets had higher total BIS scores than polydrug users (Bond et al. 2003; Curran et al. 2003), and both current users and former users with a lifetime consumption of 1105.85 tablets had higher motor impulsivity than cannabis users (Bond et al. 2003; Curran et al. 2003). At baseline, Ecstasy users reporting a lifetime consumption of 271.3 tablets had higher non-planning impulsivity and Sensation Seeking Scale (SSS) experience-seeking than cannabis users (Daumann et al. 2004). However, eighteen months later, no differences in impulsivity were detected in these groups, and continuing Ecstasy use was not associated with any changes in

impulsivity. Neither Ecstasy users reporting heavy (lifetime consumption = 363.8 tablets), nor those reporting light (lifetime consumption = 20.21 tablets) consumption had higher scores on the IVE Impulsiveness scale than non-drug user or cannabis user controls (Dafters et al. 2004). Current Ecstasy users with a lifetime consumption of 817.1 tablets, and former users with a lifetime consumption of 767.9 tablets (Thomasius et al. 2003) did not differ from polydrug users or non-drug users on Go/No Go task performance, and another study found that 30 light (lifetime consumption = 39.5 tablets) and 30 heavy (lifetime consumption = 503.2 tablets) Ecstasy users did not differ from 30 cannabis user controls on Go/No Go task performance (Gouzoulis-Mayfrank et al. 2003). Since Thomasius' samples used Ecstasy as extensively as the sample studied by Bond and colleagues, it seems that impulsivity is not associated with lifetime consumption of Ecstasy. If impulsivity is a trait seen in substance users, then the low number of recent studies finding greater impulsivity in Ecstasy users may be the result of more studies relying on cannabis user or polydrug user controls. However, studies that found significant differences employed polydrug or cannabis user controls, so it is still possible that regular Ecstasy use is related to greater impulsivity. Overall, it seems that the association between impulsivity and regular Ecstasy use remains inconclusive, and the risk of increased impulsivity faced by people taking part in clinical trials is likewise extremely low.

Cognitive Function

As first noted in the IB, regular Ecstasy use has been associated with reduced performance on measures of neurocognitive function, particularly on measures of verbal recall and executive function, defined as the ability to plan, make decisions, and regulate behavior (as inhibiting responses). The majority of studies reviewed in the 2002 update to the IB continued to find reductions in verbal memory (see Fox et al. 2001A; Morgan et al. 2002; Reneman et al. 2001B: Reneman et al. 2001C), visual memory (Fox et al. 2002) and executive function (Zakzanis and Young 2001). However, other studies failed to find an association between Ecstasy use and verbal (Fox et al. 2001B) or verbal and non-verbal (Simon et al. 2002) memory, with Simon and colleagues finding instead that regular cannabis use had a stronger link to reductions in memory. Studies of cognitive function in Ecstasy users are marked by the methodological flaws found in studies of psychological function in Ecstasy users, as has been discussed in the IB and in other reviews of the literature. Nevertheless, many of the studies reviewed continue to find a link between repeated Ecstasy use and subtle but detectable deficits in memory and executive function. At the same time, a review of study findings in 2002 also noted a dissociation between these subtle impairments in cognitive function and indicators of reduced serotonin function (see for example Gijsman et al. 2002 versus Verkes et al. 2001), suggesting that impaired cognitive function cannot serve as an indicator of reduced serotonin function.

Since the completion of the 2002 update to the IB, research teams in Europe and North America have published 13 studies of cognitive function in Ecstasy users (Alting von Geusau et al. 2004; Back-Madruga et al. 2004; Curran et al. 2003; Dafters et al. 2004; Daumann et al. 2003A; Daumann et al. 2003B; Gouzoulis-Mayfrank et al. 2003: Halpern

et al. 2004; Hanson and Luciana 2004; Jacobsen et al. 2004; McCardle et al. 2004; Thomasius et al. 2003; Wareing et al. 2004), and the results of an on-line survey of perceived cognitive function in Ecstasy users (Rodgers et al. 2003) has also been published. In addition to the original research studies described above, one researcher performed a quantitative review of the effects of Ecstasy use on memory (Verbaten et al. 2003).

Table 2
Papers and tests of cognitive function, and numbers of significant findings.
Sig = Significant, across all groups of Ecstasy users if more than one group present. Qualified sig = significant only in group of Ecstasy users, or only in some measures, or no longer significant when analyses controlled for one or more other substance. NS = Not significant, across all groups of Ecstasy user tested if more than one group.

Function measured	% papers assessed?	% signif	Sig.	Qualified Sig,	NS
Immediate memory	8/13	6/24 (25%)	1	5	2
Delayed memory	7/13	9/27 (33%)	1	4	2
Verbal memory	8/13	19/48 (40%)	1	6	1
Visual memory	4/13	3/14 (21%)	0	2*	2
Working memory	13/13	16/57 (28%)	3	5	5
Executive Function	7/13	16/50 (32%)**	1	3*	3
Attention	6/13	8/30 (26%)	2	1	3
Information processing	4/13	1/14 (7%)	0	1	3
Psychomotor speed	4/13	2/18 (11%)	0	2	2

*Trend reported for at one paper.
**27 additional tests were significant in men only -

Domains of cognitive function assessed include attention (Curran et al. 2003; Dafters et al. 2004; Gouzoulis-Mayfrank et al. 2003; Hanson and Luciana 2004; Jacobsen et al. 2004; Thomasius et al. 2003), executive function (Back-Madruga et al. 2004; Curran et al. 2003; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Hanson and Luciana; Thomasius et al. 2003; Alting Von Geusau et al. 2004), memory (Back-Madruga et al. 2004; Curran et al. 2003; Daumann et al. 2003A; Daumann et al. 2003B; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Hanson and Luciana 2004; Thomasius et al. 2003; Wareing et al. 2004), and other functions, such as information processing speed (Back-Madruga et al. 2004; Halpern et al. 2004; Thomasius et al. 2003). While most of the studies detected differences between Ecstasy users and controls in cognitive function, the majority of the studies qualified their findings, noting that differences in Ecstasy use patterns, use of other drugs, or other variables, such as diagnosis with a drug abuse disorder, may also explain some of the differences in cognitive function. None of the

studies in Ecstasy users imply that exposure to a small number of doses of MDMA produce the same impairments in cognitive function seen after repeated Ecstasy use in uncontrolled settings, and a number of studies even suggest that the risk of impaired cognitive function is negligible in light or moderate Ecstasy users. Extrapolating from these findings suggests that the risk of impaired cognitive function associated with taking part in a clinical trial of MDMA is minimal. As already noted in the discussion of clinical trials, data presented from prospective studies of cognitive function in people taking MDMA in controlled settings have so far failed to detect any cognitive deficits Studies in Ecstasy users only serve to inform an estimation of the upper limits of potential risk in these studies.

Attention

As reported in the IB and the 2002 update of this document, researchers have generally failed to detect differences in attentional processes (e.g. Gouzoulis-Mayfrank et al. 2000; Rodgers 2000; Zakzanis and Young 20001), though some studies report that attention is affected in Ecstasy users (McCann et al. 1999).

Six reports appearing in 2003 and early 2004 assessed attention or processes relating to attention in Ecstasy users (Curran et al. 2003; Dafters et al. 2004; Gouzoulis-Mayfrank et al. 2003; Hanson and Luciana 2004; Jacobsen et al. 2004; Thomasius et al. 2003). Of these six studies, three reported finding that Ecstasy users had some impairments in attentional processes (Dafters et al. 2004; Hanson and Luciana 2004; Jacobsen et al. 2004), and one report found an indication of altered attentional processes in current and former Ecstasy users (Curran et al. 2003). Dafters and colleagues found that both 19 "moderate" Ecstasy users (lifetime consumption of 20.21 tablets) and 16 "heavy" Ecstasy users (lifetime consumption of 363.8 tablets) did less well at tracking the movements of a simulated "elevator" when compared with 19 non-drug users (Dafters et al. 2004). However, Ecstasy users' performance did not differ significantly from that of 15 cannabis user controls. In another study, 26 Ecstasy users reporting 64.9 occasions of Ecstasy use made more errors of omission in a letter cancellation task (failing to cancel a letter) when compared with 26 non-drug using controls, though without differences in response time or in errors of commission (Hanson and Luciana 2004). Jacobsen and colleagues reported that six adolescent Ecstasy users with at least ten episodes of Ecstasy use took longer to decide whether a given stimulus was a word or a non-word than six mostly cannabis-using controls, though in most cases error rate was similar in both groups. This study also reported an inverse association between response accuracy and number of times Ecstasy was used in the word/non word task, despite failing to detect impaired task accuracy in Ecstasy users. Jacobsen and colleagues fail to provide basic information on use parameters for Ecstasy or other drugs, and sample sizes are extremely small, so it is possible that study findings will not be replicated in larger studies. Finally, in a study of male Ecstasy users and cannabis users, 32 cannabis users performed a digit cancellation task more rapidly on the second administration of the task than 32 current (lifetime use = 527.8 tablets, period of abstinence = 39 days) and 32 former Ecstasy users (lifetime consumption = 1105.8, period of abstinence = 873 days), and both current and former Ecstasy users failed to increase speed of performance when the task was administered for

a second time (Curran et al. 2003). These findings suggest that Ecstasy users did not benefit from a practice effect, which could be interpreted as a sign of impaired attention, though Ecstasy users still performed the task as accurately as controls. It should also be noted that one of the studies that failed to find any overall effects of Ecstasy use on attention still found that when the sample was divided into Ecstasy users diagnosed with substance abuse disorders (n = 14, lifetime Ecstasy consumption = 95.4 occasions) and those without any drug abuse disorder diagnoses (n = 12, lifetime Ecstasy consumption = 29.3 occasions), Ecstasy users with substance abuse diagnoses took longer to perform a letter cancellation task than users without these diagnoses (Hanson and Luciana 2004).

Jacobsen and colleagues also reported that lifetime Ecstasy consumption was correlated with task accuracy on the word/non-word task, and that age of onset of use was associated with accuracy as well. In this study, earlier age of onset of Ecstasy use was associated with impaired task accuracy. However, as noted above, the sample size studied by Jacobsen and colleagues is very small, even by comparison with the generally small samples used in studies of Ecstasy users, making the findings less reliable.

Studies that failed to detect impaired attentional processes employed the Go/No Go task (Gouzoulis-Mayfrank et al. 2003; Thomasius et al. 2003), digit or letter cancellation tasks (Curran et al. 2003), and other tasks, such as visual scanning (Gouzoulis-Mayfrank et al. 2003). These studies compared Ecstasy users with non-drug users (Thomasius et al. 2003), cannabis users (Curran et al. 2003; Gouzoulis-Mayfrank et al. 2003) and a well-matched sample of polydrug users (Thomasius et al. 2003). Samples of Ecstasy users included current and former users reporting lifetime Ecstasy consumption of above 500 tablets (Thomasius et al. 2003), as well as Ecstasy users reporting lower levels of lifetime consumption (for instance, moderate users averaged a lifetime consumption of 39.5 tablets in the study of Gouzoulis-Mayfrank and colleagues).

Recent publications do not arrive at any new conclusions not previously reported in the IB or the 2002 revision of the IB. While it is true that one study reported on differences in attentional processes in adolescents only reporting 10 occasions of Ecstasy use, issues such as sample size, failure to report on any other aspect of Ecstasy use, including number of tablets taken per session, and issues relating to adolescent versus adult substance users make it difficult to generalize from these findings. As previously noted in the IB and in the 2002 revision to the IB, most studies failed to detect a link between repeated Ecstasy use and attention. It is notable that studies of samples reporting relatively high rates of Ecstasy consumption (e.g. Thomasius et al. 2003) did not detect differences in attentional function, while studies of Ecstasy users reporting lower rates of consumption (e.g. Hanson and Luciana) reported finding differences. Such comparisons suggest that an Ecstasy use parameter other than lifetime consumption, or some other factor independent of Ecstasy use, might lead to impaired attentional function in Ecstasy users.

Since one study found that deficits in attentional processes seen in Ecstasy users was seen in cannabis users as well, and another study examined a very small sample that was not ideally matched with respect to substance use, it seems possible that use of cannabis and

other drugs, or pre-existing conditions associated with polydrug use, may explain much of the association between Ecstasy use and impaired attentional processes. That people with diagnosed drug abuse disorders performed less well than those without them (Hanson and Luciana 2004) lends some support to a link between pre-existing factors associated with drug use and performance on these tasks. Taking into account previous assessments of attention in Ecstasy users reviewed in the IB and the 2002 update of the IB, and after reviewing current reports, it appears that repeated Ecstasy use is only weakly associated with changed or impaired attentional processes, and that risk of impaired attention in people taking part in clinical trials is extremely minimal.

Executive Function

Researchers have found impaired executive function in Ecstasy users, a domain associated with planning and decision making. The IB reported that 22.8% of 57 measures made in 11 reports detected reduced executive function in Ecstasy users, and approximately half of the studies reviewed in the 2002 revision of the IB found that Ecstasy users had reductions in executive function. In the IB, a correlation using data across studies akin to a meta-analysis found a negative relationship between lifetime Ecstasy consumption and scores on measures of executive function, implying that greater lifetime consumption of Ecstasy was associated with poorer performance on tasks of executive function.

Seven of 13 reports appearing in 2003 employed measures of executive function (Alting von Geusau et al. 2004; Back-Madruga et al. 2004; Curran et al. 2003; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Hanson and Luciana 2004; Thomasius et al. 2003). Researchers used a variety of measures, including well-known tests such as the Wisconsin Card Sort Test (WCST) (Alting von Geusau et al. 2004; Back-Madruga et al. 2004; Halpern et al. 2004; Thomasius et al. 2003), the "word fluency" task (word generation, sometimes referred to as the FAS task), (Curran et al. 2003; Halpern et al. 2004; Hanson and Luciana 2004) and the Tower of London (TOL) (Alting Von Geusau et al. 2004). Some researchers used less familiar measures, such as Plan-a-Day (Gouzoulis-Mayfrank et al. 2003), the Revised Strategy Application Test (R-SAT), a measure of planning and ability to adapt responses to changing situations (Halpern et al. 2004), and a test battery currently supported only by unpublished data (Alting Von Geusau et al. 2004).

Four out of seven studies either found that Ecstasy users scored lower on measures of executive function than controls (Alting von Geusau et al. 2004; Halpern et al. 2004; Hanson and Luciana 2004) or that lifetime Ecstasy consumption was related to performance on executive function measures (Curran et al. 2003). Additionally, one study reported a trend for Ecstasy users to score higher than controls (Back-Madruga et al. 2004), and another study found that polydrug users performed worse than Ecstasy users (Thomasius et al. 2003). However, in nearly every case, findings were qualified to some degree, with impaired executive function only seen sub-sets of Ecstasy users or on some measures.

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Hanson and Luciana reported that 26 Ecstasy users with an average lifetime Ecstasy consumption of 64.9 occasions made a greater number of errors on the verbal fluency test than 26 non-drug using controls, though they generated just as many words as the controls (Hanson and Luciana 2004). The 14 Ecstasy users in this study who were diagnosed with a substance abuse disorder (lifetime consumption = 95.4 occasions) scored lower on verbal fluency than did 12 Ecstasy users without any diagnosed drug abuse disorders (lifetime Ecstasy consumption = 29.3 tablets). A study that failed to find an overall effect of Ecstasy use on executive function found a gender effect instead (Alting Von Geusau et al. 2004). The researchers assessed executive function through several measures, including the WCST, the TOL, and the novel measure based on unpublished data. Seventeen men with a lifetime consumption of 53.85 tablets made more errors and took longer to perform a visual search task, took longer to perform a visual choice task, and performed less well on the TOL and the WCST when compared with 12 non-drug using men. By contrast, nine women reporting a lifetime consumption of 38.78 tablets scored lower on one subtest in the visual search task than 21 non-drug using women. Halpern and colleagues reported in their study of 23 Ecstasy users and 16 very moderate drug-user controls that the Ecstasy users, reporting a lifetime consumption of 60 occasions, had lower scores than the drug-user controls on the second trial of the R-SAT, but that Ecstasy users and controls did not have significantly different verbal fluency or WCST scores. However, when the researchers divided their sample into those who had used Ecstasy on fewer than 50 occasions (moderate users) and those who had used Ecstasy on 50 or more occasions (heavy users), Halpern and colleagues found that heavy users performed less well on the R-SAT, and on the WCST "categories" score, though there were still no significant differences in verbal fluency scores. An analysis controlling for age, gender and BDI scores still found that Ecstasy users scored lower on the R-SAT and on WCST "categories." It should be noted that both samples were very infrequent users of other drugs, suggesting that lower scores on these measures of executive function might relate to one or more parameter of Ecstasy use, or to factors associated with Ecstasy use. Curran and colleagues failed to detect any differences in executive function in all-male samples of current or former Ecstasy users (current users lifetime consumption = 527.8 tablets, abstinence = 39 days, former users lifetime consumption = 1105.8 tablets, abstinence = 873.6 days) when compared with 32 male cannabis user controls. However, these researchers did find an association between average dose of Ecstasy per use and performance on the verbal fluency "consonant' score (generate words sharing same first consonant) in former, but not current, users, with average dose per use for former users = 2.43 tablets. In contrast with these findings, Thomasius and colleagues found that 29 polydrug users performed worse than 30 current Ecstasy users (lifetime consumption of 817.1 tablets, time since last use = 23 days, 31 former Ecstasy users (lifetime consumption = 757.8. time since last use = 515 days) or 30 non-drug user controls on the WCST (Thomasius et al. 2003). In a study of 22 Ecstasy users reporting lifetime Ecstasy use of 74.6 occasions scored higher on the Auditory Consonant Trigrams task, a novel measure of executive function (Back-Madruga et al. 2004).

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Table 3
Assessment of Executive Function in Ecstasy Users and Significance of Results

Reference	Test	Sig, Controls	All controls	Other compare?	Type other	Lifetime consumption (Entire Sample)	Time since last use
Alting Von Geusau et al. 2004-men	D-T %Corr(vis search)	<0.05, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	D-T cost ms (vis search)	<0.05, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	D-T Cost%(vis search)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	D-T Mixing %(vis search)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	D-T Mixing ms(vis search)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	D-T RT(vis search)	<0.01, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	D-T RT(vis search)	<0.01, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	L-G %Corr (vis choice)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	L-G Cost ms (vis choice)	<0.01, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	L-G Cost% (vis choice	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	L-G Mix % (vis choice)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	L-G Mix ms (vis choice)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	L-G RT (vis choice)	<0.05, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	E-F %Corr (vis inhib)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	E-F %Corr (vis inhib)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	E-F int cost (vis inhib)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA

Reference	Test	Sig. Controls	All controls	Other compare?	Sig. Other	Lifetime Consumption (Entire Sample)	Time Since Last Use
Alting Von Geusau et al. 2004-men	E-F int cost 2 (vis inhib)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	E-F RT (vis inhib)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	Stop signal (vis cue inhibit)	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	TOL-Excess moves	<0.01, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	TOL-Plan time	<0.01, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	TOL-Total moves	<0.01, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	TOL-total time	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	WCST-# corr ambig	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	WCST-#persev	<0.05, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	WCST-ambig err	<0.05, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	WCST-concept level	<0.05, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-men	WCST-tot corr	NS, ND	ND	No	NA	53.85 +/- 35.56	NA
Alting Von Geusau et al. 2004-women	D-T %Corr(vis search)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	D-T cost ms (vis search)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	D-T Cost%(vis search)	<0.05, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	D-T Mixing %(vis search)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	D-T Mixing ms(vis search)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA

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Reference	Test	Sig. Controls	All controls	Other compare?	Type other	Lifetime Consumption	Time since Last Use
Alting Von Geusau et al. 2004-women	D-T RT(vis search)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	L-G %Corr (vis choice)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	L-G Cost ms (vis choice)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	L-G Cost% (vis choice	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	L-G Mix % (vis choice)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	L-G Mix ms (vis choice)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	L-G RT (vis choice)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	E-F %Corr (vis inhib)	<0.05, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	E-F int cost (vis inhib)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	E-F int cost 2 (vis inhib)	<0.05, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	E-F RT (vis inhib)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	Stop signal (vis cue inhibit)	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	TOL-Excess moves	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	TOL-Plan time	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	TOL-Total moves	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	TOL-total time	NS, ND	ND	No	NA	38.78 +/- 14.95	NA

Reference	Test	Sig. Controls	All controls	Other compare?	Type other	Lifetime Consumption	Time since Last Use
Alting Von Geusau et al. 2004-women	WCST-# corr ambig	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	WCST-#persev	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	WCST-ambig err	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	WCST-concept level	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Alting Von Geusau et al. 2004-women	WCST-tot corr	NS, ND	ND	No	NA	38.78 +/- 14.95	NA
Back-Madruga et al 2004	ACT (trigrams)	Trend, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	FAS	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	Stroop C	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	WCST categories	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	WCST concept level	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	WCST errors	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	WCST fail set	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	WCST persevere	NS, CU	CU	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/-178
Curran et al. 2003-Current	FAS-categories	NS, CU	CU	No	NA	527.8 +/- 734.5	39 +/- 22.6
Curran et al. 2003-Current	FAS-letters	NS, CU	CU	No	NA	1105.85 +/- 1923.03	39 +/- 22.6
Curran et al. 2003-Former	FAS-categories	NS, CU	CU	No	NA	1105.85 +/- 1923.03	873.6 +/- 655.2
Curran et al. 2003-Former	FAS-letters	NS, CU	CU	No	NA	1105.85 +/- 1923.03	873.6 +/- 655.2

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Reference	Test	Sig. Controls	All controls	Other compare?	Type other	Lifetime Consumption	Time since Last Use
Gouzoulis-Mayfrank et al. 2003-light	Plan-A-Day	NS, CU	CU	No	NA	39.5 +/- 18	242.3 +/- 401.4
Gouzoulis-Mayfrank et al. 2003-heavy	Plan-A-Day	NS, CU	CU	No	NA	503.2 +/- 555.5	194.8 +/- 394.8
Halpern et al. 2004	FAS-Words	NS, Lite PD	Lite PD	Yes, NS	Moderate, heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	FAS-Perseveration	NS, Lite PD	Lite PD	Yes, NS	Moderate, heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	R-SAT Total 1	NS, Lite PD	Lite PD	Yes, <0.01	Moderate, heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	R-SAT Tot no first page	NS, Lite PD	Lite PD	Yes, <0.01	Moderate, heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	WCST-Categories	NS, Lite PD	Lite PD	Yes, <0.05	Moderate, heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	WCST-persevere	NS, Lite PD	Lite PD	Yes, NS	Moderate, heavy	med = 60 oc	Med appr. 62.4
Hanson and Luciana 2004	FAS Errors	<0.05	ND	Yes, NS	Drug abuse diagnosis	64.9 +/- 122.9 oc	76.3 +/- 73.5
Hanson and Luciana 2004	FAS Inaprop word	NS, ND	ND	Yes, NS	Drug abuse diagnosis	64.9 +/- 122.9 oc	76.3 +/- 73.5
Hanson and Luciana 2004	FAS persevere	NS, ND	ND	Yes, NS	Drug abuse diagnosis	64.9 +/- 122.9 oc	76.3 +/- 73.5
Hanson and Luciana 2004	FAS total	NS, ND	ND	Yes, <0.05	Drug abuse diagnosis	64.9 +/- 122.9 oc	76.3 +/- 73.5
Thomasius et al. 2003-current users	WCST-failure maintain set	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	WCST-number categories	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	WCST-persevere	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-former users	WCST-failure maintain set	NS, PD & ND	PD, ND	No	NA	757.9 +/- 579	515 +/-495

Reference	Test	Sig. Controls	All controls	Other compare?	Type other	Lifetime Consumption	Time since Last Use
Thomasius et al. 2003-former users	WCST-number categories	NS, PD & ND	PD, ND	No	NA	757.9 +/-579	515 +/-495
Thomasius et al. 2003-former users	WCST-persevere	NS, PD & ND	PD, ND	No	NA	757.9 +/-579	515 +/-495

CU = Cannabis users, ND = Drug-naïve (non-drug users), PD = Polydrug users.
NS = Not significant.

While there is some evidence for an association between parameters of Ecstasy use and impaired executive function, findings are inconclusive. Upon reviewing all papers, it appears that reduced executive function is unrelated to lifetime Ecstasy consumption, as several studies that failed to find any differences had notably higher levels of lifetime Ecstasy consumption than studies finding lower scores on measures of executive function (for example, compare Thomasius et al. 2003 and Hanson and Luciana 2004). Halpern and colleagues found an association between log-transformed lifetime Ecstasy consumption (in occasions) and a WCST score, but they failed to find an association between lifetime Ecstasy consumption and R-SAT performance. Likewise, while Curran and colleagues found an association between average Ecstasy dose per use and a verbal fluency score in former users, they failed to detect the same relationship in current users.

There are some difficulties with interpreting study findings. The sample size used by Hanson and colleagues is within the range of commonly used samples for neurocognitive studies in Ecstasy users. However, controls may not have been completely matched on education, since all controls were university students, whereas slightly less than half of the Ecstasy users were students, with the rest being recruited by friends. Only one study previous to that of Alting Von Geusau and colleagues has reported gender differences in cognitive function in Ecstasy users (Bolla et al. 1998). While this study also found women less affected than men, it is notable that no other studies have reported similar gender effects. Since men in this sample had higher rates of Ecstasy consumption as assessed through several parameters of drug use (lifetime consumption as noted above, frequency of use, men = 1.96 days per month, women 1.44 days per month), it is possible that the apparent gender effect instead reflects differences in patterns of Ecstasy use. As well, the number of Ecstasy-using men are more well-matched in number with controls (12 versus 17), whereas the number of women Ecstasy users is smaller (9 versus 21 controls), and thus more vulnerable to apparent differences relating to intersubject variation.

Two of the studies that failed to find any differences in executive function employed polydrug user or cannabis user controls (Curran et al. 2003; Thomasius et al. 2003). In comparison, it is notable that at least some of the previous reports finding decrements in executive function failed to employ polydrug user controls (e.g. Bhattachary and Powell 2001; Wareing et al. 2000) or did not use polydrug user controls well-matched for

substance use (e.g. Heffernan et al. 2001). However, it should also be noted that one of the studies that found impaired executive function in Ecstasy users carefully matched samples for use of other drugs (Halpern et al. 2004). Considering findings from all recent studies, it seems that a factor associated with Ecstasy use and use of other drugs might be associated with performance on executive function tasks. Whether repeated Ecstasy use itself or some other factor is responsible for the association is less clear.

Earlier reviews of the literature tended to find a slightly greater number of studies finding associations between regular Ecstasy use and executive function (see the IB and the 2002 update to the IB). Findings in recent publications support a link between Ecstasy use and lower scores on measures of executive function, but they also raise questions about the nature of this link. It may be the case that in addition to Ecstasy use itself, other factors, such as use of other drugs, or a pre-existing condition associated with polysubstance abuse, may also be associated with reductions in executive function. The two studies that were most careful in controlling for the effects of substance use generated conflicting findings (Halpern et al. 2004; Thomasius et al. 2003), making it difficult to rule out either Ecstasy use, or other factors, as related to reductions in executive function. Recent publications offer support for a possible relationship between lifetime Ecstasy consumption, or factors associated with lifetime Ecstasy consumption, and impaired executive function, and they also point toward an association between impaired executive function and substance use more generally. An examination of these findings, along with past findings supports the risk estimation stated in the IB. Human volunteers in clinical trials may face a risk of impaired executive function, but the risk is minimal.

Memory

One finding consistently reported in the IB and in the 2002 revision to the IB is an association between repeated use of Ecstasy and lower scores on measures of memory, especially verbal memory. Thirty of 70 tests performed in 13 studies, or 42.9% of the research examined in the IB, found that Ecstasy users performed less well than controls. Of those studies, 55.8% of the measures of verbal recall detected differences, while only 16% of measures of visual recall detected a difference. A chi-square analysis performed in the IB demonstrated that even after accounting for the greater number of verbal recall tests, there were fewer significant findings of impaired visual recall. One of the only longitudinal assessments of cognitive function in Ecstasy users reported that Ecstasy users' scores on a measure of memory declined over time (Zakzanis and Young 2001). A review of research published or presented in 2002 continued to find decrements in verbal recall in Ecstasy users, though several studies failed to detect this decrement. As well, some studies published in 2002 reported finding impaired verbal recall (Fox et al. 2002). Some researchers have found that cannabis use may be associated with lower scores on at least some measures of memory (Croft et al. 2000; Morgan et al. 1998; Simon et al. 2002), but in general research supports a link between Ecstasy use and impaired memory. A discussion in the IB of some alternative hypotheses for the link between repeated Ecstasy use and impaired memory suggests that with the exception of use of other substances, these variables, such as loss of sleep or frequent attendance of dance events, do not explain the association between Ecstasy use and impaired memory.

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Thirteen papers published in 2003 to early 2004 assessed memory function in Ecstasy users and non-Ecstasy using controls. Five of these papers assessed working memory only (Daumann et al. 2003A; Daumann et al. 2003B; Jacobsen et al. 2004; Alting Von Geusau et al. 2004; Wareing et al. 2004), and eight papers measured other forms of memory as well (Back-Madruga et al. 2004; Curran et al. 2003; Dafters et al. 2004; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Hanson and Luciana 2004; McCardle et al. 2004; Thomasius et al. 2003). Probably on the basis of previous reports, some studies examined verbal recall only (Curran et al. 2003; Dafters et al. 2004; Hanson and Luciana 2004; Thomasius et al 2003), though three studies only assessed visual working memory (Daumann et al. 2003A; Daumann et al. 2003B; Wareing et al. 2004).

Ecstasy users scored lower than controls on at least one measure of memory in eight of thirteen papers (Back-Madruga et al. 2004; Curran et al. 2003; Dafters et al. 2004; Daumann et al. 2003A; Daumann et al. 2003B; Gouzoulis-Mayfrank et al. 2003; Hanson and Luciana 2003; Thomasius et al. 2003; Wareing et al. 2003). However, findings were often qualified, with six studies (Back-Madruga et al. 2004; Curran et al. 2003; Dafters et al. 2004; Gouzoulis-Mayfrank et al. 2003; Thomasius et al. 2003; Von Geusau et al. 2004) finding impairment in only some groups of Ecstasy users, or reporting that other factors, such as gender or cannabis use, were also associated with impaired memory. In addition, one study found that Ecstasy users diagnosed with substance abuse disorders had greater decrements in memory than Ecstasy users without substance abuse disorders (Hanson and Luciana 2004), and another study reported finding poorer performance in only one measure of visual working memory in heavy Ecstasy users without finding any differences in verbal recall (Halpern et al. 2004).

Working memory

Thirteen papers examined working memory in Ecstasy users and controls (Alting Von Geusau et al. 2004; Back-Madruga et al. 2004; Curran et al. 2003; Dafters et al. 2004; Daumann et al. 2003A; Daumann et al. 2003B; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Hanson and Luciana 2004; Jacobsen et al. 2004; McCardle et al. 2004; Thomasius et al. 2003; Wareing et al. 2004). Researchers assessed working memory with well-known measures, such as Digit Span (Back-Madruga et al. 2004; Dafters et al. 2004; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; McCardle et al. 2004; Thomasius et al. 2003) and the n-back task (Daumann et al. 2003A; Daumann et al. 2003B; Gouzoulis-Mayfrank et al. 2003; Jacobsen et al. 2004), and less familiar measures, such as measures of visual working memory (Alting Von Geusau et al. 2004; Halpern et al. 2004; Hanson and Luciana 2004; Wareing et al. 2004). Other measures were used as well, including serial sevens (Back-Madruga et al. 2004; Curran et al. 2003), or assessments of working memory and attention (Curran et al. 2003).

Eight of thirteen studies reported significant differences on performance on some measures of working memory in at least some groups of Ecstasy users (Alting von Geusau et al. 2004; Curran et al. 2003; Daumann et al. 2003A; Daumann et al. 2003B' Halpern et al. 2004; Hanson and Luciana 2004; McCardle et al. 2004; Wareing et al.

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2004), but with five of eight studies qualifying findings. A study comparing all-male samples of 32 current Ecstasy users (time since last use = 39 days), 32 former Ecstasy users (time since last use = 873.6 days) and 32 cannabis-using controls found that former Ecstasy users, who reported a lifetime consumption of 1105.8 tablets, had lower scores on a task involving visual information processing and executive function (the RVIP) and had lower Serial Sevens scores than cannabis users, but that current users performed similarly to controls (Curran et al. 2003). A study assessing working memory with the n-back task, which requires participants to delay to a visually presented number or letter for one or more successive presentations, in 8 "pure" Ecstasy users with a lifetime Ecstasy consumption of 74.5 tablets, eight Ecstasy users reporting greater use of other substances, and a lifetime consumption of 56.3 tablets, and non-drug using controls (Daumann et al. 2003b). Daumann and colleagues found slower response times to the n-back task for both "pure" and polydrug using Ecstasy users, but no differences in number of correct responses. In a study performed by Hanson and Luciana, 26 Ecstasy users with lifetime Ecstasy use of 64.9 occasions had lower scores than non-drug using controls on a measure of visual working memory when they had to delay their responses (Hanson and Luciana 2004), but Ecstasy users nevertheless responded more accurately. The same study that found gender effects on measures of executive function (Alting Von Geusau et al. 2004) also found that male Ecstasy users responded more slowly to a task assessing working memory and executive function than non-drug using controls when under increasing memory load (Alting von Geusau et al. 2004). In a study comparing six adolescent Ecstasy users (lifetime number of occasions = 10) and six adolescent moderate (mostly cannabis-using) polydrug user controls found a relationship between number of episodes of Ecstasy use and accuracy on the n-back task, but failed to report whether there were group differences on this task (Jacobsen et al. 2004). McCardle and colleagues reported that 17 Ecstasy users (lifetime consumption not reported; median = 4 to 9 occasions, range = 2 to over 30 occasions) scored lower on Forward Digit Span scores than 15 cannabis user controls, but the groups did not have significantly different scores on Digit Span-Backwards. Halpern and colleagues found that 23 Ecstasy users reporting very little use of other substances, (lifetime consumption of Ecstasy on an average of 60 occasions) did not have significantly lower Digit Span or spatial span scores than 16 controls matched for light use of other drugs (Halpern et al. 2004). When the sample of Ecstasy users was divided into moderate users (fewer than 50 occasions of use) and heavy users (50 or more occasions of use), Halpern and colleagues found that heavy Ecstasy users had lower visual (Spatial Span) working memory scores than controls, but that controls and heavy Ecstasy users still did not differ significantly on Digit Span scores. Moderate Ecstasy users in this study did not have lower scores than controls on either Spatial or Digit Span. A study of 25 current Ecstasy users (lifetime Ecstasy consumption = 655.6 tablets, time since last use = 23 days), 10 former users (lifetime Ecstasy consumption = 469.2 tablets, time since last use = 755.5 days) and polydrug user controls found that current and former users performed less well than polydrug users on simple spatial span (Wareing et al. 2004). However, Wareing and colleagues did not detect significant differences in performance on a more complex version of the task requiring participants to generate strings of letters or numeric sequences. Lastly, another study by Daumann and colleagues that assessed working memory with the n-back task in 11 heavy Ecstasy users (lifetime Ecstasy consumption =

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258.2 tablets), 11 moderate Ecstasy users (lifetime consumption = 27.4 tablets), and 11 moderate polydrug users (Daumann et al. 2003A) reported a trend for heavy, but not moderate, users to take longer to respond to the task and to make more mistakes on the most difficult level of the task. However, heavy Ecstasy users in this study performed similarly to moderate users and controls on easier levels of the n-back task.

Curran and associates found an association between frequency of Ecstasy use in former Ecstasy users and performance on the digit cancellation task described earlier in the section on attention (Curran et al. 2003), with greater frequency of use associated with spotting fewer targets. The researchers did not detect such a relationship in current users, an unsurprising result given that current Ecstasy users did not perform significantly differently from cannabis-user controls.

Studies that did not detect any differences in working memory between Ecstasy users and controls included four of five studies using Digit Span (Back-Madruga et al. 2004; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004, for total sample; Thomasius et al. 2003). While Hanson and Luciana reported that Ecstasy users scored lower on aspects of a measure of visual working memory, they failed to detect differences in scores on Digit Span or response to emotional faces (Hanson and Luciana 2004). Halpern and colleagues reported similar findings in a comparison of 23 Ecstasy users reporting 50 or more occasions of use and 16 very light drug-using controls, with Ecstasy users scoring lower on a measure of visual memory, but not on Digit Span (Halpern et al. 2004).

An examination of current publications suggests that lifetime Ecstasy use may not be associated with working memory performance, since no significant differences were found in samples reporting higher Ecstasy consumption than samples where significant differences were found. Likewise, presence of lower working memory scores in Ecstasy users did not seem to depend on the type of controls used in a study, as differences in working memory were found with studies with non-drug using, cannabis-using, and polydrug using controls (Curran et al. 2003; Daumann et al. 2003A; Daumann et al. 2003B; Halpern et al. 2004; Wareing et al. 2003), while at the same time, studies failing to find any differences also employed each type of control (Back-Madruga et al. 2003; Gouzoulis-Mayfrank et al. 2003; Thomasius et al. 2003). Besides the relationship between frequency of use and performance on serial sevens in former Ecstasy users (Curran et al. 2003) and a trend for cannabis use to be associated with visual working memory scores (Wareing et al. 2004), most studies failed to find associations between drug use parameters and working memory scores. Hence it is unclear what factor or factors lie behind the lower working memory scores in Ecstasy users. However, it does appear that perhaps surprisingly, there is more support for impaired visual working memory in Ecstasy users than there is for impaired verbal working memory. This stands in contrast to the more common finding of impaired verbal recall in Ecstasy users.

After examining all recent publications, it appears that recent reports continue to offer inconclusive evidence for a link between repeated Ecstasy use and impaired verbal and visual working memory. Since up to half of the studies detected reductions in working memory in at least some groups of Ecstasy users, it still seems that Ecstasy use, or some

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factor associated with Ecstasy use, affects working memory. However, given the lack of any clear pattern of findings across studies, it is not clear what these factors might be. In contrast with earlier reviews, it seems that Ecstasy use is more likely to affect visual working memory than verbal working memory. When compared with previous research, current research findings are less conclusive. Nevertheless, these findings do not greatly alter estimated risk of impaired working memory for participants in clinical trials given in the IB. Treating studies of Ecstasy users as a conservative upper limit for risk estimation, people receiving MDMA in controlled settings are likely to face minimal risk of impaired working memory.

Memory, Verbal and Visual

Eight papers assessed verbal or visual memory (Back-Madruga et al. 2004; Curran et al. 2003; Dafters et al. 2004; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Hanson and Luciana 2004; McCardle et al. 2004; Thomasius et al. 2003), and seven of eight publications reported lower scores in at least some Ecstasy users on one or more measure of memory. Two studies reported that differences in lifetime Ecstasy consumption were associated with presence or degree of reduction in memory (Back-Madruga et al. 2004; Gouzoulis-Mayfrank et al. 2003), while other studies reported a counter-intuitive association between more prolonged abstinence from Ecstasy and reductions in memory function (Curran et al. 2003; Thomasius et al. 2003). One study found that Ecstasy users scored lower than controls, but concluded that cannabis use, and not Ecstasy use, was responsible for this effect (Dafters et al. 2004), and another study reported that diagnosis with a substance abuse disorder was associated with additional reductions in memory in Ecstasy users (Hanson and Luciana 2004).

Measures of verbal memory included the Auditory Verbal Learning Test (AVLT) and similar list-recall tasks (Back-Madruga et al. 2004; Curran et al. 2003; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; McCardle et al. 2004; Thomasius et al. 2003) and Rivermead Behavioral Memory Test-story or similar prose recall tasks (Curran et al. 2003; Dafters et al. 2004; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Hanson and Luciana 2004; Thomasius et al. 2003). Visual memory was assessed with visual pair-association tasks (Back-Madruga et al. 2004; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Thomasius et al. 2003), the Rey-Osterrieth figure (Back-Madruga et al. 2004; Halpern et al. 2004) or assessments of spatial memory (Gouzoulis-Mayfrank et al. 2003;).

Prose recall tasks were especially likely to detect impaired verbal memory in Ecstasy users, with five of six studies that used prose recall tasks finding that at least some Ecstasy users scored lower on prose recall tasks than at least one group of controls (Curran et al. 2003; Dafters et al. 2004; Gouzoulis-Mayfrank et al. 2003; Hanson and Luciana 2004; Thomasius et al. 2003). Dafters and colleagues reported that both light (lifetime consumption of 20.21 tablets) and heavy (lifetime consumption of 363.8 tablets) Ecstasy users had lower story recall scores than non-drug using controls, but they also found that neither group of Ecstasy users had significantly lower scores than cannabis-using controls (Dafter et al. 2003). A study of 30 heavy Ecstasy users (lifetime 503.2),

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30 light users (lifetime consumption = 39.5 tablets), and 30 cannabis user controls found that heavy users, but not light users, differed from controls on both immediate and delayed story recall (Gouzoulis-Mayfrank et al. 2003). In a study assessing immediate and delayed prose recall scores in 26 Ecstasy users with lifetime use of 64.9 occasions found that Ecstasy users had lower age-corrected percentile scores on both immediate and delayed recall (Hanson and Luciana 2004), though it is notable that comparisons were made with established test norms and not with a sample of controls. Hanson and Luciana also found that the 14 Ecstasy users with substance use disorders (lifetime Ecstasy consumption = 95.4 occasions) scored lower on immediate and delayed prose recall than 12 Ecstasy users not diagnosed with substance use disorders (lifetime Ecstasy consumption = 29.3 occasions). Lastly, Thomasius and colleagues reported that 31 former Ecstasy users (time since last use = 515 days scored lower than 30 non-drug user controls on immediate and delayed story recall, though their scores were not significantly lower than those of 29 polydrug users. However, immediate and delayed story recall scores were similar in 30 current users (time since last use = 23 days) and both groups of controls. In addition, there was a trend for former users in the study of Curran and colleagues (time since last use = 841.3 days), but not current users (time since last use = 39 days) to perform less well on either immediate or delayed story recall. While Halpern and colleagues noted that 23 Ecstasy users did perform less well on a prose recall task than 16 light polydrug user controls (Halpern et al. 2004), these differences were not significant, and when the sample was divided into moderate users (fewer than 50 occasions of use) and heavy (50 or more occasions of use), even heavy users reporting 50 or more occasions of use did not have lower scores than controls.

Researchers employing other measures of verbal recall, such as the AVLT or similar measures involving lists of paired associations sometimes detected differences between Ecstasy users and controls, with four of six studies reporting lower scores in at least one group of Ecstasy users (Curran et al. 2003, former users on delayed recall only, Gouzoulis-Mayfrank et al. 2003, delayed recall in heavy users only, McCardle et al. 2004; Thomasius et al. 2003, former users versus non-drug users only). However, immediate recall scores in these studies were usually similar to those of non-drug using (Thomasius et al. 2003), polydrug using (Thomasius et al. 2003) or cannabis using (Curran et al. 2003; Gouzoulis-Mayfrank et al. 2003; McCardle et al. 2004) controls. AS well, investigations comparing both current and former Ecstasy users failed to find lower AVLT scores in current users (Curran et al. 2003; Thomasius et al. 2003). Halpern and colleagues reported that 23 Ecstasy users with an average lifetime use of 60 occasions did not have significantly lower list learning scores than 16 light polydrug user controls matched for drug use (Halpern et al. 2004). Dividing the sample of Ecstasy users into heavy users (50 or more occasions of use) and moderate users (fewer than 50 occasions of use) failed to find lower scores in heavy Ecstasy users. Another study that compared list learning scores in 22 Ecstasy users (lifetime exposure = 74.6 occasions) and 28 non-drug using controls selected from past ("archival") data even found a trend for Ecstasy users to score higher on delayed AVLT than controls (Back-Madruga et al. 2004).

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Table 4:
Assessment of Verbal Memory in Ecstasy Users and Significance of Results

Reference	Test	Sig, Controls	All controls	Other compare?	Type other	Lifetime consumption (Entire sample)	Time since last use
Back-Madruga et al 2004	AVLT 5	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	AVLT 7	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	AVLT8	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	AVLTDelayed (Recog)	NS, ND, trend*	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	Logical Memory	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Back-Madruga et al 2004	Logical Memory 1	NS, ND	ND	Yes, NS	Moderate, heavy	74.6 +/- 100.6 oc	178 +/- 178
Curran et al. 2003-Current	Prose Recall-Immediate	NS, CU	CU	No	NA	527.8 +/- 734.5	39 +/- 22.6
Curran et al. 2003-Current	Prose Recall-Delayed	NS, CU	CU	No	NA	527.8 +/- 734.5	39 +/- 22.6
Curran et al. 2003-Current	Reminders-1	NS, CU	CU	No	NA	527.8 +/- 734.5	39 +/- 22.6
Curran et al. 2003-Current	Reminders 3-1	NS, CU	CU	No	NA	527.8 +/- 734.5	39 +/- 22.6
Curran et al. 2003-Current	Reminders-Delayed	NS, CU	CU	No	NA	527.8 +/- 734.5	39 +/- 22.6
Curran et al. 2003-Former	Prose Recall-Immediate	Trend = 0.08, CU	CU	No	NA	1105.85 +/- 1923.03	873.6 +/- 655.2
Curran et al. 2003-Former	Prose Recall-Delayed	Trend = 0.09, CU	CU	No	NA	1105.85 +/- 1923.03	873.6 +/- 655.2
Curran et al. 2003-Former	Reminders-1	NS, CU	CU	No	NA	1105.85 +/- 1923.03	873.6 +/- 655.2
Curran et al. 2003-Former	Reminders 3-1	NS, CU	CU	No	NA	1105.85 +/- 1923.03	873.6 +/- 655.2
Curran et al. 2003-Former	Reminders-Delayed	NS, CU	CU	No	NA	1105 +/- 1923.03	873.8 +/- 652.2
Gouzoulis-Mayfrank et al. 2003-light	German-Turkish (word list)-Immediate	NS, CU	CU	No	NA	39.5 +/- 18	242.3 +/- 401.4

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Reference	Test	Sig, Controls	All controls	Other compare?	Type other	Lifetime consumption (Entire sample)	Time since last use
Dafters et al. 2004-low use	Free Recall	<0.001 ND, NS CU	CU, ND	No	NA	20.21 +/- 10.5	>=7 +/- NA
Dafters et al. 2004-low use	Story Immediate	<0.05 ND, NS CU	CU, ND	No	NA	20.21 +/- 10.5	>=7 +/- NA
Dafters et al. 2004-low use	Story Delayed	<0.05 ND, NS CU	CU, ND	No	NA	20.21 +- 10.5	>=7 +/- NA
Dafters et al. 2004-high use	Free recall	<0.001 ND, NS CU	CU, ND	No	NA	363.8 +/- 532.7	>=7 +/- NA
Dafters et al. 2004-high use	Story Immeidate	<0.05 ND, NS CU	CU, ND	No	NA	363.8 +/- 532.7	>=7 +/- NA
Dafters et al. 2004-high use	Story Delayed	<0.05 ND, NS CU	CU, ND	No	NA	363.8 +/- 532.7	>=7 +/- NA
Gouzoulis-Mayfrank et al. 2003-light	German-Turkish (word list)-delayed	NS, CU	CU	No	NA	39.5 +/- 18	242.3 +/- 401.4
Gouzoulis-Mayfrank et et al. 2003-light	Library (like RBMT-story)-immediate	NS, CU	CU	No	NA	39.5 +/- 18	242.3 +/- 401.4
Gouzoulis-Mayfrank et al. 2003-light	Library (like RBMT Story)-delayed	NS, CU	CU	No	NA	39.5 +/- 18	242.3 +/- 401.4
Gouzoulis-Mayfrank et al. 2003-heavy	German-Turkish (word list)-Immediate	NS, CU	CU	No	NA	503.2 +/- 555.5	194.8 +/- 394.8
Gouzoulis-Mayfrank et al. 2003-heavy	German-Turkish (word list)-delayed	<0.05, CU	CU	No	NA	503.2 +/- 555.5	194.8 +/- 394.8
Gouzoulis-Mayfrank et al. 2003-heavy	Library (like RBMT Story)-immediate	<0.05, CU	CU	No	NA	503.2 +/- 555.5	194.8 +/- 394.8
Gouzoulis-Mayfrank et al. 2003-heavy	Library (like RBMT Story)-Delayed	<0.05, CU	CU	No	NA	503.2 +/- 555.5	194.8 +/- 394.8
Halpern et al. 2004	Logical Memory-Immediate	NS, Lite PD	Lite PD	Yes, NS	Moderate, heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	Logical Memory-Delayed	NS, Lite PD	Lite PD	Yes, NS	Moderate, heavy	med = 60 oc	Med appr. 62.4

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Reference	Test	Sig, Controls	All controls	Other compare?	Type other	Lifetime consumption	Time since last use
Halpern et al. 2004	Verbal Paired Associates-Immediate	NS, Lite PD	Lite PD	Yes, NS	Moderate, heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	Verbal Paired Associates-Delayed	NS, Lite PD	Lite PD	Yes, NS	Moderate, heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	CVMT (like AVLT) Trial 1	NS, Lite PD	Lite PD	Yes, NS	Moderate, heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	CVMT Trial 5	NS, Lite PD	Lite PD	Yes, NS	Moderate, heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	CVMT 1-5 Total	NS, Lite PD	Lite PD	Yes, NS	Moderate, Heavy	med = 60 oc	Med appr. 62.4
Halpern et al. 2004	CVMT Trial B	NS, Lite PD	Lite PD	Yes, NS	Moderate, Heavy	med = 60 oc	Med appr. 62.4
Hanson and Luciana 2004	Story Recall –Immediate	<0.001, ND	ND	Yes, <0.01	Drug abuse diagnosis	64.9 +/- 122.9 oc	76.3 +/- 73.5
Hanson and Luciana 2004	Story Recall-Delay	<0.001, ND	ND	Yes, <0.01	Drug abuse diagnosis	64.9 +/- 122.9 oc	76.3 +/- 73.5
McCardle et al. 2004	RAVLT-Immediate	NS, CU	CU	No	NA	med “4 to 9 oc”	31.5 +/-NA
McCardle et al. 2004	RAVLT-5	<0.05, CU	CU	No	NA	med “4 to 9 oc”	31.5 +/-NA
McCardle et al. 2004	RAVLT-7	NS, CU	CU	No	NA	med “4 to 9 oc”	31.5 +/-NA
McCardle et al. 2004	RAVLT-Delayed	<0.01, CU	CU	No	NA	med “4 to 9 oc”	31.5 +/-NA
McCardle et al. 2004	RAVLT-Learning rate	NS, CU	CU	No	NA	med “4 to 9 oc”	31.5 +/-NA
Thomasius et al. 2003-current users	AVLT 6 (new list)	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	AVLT 7	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	AVLT 7-5	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14

Reference	Test	Sig, Controls	All controls	Other compare?	Type other	Lifetime consumption (Entire sample)	Time since last use
Thomasius et al. 2003-current users	AVLT 8-7	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	AVLT-1	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	AVT-5	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	AVTL sum 1 to 5	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	AVLT 8 (delayed)	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	AVLT 5-1 (learning	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	LGT-3 "telephone"	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	RBMT-Delayed recall	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	RBMT-Im-Del	NS, PD & ND	PD, ND	No	NA	817.1 +/- 1133.9	23 +/- 16.14
Thomasius et al. 2003-current users	RBMT-Immediate recall	NS, PD & ND	PD, ND	PD, ND	No	NA	23 +/- 16.14
Thomasius et al. 2003-former users	AVLT 6 (new list)	<0.01, ND, NS PD	PD, ND	No	NA	757.9 +/- 579	515 +/-495
Thomasius et al. 2003-former users	AVLT 7	NS ND & PD	PD, ND	No	NA	757.9 +/- 579	515 +/-495
Thomasius et al. 2003-former users	AVLT 7-5	NS ND & PD	PD, ND	No	NA	757.9 +/- 579	515 +/-495
Thomasius et al. 2003-former users	AVLT 8-7	NS ND & PD	PD, ND	No	NA	757.9 +/- 579	515 +/-495
Thomasius et al. 2003-former users	AVLT-1	NS ND & PD	PD, ND	No	NA	757.9 +/- 579	515 +/-495
Thomasius et al. 2003-former users	AVT-5	NS ND & PD	PD, ND	No	NA	757.9 +/- 579	515 +/-495

Reference	Test	Sig, Controls	All controls	Other compare?	Type other	Lifetime consumption (Entire sample)	Time since last use
Thomasius et al. 2003-former users	AVTL sum 1 to 5	<0.05 ND, NS PD	PD, ND	No	NA	757.9 +/-579	515 +/-495
Thomasius et al. 2003-former users	AVLT 8	NS ND & PD	PD, ND	No	NA	757.9 +/-579	515 +/-495
Thomasius et al. 2003-former users	AVLT 5- 1	NS ND & PD	PD, ND	No	NA	757.9 +/-579	515 +/-495
Thomasius et al. 2003-former users	LGT-3 "telephone"	NS ND & PD	PD, ND	No	NA	757.9 +/-579	515 +/-495
Thomasius et al. 2003-former users	RBMT-Delayed recall	<0.05 ND, NS PD	PD, ND	No	NA	757.9 +/-579	515 +/-495
Thomasius et al. 2003-former users	RBMT-Im-Del	NS, PD & ND	PD, ND	No	NA	757.9 +/-579	515 +/-495
Thomasius et al. 2003-former users	RBMT-Immediate recall	<0.05 ND, NS PD	PD, ND	No	NA	757.9 +/-579	515 +/-495

CU = Cannabis users, ND = Drug-naïve (non-drug users), PD = Polydrug users. NS = Non-significant.

It should be noted that Ecstasy users studied by Back-Madruga and colleagues were, on average, significantly older than samples assessed in most studies (average age was 37, average for controls = 39), and participants in this study reported considerably less use of stimulants, more use of psychedelics, and less prevalence of cannabis use than is usually seen in studies of Ecstasy users, including those reviewed here. It is perhaps also significant that the Ecstasy users studied by Halpern and colleagues were even more moderate in their use of other drugs than those studied by Back-Madruga and associates, and like Back-Madruga et al, they also failed to find significant differences in performance on the AVLT. Given the past history of detectable differences in performance on list-learning tasks (see, for instance, Fox et al. 2001A; Gouzoulis-Mayfrank et al. 2000; Reneman et al. 2001B), it is surprising that many recent reports offered only qualified support for impaired list recall in Ecstasy users, and that some studies failed to find this difference.

In addition to between-group analyses, researchers have performed correlational and regression analyses of verbal recall scores, with drug use parameters as predictors (Curran et al. 2003; Dafters et al. 2004; Gouzoulis-Mayfrank et al. 2003; Thomasius et al. 2003; Back-Madruga et al. 2003). Lifetime Ecstasy consumption was associated with AVLT-Delayed Recall for current and former users (Thomasius et al. 2003). Average dose per use was associated with AVLT-Immediate recall (Thomasius et al. 2003). This is somewhat surprising, given that lower scores were only seen in former users, yet the two groups do not report greatly differing average dose per use (current users = 3.95

tablets per use, former users = 4.06 tablets per use). Duration of use was associated with verbal memory scores in both current and former Ecstasy users, albeit on different measures (Curran et al. 2003), with the association in current users linking duration of use and immediate and delayed story recall, and scores on a list-learning task somewhat similar to the AVLT linked to duration of use in former users. Gouzoulis-Mayfrank and colleagues found that frequency of use was correlated with performance on immediate prose recall, as assessed by LGT-Library. It is interesting that lower scores were only seen in heavy Ecstasy users, and that heavy Ecstasy users reported using Ecstasy 4.5 times a month, whereas moderate users reported using Ecstasy 1.8 times a month. Thomasius and colleagues found that cannabis use was associated with immediate and delayed prose recall in their comparison of 30 current and 31 former Ecstasy users, 29 drug-using and 30 non-drug using controls (Thomasius et al. 2003). They also found that cannabis use was associated with performance on AVLT6, a subtest measuring degree of interference with list learning apparent when a new list is introduced, and cocaine use was also associated with degree of AVLT list learning.

Verbal recall is one of the few domains of cognitive function consistently associated with Ecstasy use, and with various parameters of Ecstasy use, suggesting that Ecstasy use, or one or more factors associated with Ecstasy use, affects verbal recall. Neither findings of group differences nor findings of associations in these retrospective studies can be considered evidence of a causal relationship. Nevertheless, it is of interest that other functional domains are not as frequently or consistently associated with Ecstasy use as this one (see discussion in IB). In contrast with findings in these studies of Ecstasy users, researchers have failed to find reduced memory in people given one or two doses of MDMA in controlled settings (Grob et al, Unpublished; Ludewig et al. 2003; Vollenweider et al. 2001). Keeping this in mind while recognizing the possibility of a link between MDMA and reduced verbal recall, it seems research participants in clinical trials of MDMA face minimal risk of reductions in verbal recall, as stated in the first review.

Only one of four studies assessing visual recall found Ecstasy users scoring lower than controls (Gouzoulis-Mayfrank et al. 2003). However, in this comparison of 30 moderate Ecstasy users (lifetime consumption = 39.5 tablets), 30 heavy Ecstasy user (lifetime consumption = 503.2 tablets), and 30 cannabis user controls, only a trend was found for lower scores in heavy users when compared with controls. (Moderate Ecstasy users did fare less well than controls, but not at a statistically significant level). Back-Madruga and associates reported that dividing their sample of 22 Ecstasy users into 11 light users (lifetime consumption = 9.45 occasions) and “heavy” users (lifetime consumption = 133.45 occasions) via median split, the researchers found that those reporting higher lifetime Ecstasy consumption had lower scores on Rey-Osterrieth figure recall, and an increased rate of “false alarm” errors on a visual memory test (the CVMT) (Back-Madruga et al. 2004). However, their initial comparison failed to find any differences in visual recall when all Ecstasy users (lifetime use = 74.6 occasions of use) were compared with 28 non-drug using controls. Visual reproduction scores and Rey-Osterrieth scores were not significantly different in 23 Ecstasy users with a lifetime consumption of 60 occasions and 16 light polydrug user controls (Halpern et al. 2004), and heavy users from

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this sample did not perform significantly worse than controls. Lastly, Thomasius and colleagues did not find any difference in visual recall when 30 current (lifetime consumption = 817.1 tablets, period of abstinence = 23 days) or 31 former (lifetime consumption = 757.9 tablets, period of abstinence = 515 days) Ecstasy users were compared with 29 polydrug using or with 30 non-drug using controls (Thomasius et al. 2003). In two of four studies, effects were only seen in people reporting greater Ecstasy use, and in the other two, no effects were seen at all. However, samples of current and former users reporting much higher use than that reported in either of the studies finding effects in heavy Ecstasy users (e.g. compare the "heavy" users of Gouzoulis-Mayfrank et al. with current users in Thomasius et al. 2003) seemed to perform similarly to controls, raising issues about the nature of the association between lifetime Ecstasy consumption and impaired visual memory.

Correlations and regression analyses found a few associations between parameters of Ecstasy use and performance on measures of visual memory. Lifetime Ecstasy use was associated with lower scores on the CVMT (false alarms and recognition) in a sample of 22 Ecstasy users (Back-Madruga et al. 2004), and immediate and delayed recall on a visual list-learning task (LGT-Logos) were associated with frequency of Ecstasy use in a study of moderate and heavy Ecstasy users (Gouzoulis-Mayfrank et al. 2003). As noted in the discussion of verbal recall, this correlation is consonant with findings of lower scores only in heavy Ecstasy users, since they reported more frequent use than moderate users.

Visual recall is examined less frequently than verbal recall, and when it is examined, results are less certain and more qualified than for verbal recall, and studies published in 2003 continue this trend. Some parameters of Ecstasy use, or factors related to these parameters, seem to be related to performance on visual recall tasks. Since reductions in visual memory are not consistently detected across samples, it seems likely that other factors may at least partially explain this association when it is found. It appears that risk of impaired visual memory associated with clinical trials of MDMA is very low.

In conclusion, recently published reports assessing verbal and visual memory in Ecstasy users continue to find an association between regular Ecstasy use and performance on tests of memory. This seems especially true for measures of visual working memory and verbal memory. Unlike previous research, recent studies employed more sophisticated research designs, including the use of samples more appropriately matched on drug use. Perhaps as a result, these studies have reported a greater number of qualifications to their findings. Note that at least one study found that while current or former Ecstasy users scored lower on measures of memory than non-drug users, they did not always score lower than cannabis users or polydrug users (Dafters et al. 2004; Thomasius et al. 2003). It also appears that people who report a lifetime consumption lower than 50 tablets or occasions perform similarly to non-drug users (Back-Madruga et al. 2003; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004). These findings suggest that impairments in memory may be related either to degree of lifetime exposure or to factors associated with lifetime exposure, including pre-existing factors and use of other drugs. As well, it seems that diagnosis with a substance abuse disorder may also be related to reductions in

memory function (Hanson and Luciana 2004), a finding that supports a role for one or ore pre-existing factor. None of the recent findings concerning memory significantly alter the risk assessments put forward in the IB or in the 2002 update to the IB, except perhaps to further qualify it by noting that moderate repeated use of Ecstasy may have little or no association with lower scores on measures of memory. People taking part in clinical trials of MDMA are likely to face a risk of impaired working, verbal or visual memory, but these risks are minimal.

Quantitative Review of Verbal Recall

At the time when the 2002 update to the IB was completed, the only quantitative review of studies of cognitive function consisted of the analyses presented in the IB (Baggott et al. 2001). Those analyses the specific test scores from each study that exhibited the greatest difference between Ecstasy users and controls, and was thus designed to find associations between parameters of Ecstasy use and impairments in cognition. These analyses detected an associations between scores on measures of executive function and lifetime Ecstasy consumption, and a relationship between executive function scores and period of abstinence from use. However, these analyses failed to find significant associations between memory function and any of the ecstasy use parameters examined. Subsequent to the completion 2002 update of the IB, Verbaten (2003) published a meta-analysis using methods similar to those used in the IB. Verbaten examined ten studies featuring Ecstasy users who had abstained for at least a week prior to assessment, and he examined immediate (referred to in the paper as short-term), delayed (referred to as long-term) verbal memory, and attention across these studies. The study also performed regression analyses to detect possible effects of lifetime Ecstasy and cannabis use. The author also applied a statistic meant to account for the possibility of unpublished, and negative (non-significant) findings, that would alter meta-analysis findings if they were published.

After conducting these analyses, Verbaten found a consistent difference between Ecstasy users and controls on immediate and delayed verbal memory, but not in attention or task performance. Verbaten also reported that lifetime Ecstasy use was not associated with reduced immediate or delayed verbal memory. A second analysis that controlled for the effects of cannabis use still found that Ecstasy users across studies scored lower on measures of immediate memory, but failed to find any differences on measures of delayed memory. Though the author found a “step-wise” association between lifetime Ecstasy consumption and lower verbal memory scores, Verbaten did not interpret this as supporting claims that a “single dose” of Ecstasy leads to impaired verbal memory, due to the lack of any studies assessing this relationship, and due to the fact (noted in this review as well) that lifetime Ecstasy consumption in a given study does not predict the likelihood of its finding impaired memory. It should be noted Verbaten failed to address the possibility of there being a bias for publishing studies reporting undesirable effects of illicit drugs, and he failed to acknowledge or account for differences in measures and types of controls used in the studies reviewed. Nevertheless, the analysis raises some of the same issues and reaches similar conclusions to those reached in this review. For instance, even though a number of studies have only detected impaired memory function

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in heavy Ecstasy users (Back-Madruga et al. 2004; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004), these studies did not always report associations between lifetime use and performance on measures of memory. Like many of the studies published in 2003, this meta-analysis of earlier reports suggests that impaired memory in Ecstasy users may be due in part to one or more parameter of Ecstasy use, or factors associated with Ecstasy use, but that at least one aspect of memory is also associated with cannabis use, or factors associated with cannabis use. It also appears that this meta-analysis also does not support claims that even one or two doses of MDMA will affect verbal memory.

Other Functional Domains

Researchers also assessed other functional domains besides those of attention, executive function and memory. These include information processing (Back-Madruga et al. 2004; Halpern et al. 2004; McCardle et al. 2004; Thomasius et al. 2003), language (Back-Madruga et al. 2004), motor function (Halpern et al. 2004; Hanson and Luciana 2004; McCardle et al. 2004; Thomasius et al. 2003) and visual-spatial skills (Back-Madruga et al. 2004; Thomasius et al. 2003). Only two of five studies found Ecstasy users had lower scores in one of these domains (Halpern et al. 2004; Hanson and Luciana 2004).

None of the four studies assessing information processing speed with the Digit Symbol test detected lower scores in Ecstasy users. 22 Ecstasy users who had used Ecstasy on an average of 74.6 occasions had similar Digit Symbol scores to 28 non-drug user controls (Back-Madruga et al. 2004). Thomasius and colleagues failed to detect any differences in the Digit Symbol scores of 30 current (period of abstinence = 23 days, lifetime consumption = 817.1 tablets) or 31 former Ecstasy users (period of abstinence = 515 days, lifetime consumption = 757.8 tablets) when compared with 29 polydrug user and 30 non-drug user controls (Thomasius et al. 2003). A sample of 17 Ecstasy users (lifetime consumption not reported, median 4 to 9 occasions) and 16 cannabis user controls failed to detect any differences in Digit Symbol scores (McCardle et al. 2004). Halpern and colleagues found that 23 Ecstasy users (lifetime consumption = 60 occasions) performed similarly to 16 light polydrug user controls (Halpern et al. 2004). It is notable that in contrast with Digit Symbol performance, Halpern and colleagues found that Ecstasy users scored lower on another measure of information processing, the Stroop task.

Only two studies assessed Ecstasy users on the Stroop test, a task measuring information processing and cognitive interference produced by contradictory color and word information (Back-Madruga et al. 2004; Halpern et al. 2004), with one research team finding significant differences in Stroop task performance, and the other failing to find any differences. Halpern and colleagues failed to find significant differences in Stroop task in 23 Ecstasy users (lifetime consumption = 60 occasions) and 16 controls matched for Ecstasy users with respect to very moderate polydrug use. However, when the sample of Ecstasy users was divided into 12 moderate users (fewer than 50 occasions) and 11 heavy users (50 or more occasions), these researchers found significantly increased interference in heavy users, but not in moderate users. Furthermore, the researchers found an association between log transformed lifetime Ecstasy consumption and Stroop interference scores, with greater lifetime Ecstasy use associated with greater Stroop task interference. However, another study employing the Stroop task failed to find any

differences in performance in 22 Ecstasy reporting lifetime consumption on74.6 occasions and 28 archival controls matched for gender and age (Back-Madruga et al. 2004). It is notable that samples examined in both studies are unusual in their generally moderate use of substances other than Ecstasy, though participants in the study of Back-Madruga and colleagues were generally older and had a more extensive history of polydrug use than those studied by Halpern and colleagues. It is not clear why the two studies reported conflicting findings.

Only Back-Madruga and colleagues compared language skills in the same sample of 22 Ecstasy users and 28 controls described above, via Boston Naming Test. They found the two groups performed similarly on the task, though 11 Ecstasy users reporting higher Ecstasy use (133.45 occasions) performed less well on this task than the Ecstasy users reporting fewer episodes of use (lifetime consumption = 9.45 occasions).

Researchers assessed motor skills with the Grooved Pegboard and Finger Tapping test (Hanson and Luciana 2004), and the Trail Making Test (Halpern et al. 2004; McCardle et al. 2004; Thomasius et al. 2003). Two of four studies found impaired performance in at least some groups of Ecstasy users, but these were often qualified by other findings. While there were few performance differences between 26 Ecstasy users reporting 64.9 occasions of use and 26 non-user controls, Hanson and Luciana found that Ecstasy users had slower finger tapping rates when they tapped with the dominant hand (Hanson and Luciana 2004). The same researchers also reported that 14 Ecstasy users diagnosed with a substance abuse disorder, and reporting lifetime consumption of 95.4 occasions, had lower scores on one subtest of the Grooved Pegboard test for the non-dominant hand. However, no differences were seen for the sample as a whole, or in the 12 Ecstasy users without any diagnosed drug abuse disorders, who reported lifetime Ecstasy use of 29.3 occasions. In a similar vein, Halpern and colleagues found that Ecstasy users reporting over 50 occasions of use erred more on the Trail Making Test than controls (Halpern et al. 2004), but failed to find overall differences in performance on this test of motor skills when the entire sample of 23 Ecstasy users was compared with 16 light polydrug user controls. These results suggest that some difficulties in psychomotor skills are associated with heavier Ecstasy use. In contrast, Thomasius and colleagues did not find any performance differences on the Trail Making Test between 30 current (time since last use = 23 days) or 31 former (time since last use = 515 days) Ecstasy users and 30 non-drug user or polydrug user controls. McCardle and colleagues also failed to detect differences in Trail Making Test performance in a sample of 17 Ecstasy users reporting a median of four to nine occasions of use, and 16 cannabis user controls (McCardle et al. 2004). Since the current and former users studied by Thomasius and colleagues reported higher rates of Ecstasy use than Ecstasy users in the sample examined by Hanson and Luciana, it seems unlikely that lifetime consumption of Ecstasy is related to these differences. (Lifetime Ecstasy consumption for Thomasius et al. 2003 provided in discussion of information processing). Since Hanson and Luciana note that Ecstasy users with drug abuse disorders demonstrate a greater number of motor skill differences than those without this diagnoses, the differences may relate to mood or psychological problems, or other pre-existing factors associated with drug abuse disorders.

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Visual-spatial skills were assessed through the Block Design and Rey-Osterrieth Figure tasks in a sample of 22 Ecstasy users (lifetime Ecstasy consumption = 74.6 occasions) and 28 non-drug user controls (Back-Madruga). Visual-spatial skills may also have been assessed by Thomasius and colleagues via a test referred to as Logical Figures in 30 current Ecstasy users (lifetime consumption = 817.1 tablets, time since last use = 23 days), 31 former Ecstasy users (lifetime consumption = 757.9, time since last use 515 days), 29 polydrug users and 30 non-drug users. Halpern and colleagues compared performance on Block Design and Rey-Osterrieth figure production in 23 Ecstasy users (lifetime consumption = 60 occasions) and 16 light polydrug users. None of these studies reported any significant differences between Ecstasy users and controls in visual-spatial skills. These findings are similar to those in previous studies that failed to find an association between Ecstasy use and visual-spatial skills.

More generally speaking, recent publications examining information processing, motor skills and other domains of cognitive function report findings similar to those seen in previous publications. While impaired performance in these domains is sometimes detected, detection is rarely consistent across studies, and it does not seem that samples reporting greater Ecstasy use were more likely to exhibit impaired performance than Ecstasy users reporting less use of Ecstasy. After considering studies in repeated Ecstasy users, it appears that people in clinical trials of MDMA face only very minimal risk of changes in these functional domains.

Perceived Cognitive Function

The 2002 update to the IB discussed findings from an on-line survey of self-reported memory function in Ecstasy users (Rodgers et al. 2001). The survey found cannabis use more closely associated with perceived difficulties in recalling past occurrences, referred to as "retrospective" memory, and Ecstasy use more closely tied to perceived difficulties in remembering to perform routine or planned (future) tasks, referred to as "prospective memory." The review noted the difficulties with drawing conclusions from studies relying on self-reports of memory difficulties, and noted that other studies had found dissociations between perceived difficulties attributed to Ecstasy use and scores on observer-rated measures (e.g. Fox et al. 2001B). Furthermore, the only researchers to assess prospective memory with an observer-scored scale failed to find any decline in prospective memory a year after continued Ecstasy use, even though the same researchers did detect a decline in other memory scores (Zakzanis and Young 2001).

Sine the completion of that review, Rodgers and colleagues report findings from another on-line survey that appears to gather data from a separate sample of drug users (Rodgers et al. 2003), but uses the same measures employed in the first survey. They included 199 of 282 Ecstasy users in their sample, and did not compare scores on two of three prospective memory scale scores because they proved unreliable in this sample. Rodgers and colleagues found that Ecstasy use was associated with a perceived increase in difficulties with long-term prospective memory, and far weaker and non-significant effects on self-reported retrospective memory. Frequency of cannabis use, on the other hand, was associated perceived problems with (retrospective) memory, and not with

prospective memory problems. Ecstasy users also made more errors when completing surveys, with greater lifetime Ecstasy use associated making a greater number of errors made on the surveys. In contrast, use of LSD and frequency of cannabis use were associated with making fewer errors on the survey.

It is difficult to establish lifetime Ecstasy consumption in this sample, since the authors chose to report only ranges of use (e.g. 1-9, 10-99 occasions), and divided these figures between men and women participants. However, using a rough estimate, it appears that Ecstasy users in this sample reported a lifetime consumption of 19.37 occasions. While the sample size used in this study is impressive, measures of perceived memory cannot be considered equivalent to assessing memory through objectively scored measures, as already noted when discussing previous on-line survey results. There are also a number of plausible explanations accounting for Ecstasy users making a greater number of errors on surveys that do not necessarily relate to prospective memory, such as impulsivity or distractibility. It is also notable that the authors discarded 84 subjects who reached the survey through a harm reduction site, stating explicitly that these individuals differed from the rest of the sample in that they did not report experiencing any memory difficulties. The choice was apparently made in an attempt to avoid the deliberate alteration of responses, and to deal with the possibility that neuroprotective techniques discussed on harm reduction sites had beneficial effects. Regardless of the reasons for removing these respondents from further analyses, the removal increased the likelihood of detecting perceived memory difficulties in the sample of Ecstasy users. It is intriguing that the survey found Ecstasy users to perceive themselves as having difficulties remembering to make planned responses, given the focus of most studies on retrospective memory. Intriguing as these results may be, these results cannot be used in an estimation of effects of Ecstasy use because of their failure to confirm perceived difficulties with objectively scored measures.

Cognitive Function and Serotonin Function

As discussed in the 2002 revision to the IB, findings from a number of studies support a dissociation between presumed indicators of serotonin function and performance on measures of cognitive function in Ecstasy users, with measures in one domain failing to predict results in the other domain. While this dissociation might be related to the use of novel or controversial means of assessment in either area of function, the lack of a clear relationship between indicators of brain serotonin levels and scores on measures of various cognitive functions suggests that cognitive function should not be treated as an indirect measure of serotonin function.

Findings supportive of a dissociation between serotonin function and neurocognitive function continue to appear subsequent to the 2002 revision of the IB. Most notably, two studies conducted in nearly identical samples of current Ecstasy users, former Ecstasy users, polydrug users and non-drug users found that current users had fewer serotonin transporter sites, but that former Ecstasy users had lower scores on measures of memory (Buchert et al. 2003; Thomasius et al. 2003). Note also the recent report finding lower scores on measures of executive function in men who used Ecstasy, but not in women

(Alting Von Geusau et al. 2004). This finding stands in contrast to an earlier report that found lower numbers of presumed serotonin transporter sites in heavy Ecstasy users who were women, and not men (Reneman et al. 2001A).

Other studies appearing in 2003 lend support to a dissociation between results on measures of cognitive function and measures of serotonin function. Researchers in England sought to examine serotonin function and cognitive function by manipulating available tryptophan (precursor to serotonin) in samples of male current (abstinent for 39 days, lifetime consumption of 527.8 tablets) and former (abstinent for 873.6 days, lifetime consumption of 1105.8 tablets) Ecstasy users, and in cannabis user controls (Curran et al. 2003). Curran and colleagues had begun with the expectation that tryptophan depletion would exacerbate impaired memory and executive function in Ecstasy users, and that augmenting tryptophan would improve performance on these measures. They hypothesized that if changes in serotonin function were transient, then current Ecstasy users would be sensitive to tryptophan manipulation, whereas sensitivity in both current and former Ecstasy users would be evidence for permanent or very long-term changes in serotonin function. Contrary to expectations, the researchers found that delayed prose recall was sensitive to tryptophan manipulation in former Ecstasy users, and not current users (lifetime consumption = 527.8 tablets). They also found a trend for immediate prose recall to be sensitive to tryptophan manipulation, with this finding also only in former Ecstasy users. Former Ecstasy users in this study also performed less well on the RVIP, a measure of information processing and executive function, a measure that showed sensitivity to tryptophan manipulation for all groups (that is, current users, former users and cannabis users all performed better under tryptophan augmentation than after tryptophan depletion). However, though former Ecstasy users had lower scores on several measures of memory at baseline, and both current and former Ecstasy users showed less of a practice effect on a measure of attention, these measures were not sensitive to tryptophan manipulation. Furthermore, as discussed below under "Other Domains Assessed in Ecstasy Users," former Ecstasy users with greater changes in plasma tryptophan after tryptophan augmentation had lower scores on prose recall, and current users with greater changes in plasma tryptophan after tryptophan manipulation had lower scores on a measure of executive function. At the least, these findings suggest that the relationship between serotonin function and cognitive function is not simple, and that measures of neurocognitive function cannot serve as indirect measures of serotonin function. In turn, findings like these and the ones described above suggest that impaired cognitive function in Ecstasy users cannot be treated as an indicator of MDMA-induced harm to the human serotonin system.

Cognitive Function-Summary and Conclusions:

While most research findings reviewed here reported findings that are not in conflict with earlier reports reviewed in the IB and in the 2002 update to the IB, there are a few new developments of note in studies of Ecstasy users. One novel finding is of impaired memory and executive function in former, but not current, Ecstasy users, noted in two recent publications (Curran et al. 2003; Thomasius et al. 2003). These effects may be the result of one or more overlapping factors. These include differences in use of other

drugs, injury and regrowth of serotonin axons, or pre-existing conditions associated with substance use and the decision to abstain from further Ecstasy use. Another development is the relative increase in studies finding impaired visual working memory in Ecstasy users (Curran et al. 2003; Daumann et al. 2003a; Daumann et al. 2003b), even when no differences in verbal working memory were detected (Halpern et al. 2004, for heavy users; Hanson and Luciana 2004). The significance of this finding is unclear, but suggests that impairments in working memory are not restricted to verbal working memory. It is also notable that two studies that employed samples of Ecstasy users reporting comparably lower use of other drugs also failed to detect changes in verbal recall (Back-Madruga et al. 2004; Halpern et al. 2004). However, other research teams that employed samples fairly well-matched on drug use did find impairments in memory or executive function (Gouzoulis-Mayfrank et al. 2003), but only in people reporting use of more than 80 tablets. It is notable that both Halpern and colleagues and Back-Madruga and colleagues also found heavier lifetime use of Ecstasy was associated with lower scores on measures of visual recall, information processing and executive function. When taken together, these developments suggest that the association between Ecstasy use and impaired cognitive function is complex and may involve several factors, including factors not directly related to Ecstasy use, but they do not significantly increase or decrease the initial risk assessment made for participants in clinical trials of MDMA.

It is important to remember that reliance on studies of Ecstasy users to calculate such risks will produce, at best, a very conservative risk estimate with respect to clinical trials, since the doses, dose regimens and settings used in clinical trials differ from those employed by most Ecstasy users. As discussed in the section on clinical trials, assessments performed before and after MDMA administration suggest that participants receiving MDMA in the course of research studies face only minimal risk of reductions in any domains of cognitive function (Ludewig et al. 2003). A review of past and current research in Ecstasy users continues to indicate possible links between MDMA and subtle but detectable impairments in specific areas of cognitive function, but not in other areas. In all cases, risk of such cognitive impairments is expected to be minimal for participants in clinical trials.

Imaging Studies

Subsequent to the completion of the 2002 update to the IB, five studies have assessed brain structure (Buchert et al. 2003; Cowan et al. 2003) or function (Daumann et al. 2003a; 2003b; Jacobsen et al. 2004) in samples of Ecstasy users. Only one of the studies sought to detect changes in serotonin function (Buchert et al. 2003), while the others either assessed structural features with an unknown relationships to serotonin function (Cowan et al. 2003), or examined brain function in response to specific tasks (Daumann et al. 2003a; 2003b; Jacobsen et al. 2004).

A team of researchers in Germany (Buchert et al. 2003; Thomasius et al. 2003) assessed serotonin transporter uptake (SERT) site density in matched samples of 30 current Ecstasy users (lifetime consumption = 827 tablets, days since last use = 24 days), 29 former Ecstasy users (lifetime consumption = 793 tablets, days since last use = 514 days),

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29 polydrug users and 29 non-drug users through the radioligand (radioactive drug that binds to a specific site) McN5652. The same ligand was also used in an earlier report that found lower McN5652 binding in Ecstasy users (McCann et al. 1998), interpreted as an indicator of fewer serotonin transporter sites. It should be noted that this radioligand can image subcortical areas, but it cannot provide images of cortical areas. Thomasius and colleagues found that current Ecstasy users had lower specific McN5652 binding in mesencephalon (midbrain) and thalamus that was 4% to 6% lower than binding in former Ecstasy users, polydrug users or non-drug users. Slightly fewer SERT sites in current Ecstasy users, but not in former users, may be interpreted as an indication of non-neurotoxic changes in serotonin function, evidence of neurotoxicity and regrowth of affected serotonin axons, or an effect of using other drugs, such as cannabis or amphetamines. If reduced serotonin transporter sites are considered indicative of neurotoxicity, then it appears that people recover from neurotoxicity after a period of abstinence. Study findings stand in contrast to those of McCann and colleagues, who reported a 70% to 80% reduction in SERT sites in Ecstasy user (McCann et al. 1998). I

Structural magnetic resonance imaging with voxel based morphometry (VBM) of the brains of 31 Ecstasy users and 29 moderate polydrug users found reduced gray matter in parts of the occipital, temporal and frontal lobe (left and right Brodmann area (BA) 18, left BA 21, and BA 45), both sides of the cerebellum, and a midline area of brainstem (Cowan et al. 2003). Because data on Ecstasy consumption is only presented in terms of "low," "medium" and "high" use in this study, lifetime consumption can only be roughly estimated as falling between 31.6 and 34.35 tablets. Lower levels of gray matter were seen in areas related to vision and language function. Differences found in this report do not match those described in other MRS studies of the brains of Ecstasy users (Chang et al. 1999; Obergriesser et al. 2001; Reneman et al. 2002C; Reneman et al. 2001c), with the exception of reduced gray matter in occipital areas, a finding also reported by Chang and colleagues (1999). In discussing their results, the authors acknowledge that the form of MRI they used is novel and that to date, there is no reason to believe their findings are indicative of serotonin toxicity in Ecstasy users. Furthermore, the researchers found associations between use of a number of other drugs and reduced gray matter in various brain areas, with those other drugs including cocaine, cannabis and hallucinogens, suggesting that study findings might relate to additive effects or interactions between drugs. Since this is a retrospective study, it is also possible that study results are at least partially due to pre-existing differences in brain structure, as those associated with the tendency toward polysubstance use. These study findings are difficult to compare with other imaging studies, as the researchers were not assessing serotonin function or specific markers of brain injury or repair, and they were not measuring activity during task performance. The significance of these findings is unclear at present, particularly considering conflicting reports from other studies using structural imaging techniques.

Three studies, two performed by the same team of researchers in Germany, used functional magnetic resonance imaging (fMRI) to assess brain activity in Ecstasy users and controls during selected tasks (Daumann et al. 2003a; Daumann et al. 2003b; Jacobsen et al. 2004). Perhaps owing to the cost or complexity of the imaging technique, all sample sizes were very small, with two studies employing fewer than ten subjects per

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condition (Daumann et al. 2003a; Jacobsen et al. 2004). Each study represents a different research design, making it difficult to make comparisons across studies. One study compared 11 heavy Ecstasy users, 11 moderate Ecstasy users and 11 non-drug user controls while they performed the "n-back" task a measure of working memory, a(Daumann et al. 2003A), another study examined brain activity during "n-back" task performance in 8 "pure" Ecstasy users, 8 polysubstance using Ecstasy users, and eight non-drug user controls (Daumann et al. 20003B), and the third study examined activity while performing measures of attention in six adolescent Ecstasy users and six adolescents described as polydrug users but who are better considered cannabis users (Jacobsen et al. 2004). Daumann and colleagues reported that all Ecstasy users displayed greater activation in right parietal areas and less activation in superior temporal regions in the study comparing heavy and moderate users and non-drug user controls (Daumann et al. 2003A). Heavy ecstasy users (lifetime consumption = 258.18 tablets) had lower activation in left superior temporal lobe and greater activation of BA 40 than moderate users (lifetime consumption of 27.36 tablets) and non-drug user controls. Another study using the same methods to compare "pure" Ecstasy users (lifetime consumption = 74.5 tablets) with "polyvalent (polydrug using) Ecstasy users (lifetime consumption = 56.25 tablets) on a working memory task found that "pure" Ecstasy users, but not polysubstance using Ecstasy users, exhibited lower activation in angular gyrus during n-back task performance (Daumann et al. 2003B). These "pure" Ecstasy users also showed greater changes in activity in premotor cortex. Lastly, the study of six adolescent Ecstasy users reporting having taken Ecstasy on an average of ten occasions and cannabis-using controls found that Ecstasy users had lower activation in the left hippocampus when performing tasks assessing selective and divided attention (Jacobsen et al. 2004). However, Jacobsen and colleagues also found fewer differences in left hippocampal activation when Ecstasy users and controls performed the most difficult n-back task (Jacobsen et al. 2004).

The significance of these differences in brain function is not clear, especially in studies that found little or no differences in task performance (Daumann et al. 2003a; Daumann et al. 2003b). It is possible that people with an earlier onset of Ecstasy use might have different responses or experience different effects than adult users, explaining results reported by Jacobsen and colleagues. Because all studies used small sample sizes and examined many brain areas, it is possible that significant findings reflect random variations in brain activity. It is not clear how these changes in brain function relate to changes in cognitive or serotonin function, and so these findings do not inform risk estimates for Ecstasy users or in relation to clinical trials of MDMA.

In summary, an examination of recently published imaging studies published subsequent to the completion of the 2002 update to the IB offer little to no indication of greater or lesser risk of changes in brain structure or activity after only a few doses of MDMA. Findings from one study might lead to a lower estimated risk for regular Ecstasy use (Buchert et al. 2003), while the significance of other research findings remains unclear (Cowan et al. 2003).

Other Areas of Investigation

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The majority of studies in Ecstasy users have focused on psychological well-being or cognitive function. However, previous research has examined other domains, such as electroencephalographic (EEG) and evoked potential (ERP) data (for example, Croft et al. 2001; Gijsman et al. 2002), neuroendocrine function (for example, Gouzoulis-Mayfrank et al. 2002?, Gerra et al. 2002) and other areas of biological function, such as plasma neurotransmitters and metabolites (Stuerenburg et al. 2002). In most cases, researchers select a function on the belief that it might be an indirect measure of serotonin function.

Researchers continue to explore these areas in their current studies in Ecstasy users. From 2003 to early 2004, researchers have assessed evoked potentials relating to auditory startle response (Heekeren et al. 2004; Quednow et al. 2004), EEG after visual stimulation (Oliveri and Calvo 2003), pain tolerance (O'Regan et al. 2004), neuroendocrine function, especially after psychological stressors (Gerra et al. 2003), plasma amino acids (Stuerenburg et al. 2003), plasma tryptophan levels before and after manipulating available tryptophan (Curran et al. 2003), and plasma levels of antioxidant vitamins and enzymes, and acetylcholine, a presumed marker of oxidative stress (Zhou et al. 2003A; Zhou et al. 2003B).

Two of these papers are described above in the section on naturalistic studies of acute and sub-acute effects of Ecstasy rather than studies of long-term effects (Oliveri and Calvo 2003; O'Regan et al. 2004), and these papers are discussed in greater detail in the section referring to naturalistic and retrospective investigations of the effects of Ecstasy. These studies found that three to four days after using Ecstasy, Ecstasy using volunteers had a decreased pain threshold, and they had an increased likelihood of seeing phosphenes after transcranial magnetic stimulation when compared with controls (Oliveri and Calvo 2003; O'Regan et al. 2003). The selected domains (pain tolerance and excitability of visual cortex) were chosen because of their presumed relationship to serotonin function. If these domains are in fact associated with serotonin function, these studies may suggest that serotonin function is changed in Ecstasy users a few days after their most recent use. It is not clear whether the effects these researchers described were a product of transient or more permanent changes. Since both studies employed retrospective study designs, and neither study performed baseline assessments, it is also possible that reduced pain tolerance and increased sensitivity to transcranial magnetic stimulation may be markers for one or more pre-existing factor or factors associated with Ecstasy use.

Two research teams, both based in Germany, investigated the acoustic startle response in Ecstasy users and controls (Heekeren et al. 2004; Quednow et al. 2004), with each team arriving at different and conflicting results. In one study, 23 Ecstasy users showed the same degree of habituation to random bursts of loud white noise, sensitization to acoustic startle, and pre-pulse inhibition (PPI, reduced startle if stimulus is preceded by a less startling stimulus) as 20 non-drug user controls (Heekeren et al. 2004). Only when Ecstasy users were divided into those reporting a lifetime consumption of fewer than 90 tablets (n = 12, average lifetime consumption = 48.3), and those who had taken 90 or more tablets over a lifetime (n = 11, average consumption = 452.9 tablets) were

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differences seen. Heekeren and colleagues found that heavy users were more likely to develop sensitization (increased response) to acoustic startle than moderate users or non-drug user controls. It is notable that those using less than 90 tablets had been abstinent for a considerably longer interval (563.3 days versus 138,6 days), and a greater number of heavy users reported taking amphetamines (eight of 12 versus three of 11), so it is possible that differences in response were related to these factors rather than to lifetime Ecstasy consumption. In the other study (Quednow et al. 2004), 20 male Ecstasy users (lifetime consumption = 424.64 tablets) exhibited a similar response to acoustic startle as 20 gender-matched cannabis users and 20 non-drug user controls, except with respect to PPI. Contrary to the authors' predictions, the Ecstasy users exhibited greater PPI than the other groups. The authors hypothesized that increased PPI might be the result of upregulation in 5HT2A receptors, as seen in abstinent Ecstasy users (Reneman et al. 2002B), participants in the previous study been abstinent from Ecstasy for at least two months, and current users reported a shorter period of abstinence than was reported by Reneman and colleagues (23.1 days in Reneman et al. 2002B versus 15.3 days in Quednow et al. 2004). It is notable that the cannabis users did report a very low level of Ecstasy consumption (lifetime consumption = 7.93 tablets), so that they are not, strictly speaking, non-Ecstasy users. However, since the Ecstasy users' consumption is degrees of magnitude greater than consumption reported in the cannabis users, it seems unlikely that the lack of differences between these groups is related to degree of Ecstasy use, especially when no differences were also seen between these groups and non-drug using controls. Recent study findings on the effects of repeated Ecstasy use on evoked response to acoustic startle are contradictory, with neither finding providing a direct indicator of serotonin toxicity from MDMA.

Neuroendocrine challenge studies, mostly employing serotonin releasers such as fenfluramine or mCPP and mostly in male Ecstasy using volunteers, have found reduced prolactin and growth hormone release after challenge (Gerra et al. 2000; 1998; McCann et al. 1999; Price et al. 1990). The 2002 update to the IB reviewed a finding found blunted neuroendocrine response to fenfluramine challenge more strongly related to cannabis use than to Ecstasy use (Gouzoulis-Mayfrank et al. 2002), and a finding of blunted growth hormone release in Ecstasy users who received the dopamine agonist bromocryptine (Gerra et al. 2002). Discussions of these studies, their significance in assessing the safety of MDMA in humans and methodological flaws are discussed in both earlier reviews.

Only one study of neuroendocrine responses in Ecstasy users has appeared subsequent to the completion of the 2002 revision of the IB (Gerra et al. 2003). In this study, plasma levels of the stress hormones ACTH and cortisol were assessed in fifteen male Ecstasy users recruited from amongst people who had contacted a drug abuse clinic (lifetime consumption = 58.9 occasions, time since last use = 21 days) and fifteen gender-matched controls from the community before and after performing two psychologically stressful tasks, doing mental arithmetic and making a public speech covering the speaker's personality, his interpersonal relationships and life goals. A week later, the researchers measured plasma growth hormone (GH) in both groups after challenge with the dopamine agonist bromocryptine. The Ecstasy users had higher baseline ACTH and

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cortisol than non-drug user controls and greater levels of ACTH and cortisol after psychological stressors. However, Gerra and colleagues found that duration of elevated ACTH and cortisol after psychological stress was higher in controls than in Ecstasy users. In line with previous findings by the same research team (Gerra et al. 2002), Ecstasy users exhibited less elevation in GH after bromocryptine challenge. It is notable that differences in neuroendocrine response were correlated with some personality measures relevant to substance use, such as novelty seeking. Given the lack of evidence for dopamine toxicity in humans and non-human primates, it is unlikely that blunted growth hormone response to bromocryptine in Ecstasy users should be interpreted as an indicator of dopamine toxicity, though it may be an indicator of changes in dopamine receptors. It is possible that pre-existing conditions, or other effects of Ecstasy use are instead responsible for blunted neuroendocrine response to bromocryptine.

Levels of tryptophan, the amino acid that serves as a precursor to serotonin, was measured at baseline and again after manipulating available tryptophan in gender matched (all male) samples of current Ecstasy users, former Ecstasy users and cannabis user controls (Curran et al. 2003). Curran and colleagues manipulated levels of available tryptophan through administering amino-acid containing beverages that either contained or did not contain tryptophan. This study also assessed mood and cognitive function and is discussed in detail in previous sections. At baseline and after tryptophan depletion, current Ecstasy users with a lifetime use of 527.8 tablets and abstinent for 39 days, former Ecstasy users with a lifetime consumption of 1105.8 tablets and abstinent for 873.6 days, and cannabis using controls had similar plasma tryptophan levels, but after tryptophan augmentation, former Ecstasy users had higher levels of free and total tryptophan than either current Ecstasy users or cannabis users. This finding may indicate changes in the process or speed of transforming tryptophan into serotonin, with these changes reflecting possible changes in serotonin function. That these changes were present in former Ecstasy users, and not current users, may be explained by one or more hypotheses, including the existence of pre-existing differences in tryptophan metabolism that also led to abstinence from Ecstasy, pre-existing sensitivity to the effects of regular Ecstasy use on serotonin function, effects arising from changes in serotonin receptors, or changes after regrowth of serotonin axons occurring after regular Ecstasy use.

The first studies examining plasma amino acids, antioxidants, vitamins, and relevant enzymes in Ecstasy users appeared in 2003. Researchers in Germany (Stuerenburg et al. 2003) studied 107 Ecstasy users (lifetime consumption varied, from 34 reporting less than 100 tablets to 30 reporting over 500 tablets), 41 polydrug users, and 11 abstinent Ecstasy users (period of abstinence not listed; current users abstinent for at least three days) found various differences amino acid concentrations (Stuerenburg et al. 2003). Differences were seen in plasma concentrations of phosphoserine (elevated), glutamate (reduced), and lysine (relationship unstated). Abstinent users also had higher concentrations of citrulline than Ecstasy users with a lifetime consumption of between 100 and 499 tablets, higher methionine than all but the heaviest current Ecstasy users, and higher histidine than all Ecstasy users. The authors do not report on possible group differences in nutritional, physical, or mental health that might potentially be related to differences in amino acid concentration, such differences in diet. Other than the authors'

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assertions of an association between increased levels of specific amino acids and psychosis, the significance of these findings, in terms of assessing risk of Ecstasy use and in terms of estimated risk to humans of MDMA remains unclear.

A team of researchers in China sought to assess oxidative stress in Ecstasy users by examining plasma concentrations of antioxidant vitamins and biological compounds (vitamins C and E, beta carotene) and enzymes (glutathione peroxidase, catalase) and the neurotransmitter acetylcholine in a sample of 120 Ecstasy users and 120 age-matched, non-drug user controls (Zhou et al. 2003A; Zhou et al. 2003B). Lifetime Ecstasy consumption is not provided, but is estimated to be between 23 and 116 tablets, Zhou and colleagues provide no information on how long people in their sample have been abstinent from Ecstasy. Ecstasy users in this study had lower levels of vitamins C and E, exhibited less activity from two enzymes implicated in free radical scavenging, and had higher levels of lipoperoxidation, a marker of oxidative stress (Zhou et al. 2003A). The researchers reported a number of correlations between what the authors referred to as "Ecstasy abuse dose" (possibly average dose per use), plasma vitamin concentrations, and enzyme activity levels, with higher "abuse dose" associated with lower levels of vitamins and less enzyme activity. The second study also reported lower levels of erythrocyte acetylcholine, and reported an association between acetylcholine levels and lipoperoxidation, with higher levels of acetylcholine associated with less lipoperoxidation (Zhou et al. 2003B). The researchers do not offer a complete report of drug use parameters in their sample, raising the issue of whether the differences they report arose from one or more specific parameters of Ecstasy use, dietary or other health behaviors relating to Ecstasy use, or use of other substances. These study findings are provocative, but do not offer strong enough support for MDMA producing long-term effects on oxidative stress because they fail to provide relevant information on drug use parameters, including period of abstinence, concomitant use of other drugs, and dietary behaviors. These findings do not increase estimated risk as stated so far, but might support claims that MDMA can produce oxidative stress in humans.

Because much of the research described in this section used novel or unusual measures with uncertain relevance to serotonin toxicity, study findings offer little in the way of informing estimates about the safety or efficacy of MDMA in clinical trials. Only the studies attempting to assess oxidative stress in Ecstasy users might prove relevant, but owing to incomplete reporting in these studies, the findings make it difficult to establish whether humans experience oxidative stress after MDMA. Hence these findings do not change original estimates of minimal risk to people taking part in clinical trials of MDMA made in previous reviews of the literature. It seems likely that risk of changes in evoked brain potential, neuroendocrine response or blood amino acids will all be lower for people given a few doses of MDMA than they are in Ecstasy users.

Overall Conclusion

Recent studies of Ecstasy users published from 2003 to 2004 included naturalistic studies of acute and sub-acute effects and studies comparing one or more group of Ecstasy users with one or more group of control. Areas of investigation included differences in mood

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and psychological well-being, anger and impulsiveness, cognitive function, brain structure and function, and other domains, such as evoked potentials and blood antioxidant levels. Findings in most areas of research are in accordance with findings previously reviewed in the IB or the 2002 update to the IB. Even findings that question whether Ecstasy use makes a unique contribution to decline in psychological well-being in Ecstasy users have appeared before in the literature. The only genuinely novel finding is that of impaired cognitive function in former, but not current, Ecstasy users in two independent studies (Curran et al. 2003; Thomasius et al. 2003), and possibly findings of altered levels of tryptophan after tryptophan augmentation, also in former Ecstasy users (Cu8rran et al. 2003). Findings from recent publications continue to support the possibility that MDMA might reduce or change serotonin function, or impair executive function or memory, while they also continue to support the conclusion that this risk is very likely to be minimal for people taking part in clinical trials. Recent studies cast doubt on a strong association between Ecstasy use and decline in psychological well-being, but they do not entirely eliminate the possibility of risk. When considered in the context of preliminary data gathered after clinical trials, studies in Ecstasy users suggest that participants in trials of MDMA may face several risks, but that in all cases these risks are minimal.

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In Vitro and Non-human animals

Introduction

To date, researchers continue to publish a wealth of studies examining the pharmacology, behavioral effects, and toxicity of MDMA in non-human animals, chiefly rodents and non-human primates. MDMA neurotoxicity is most frequently addressed, but other areas include MDMA pharmacology, toxicity in other organs or tissues, developmental toxicity studies, acute, short term and long-term behavioral effects of MDMA, self-administration studies. While examinations of MDMA pharmacology and stimulus properties are two useful ways of learning more about the acute effects of the substance and how its subjective effects are experienced by nonhuman animals, these studies are for the most part irrelevant to assessing the safety of MDMA in humans. Hence this review does not review papers addressing the acute effects or pharmacology of MDMA in non-human animals unless those effects are considered relevant to assessing the safety of human trials with MDMA. However, information in these areas of study can be found in other published literature reviews (Cole et al. 2003; Green et al 2003B).

Neurotoxicity

As discussed in the 2002 revision to the IB, the majority of studies of MDMA in non-human animals concern detecting, assessing, and understanding MDMA neurotoxicity. Some publications describe novel or previously unreported means of examining the long-term effects of MDMA on the brain, whereas others look at mediating factors, such as ambient temperature and the presence or availability of antioxidants. Still others seek to establish behavioral indicators of MDMA neurotoxicity. While most of the publications appearing after the completion of the 2002 update of the IB do not offer new information on the topic, a few developments significantly alter conclusions reached in 2002. Perhaps most significantly, one of the studies reviewed in that document has since been retracted, and provocative findings from another study published in early 2004 raises issues concerning possible differences between effects produced by experimenter-administered versus self-administered drug.

Detection and Assessment

While some recent publications continue to confirm signs of damage to serotonin axons and signs of oxidative stress in the brains of rats, mice, and guinea pigs (Fornai et al. 2003; Saadat et al. 2003), other studies quality or call these findings into question (Fantegrossi et al. 2004B; Fornai et al. 2003; Pubill et al. 2003). One study detected damage to neuron bodies in rats (Schmued et al. 2003), though another failed to find signs of cell death in mouse brain (Fornai et al. 2003a). Studies of MDMA neurotoxicity have examined the brains of rats, mice (where dopamine toxicity is expected rather than serotonin toxicity), guinea pigs, and rhesus monkeys.

In the first study reporting signs of damage to neurons themselves, rather than just axons, Schmued and colleagues reported that when brain slices from rats given 20 or 40 mg/kg

MDMA showed signs of neuronal degeneration, as assessed with the stain Fluoro-Jade B, while little or no indications of degeneration were seen in rats given 10 mg/kg. The authors noted that hyperthermia was more closely associated with signs of neuronal degeneration than MDMA dose, and they suggest that differences in rat strain, age, and body temperature might explain no previous studies have detected harm to serotonin neuron bodies. Somewhat contradictory findings were reported by Fornai and colleagues (Fornai et al. 2003a; 2003b) in studies in mice. Their studies examined brain slices of GABA-ergic cells in the striatum and substantia nigra of mice given 4 injections of 5 mg/kg every 2 hours, and they found nuclear inclusions, signs of DNA damage or repair, and other indicators of oxidative stress, but no signs of apoptosis, or cell death.

While rodent studies tended to detect signs of MDMA neurotoxicity, a study in rhesus monkeys that had self-administered MDMA approximately three times a week for an 18-month period failed to find signs of frank neurotoxicity (Fantegrossi et al. 2004B). On average, monkeys in this study self-administered cumulative doses of 2 to 4 mg/kg per hour-long session, though doses of up to 15 mg/kg were administered on at least one session. Presence of axonal degeneration was measured in vivo with PET using a radioligand (radioactively labeled drug) that binds to VMAT, a protein associated with axon terminals, and by assessing brain neurotransmitter and VMAT content after monkeys were killed, Fantegrossi and colleagues failed to detect any changes markers of axonal health, or changes in brain neurotransmitters. Brain serotonin levels were lower in monkeys that had self-administered MDMA, but the difference was not statistically significant, and no differences in brain dopamine were found. This study differed from other MDMA neurotoxicity studies in that drug administration was under the immediate control of the subject rather than being administered non-contingently by the experimenter. If the effects of experimenter-contingent (not under the subject's control) MDMA differ from those of self-administered MDMA, then nearly all MDMA neurotoxicity studies in non-human animals may need to be reconsidered, since these studies used experimenter-contingent administration. This study also suggests that when self-administered in doses similar to those used by human Ecstasy users, MDMA produces little or no changes or damage to brain serotonin neurons. However, as discussed in a later section, the study did find that monkeys were similar to humans in that they lost interest in self-administering MDMA over time, in a manner possibly analogous to "loss of magic" reported by some long-time Ecstasy users and discussed in the IB. It is possible that "loss of magic" is an indicator of harm to serotonin axons and lower brain serotonin. It is also possible that reduced interest in self-administering MDMA is instead a sign of non-neurotoxic changes in the brain, such as increased presence (upregulation) or decreased presence (downregulation) of serotonin receptors.

Findings from another study in rhesus monkeys raises questions about how doses of MDMA given to non-human primates match doses given to humans (Bowyer et al. 2003). A dose is considered equivalent across species if it produces similar levels of a drug in blood and brain. Most researchers have relied on interspecies scaling to arrive at dose equivalents for their studies, but there has long been controversy over whether interspecies scaling is an appropriate model for calculating MDMA dose equivalents (see the IB, also McCann et al. 2001; Vollenweider et al 2001; Vollenweider et al. 1999).

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Because of this controversy, some people have questioned the high and repeated doses used in nonhuman animal studies, arguing that these doses are not in fact equivalent to doses used by humans. Recently, Bowyer and colleagues collected blood from rhesus monkeys after a single dose of 10 mg/kg S-(+)-MDMA (Bowyer et al. 2003) in a study that also assessed long-term effects after four days of twice-daily dosing with 10 mg/kg S-(+)-MDMA. Plasma MDMA in these animals after the first 10 mg/kg dose was ten times the levels seen in humans given between 1 and 2 mg/kg MDMA. In agreement with these findings, a study in swine reported that plasma levels of 8 mg/kg MDMA were about eight times higher than those seen in humans after typical recreational doses (Fiege et al. 2003). Peak plasma levels of MDMA were seen 20 minutes after administration, probably as a result of administering the drug by injection rather than orally. In rhesus monkeys, MDMA half-life was 8.3 hours, a value that is very close to its half-life in humans (7 to 9 hours). Plasma MDA levels in these swine were similar to those reported in human Ecstasy-related fatalities. Bowyer and colleagues used only the S-(+) enantiomers of MDMA, while humans almost always use the racemate, and it is possible that the racemate would have produced different results. However, the study in swine used the racemate, and still reached similar findings with respect to plasma MDMA levels. Taken together, these findings suggest that dose regimens used in non-human primates are not equivalent to doses used by humans. The above findings in rhesus monkeys and swine suggest either that current interspecies scaling calculations need to be revised or that interspecies scaling is an inappropriate means of estimating dose equivalence for MDMA. If either case is true, then studies in non-human animals do not provide a basis for estimating a neurotoxic dose of MDMA in humans.

A previous report of dopamine toxicity in non-human primates after 3 injections of 2 mg/kg MDMA given within a six-hour period addressed in the 2002 revision of the IB (Ricaurte et al. 2002) has been retracted (Ricaurte et al. 2003). At the time of its publication, critics remarked on the relatively high mortality rate reported in the study, lack of evidence of dopamine toxicity in Ecstasy users, and whether the dose regimen used was genuinely reflective of doses used by most Ecstasy users (Mithoefer et al. 2003). In line with previous studies in humans (Kish et al. 2000; Reneman et al. 2002A; Semple et al. 1999), subsequent attempts to replicate study data failed, leading to the discovery that Ricaurte and colleagues had administered the psychostimulant methamphetamine to their subjects, and not MDMA. Attempts to replicate the original findings in monkeys failed to detect dopamine neurotoxicity after three oral (intragastric) doses of up to 8.6 mg/kg MDMA to squirrel monkeys within a six-hour period, or after three 4 mg/kg injections (Ricaurte 2004), suggesting that even high doses of MDMA are unlikely to reduce dopamine function in primates. Ricaurte and colleagues also failed to replicate findings in baboons. It is well-known that mice exhibit lower levels of dopamine and the dopamine metabolite DOPAC after MDMA administration, but to date, they are the only species of mammal showing signs of dopamine, and not serotonin, neurotoxicity after repeated doses of MDMA. Even a recent attempt to confirm indications of dopamine toxicity in guinea pigs (Saadat et al. 2003) failed to find it, though the study did find that MDMA produced a lesser degree of hyperthermia in guinea pigs. The retraction of the study by Ricaurte and colleagues reinforces previous studies

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suggesting that when it appears, MDMA neurotoxicity is specific for serotonin in all mammals studied so far except mice.

Some findings from a study in Dark Agouti rats, a strain lacking an enzyme involved in MDMA metabolism reported that initial dose of 12.5 mg/kg MDMA increased the degree of hyperthermia seen after subsequent, and lower, doses of 2, 4, 5 or 6 mg/kg MDMA, and this was especially true in a warm environment (Green et al. 2003A). While the authors did not report on brain neurotransmitter levels, these findings suggest that illicit Ecstasy users reporting at least one large or "binge" dose of Ecstasy may increase their chances of experiencing elevated body temperature after subsequent uses of MDMA. Bowyer and colleagues found that plasma S-(+)-MDMA levels were higher at the seventh of eight doses in a four-day S-(+)-MDMA regimen (10 mg/kg given twice daily) than after the first dose of S-(+)-MDMA (Bowyer et al. 2003). The significance of this difference is unclear, but again, it is possible that large and repeated doses of MDMA may alter MDMA metabolism or sensitivity. Another study in rats comparing the effects of repeated MDMA (four hourly doses of 5 mg/kg) at lower (16 C) versus higher (28 C) ambient temperatures detected reductions in serotonin and 5-HIAA in both conditions (McGregor et al. 2003a). However, the researchers found greater reduction in serotonin when MDMA was administered in a warm environment. The same dosing regimen produced long-term behavioral changes, such as increased anxiety (discussed below under "Behavioral changes") and apparent impairment in object memory (discussed in "Effects on Learning and Memory.") It appears that elevated body temperature exacerbates degree of reduction in serotonin after MDMA. Note that rats were hypothermic after receiving MDMA in a 16 C environment, but still exhibited some reductions in serotonin and serotonin metabolites. However, if one large dose of MDMA does increase susceptibility to elevated body temperature, and if elevated body temperature in turn plays a role in MDMA neurotoxicity in primates, then taking large doses of MDMA in warm conditions (as in nightclubs) may not be comparable to taking smaller doses of MDMA in less warm locations, as those found in clinical trials, and studies in Ecstasy users are liable to overestimate degree of harm to serotonin function posed by clinical trials with MDMA.

A study seeking to compare the neurotoxic effects of MDMA with the neurotoxic effects of methamphetamine in rats (Pubill et al. 2003), reported that methamphetamine, but not MDMA, increased astroglial and microglial activity, considered markers of tissue damage and repair. Rats in this study received either two injections of 20 mg/kg MDMA 7 hours apart for four days, or four injections of 10 mg/kg methamphetamine every 2 hours for one day, and were killed three days post-drug (MDMA and methamphetamine) or one week later (MDMA-treated rats only). MDMA did not increase microglial activity in parietal or striatal areas, and there was only a trend for increased microglial activity in hippocampus three days later, with signs of microglial activation no longer visible seven days after MDMA administration. By comparison, MDMA treated rats had signs of lower levels of serotonin transporter sites three and seven days post-MDMA, as assessed via brain paroxetine binding, whereas methamphetamine did not reduce serotonin transporter binding. The reported findings are supportive of changes in serotonin receptor regulation rather than MDMA neurotoxicity, though the researchers note

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previous studies that have found signs of axonal degeneration after MDMA. It is notable that the researchers did not detect significant hyperthermia in either MDMA or methamphetamine treated rats, raising the possibility that glial activation could have been detected in rats with elevated body temperatures.

Researchers comparing the behavioral and neurochemical effects of repeated doses of MDMA, methamphetamine, or the two combined (4 doses given every 2 hours in rats in a warm environment (28 C) (Clemens et al. 2004) found that the high-dose combination of MDMA and methamphetamine (2 mg/kg) demonstrated reduced brain serotonin and dopamine, though the low-dose (1.25 mg/kg) combination had no effect upon brain serotonin or dopamine. By comparison, MDMA alone only reduced brain serotonin, and methamphetamine alone only reduced brain dopamine. Altered brain neurochemistry is especially notable as the doses used were lower than those given in single-substance conditions (2 mg/kg versus 2 or 5 mg/kg MDMA). If these findings generalize to other species, including humans, then it may be the case that Ecstasy users are affected by the intentional or unintentional coadministration of MDMA and methamphetamine. Consequently, studies of Ecstasy users may not offer an appropriate gauge of extrapolating risk to participants in clinical trials of MDMA.

A study of the effects of delta-tetracannabinol (THC, the active ingredient in cannabis) on MDMA neurotoxicity in rats found that THC and a cannabinoid receptor agonist (activator) at least partially attenuated reductions in brain serotonin (Morley et al. 2004), with THC producing a greater attenuation of serotonin reduction than the cannabinoid receptor agonist. Rats receiving THC showed hypothermic rather than hyperthermic responses to MDMA, but coadministering another compound that prevented hypothermia did not prevent a cannabinoid receptor agonist from attenuating reductions in brain serotonin. In contrast to the findings reported above, these suggest that because they often use cannabis, Ecstasy users may be experience less risk of reduced serotonin function than if they used MDMA only, though Morley and colleagues also note that the doses of THC used in this study were high and probably do not represent doses obtained through smoking cannabis.

A team of researchers in Italy examining the role oxidative stress in MDMA neurotoxicity in mice given four 5 mg/kg injections every 2 hours (Fornai et al. 2003a; 2003b) found strong evidence of oxidative stress and damage to dopamine axons (as expected in mice), but no signs of cell death. They used multiple indicators of oxidative stress, including detection of heat shock proteins (associated with oxidative stress), levels of neurotransmitters, signs of cellular DNA damage and repair, and levels of the axon-associated protein VMAT. In vitro studies described in the same report found ubiquitin-positive inclusions in rat tumor cells incubated with MDMA, considered signs of oxidative stress.

Surprisingly, a study that sought and failed to find indicators of somatic “withdrawal” in mice given twice-daily injections of 10 mg/kg MDMA for five days also failed to find lower levels of dopamine transporter (Robledo et al. 2003). It is unclear why lower brain dopamine levels were not seen in these mice. Findings either indicate a weak association

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between brain dopamine levels and dopamine transporter abundance or a sign that MDMA neurotoxicity is not consistently produced by this dose regimen in mice.

Most researchers addressing MDMA neurotoxicity continue to be interested in finding evidence in support of specific hypotheses concerning the processes involved in MDMA neurotoxicity, and what means can be used to distinguish potentially neurotoxic compounds from non-neurotoxic ones. Studies used pharmacological challenges either intended to be neuroprotective or exacerbate neurotoxicity (Clemens et al. 2004; Morley et al. 2003; Peng and Simantov 2003; Sanchez et al. 2003; Thompson et al. 2004), altered aspects of the environment, such as ambient temperature (Green et al. 2003A; McGregor et al. 2003a) or stress (Johnson et al. 2003), and examined the effects of neurochemical lesioning (Ferrucci et al. 2003). Studies tended to support findings that oxidative stress is involved in MDMA neurotoxicity, though a team of researchers demonstrated that oxidative stress may play a greater role in MDMA toxicity in mice than in rats (Sanchez et al. 2003). Protective treatments included familiar ones, such as reduced ambient temperature, and unfamiliar ones, such as THC) (Morley et al. 2004). Other findings include the discovery that mice with lesioned norepinephrine systems had greater reductions in brain dopamine than mice with intact norepinephrine systems (Ferrucci et al. 2003), and that administering centrally active GABA-ergic drugs reduced MDMA lethality and attenuated brain dopamine reduction in mice (Peng et al. 2003).

One surprising finding reported by Johnson and associates relates to the neuroprotective effects of stress in female mice injected with four doses 15 mg/kg S-(+)-MDMA (one dose every two hours). Contrary to general expectations, mice exposed to several stressors, including restraint stress, a 16 C (61 F) environment, and exposure to ethanol, actually exhibited greater levels of brain dopamine than unstressed mice (Johnson et al. 2003). Increasing levels of corticosterone, the rodent version of cortisol, so that it matched levels in stressed animals did not attenuate MDMA effects on dopamine levels. Cool ambient temperature is already known to reduce MDMA neurotoxicity, perhaps through reducing oxidative stress or MDMA metabolism, and the effects of ethanol may be explained by direct pharmacological or neurochemical actions, but the beneficial neuroprotective effects of restraint stress remain difficult to explain. Because the authors used only S-(+)-MDMA, it is possible that these findings will not generalize to racemic MDMA. However, such findings at least raise the possibility that environmental stress does not necessarily exacerbate MDMA-induced reductions in brain monoamines.

Some researchers performed in vitro studies of serotonin and dopamine transport to see whether they could better understand aspects of neuronal transport associated with neurotoxicity (Bogen et al. 2003; Saldana et al. 2003). In vitro research using rat synaptosomes that compared synaptosomal uptake of radioactively labeled transmitter with vesicular (cellular, active) uptake conclude that vesicular uptake, and not synaptosomal uptake, is associated with the neurotoxic properties of MDMA. A comparison of the effects of 10 nM MDMA on serotonin and dopamine transport by tumor cells expressing human serotonin transporter (Saldana et al. 2003), with transport assessed at temperatures intended to mimic ordinary (37 C) and hyperthermic (40 C) body temperatures reported increasing transport of serotonin, but not dopamine, at higher

temperatures (Saldana et al. 2003). Higher ambient temperatures seemed to increase rate of serotonin transport and inhibit dopamine transport, leading the researchers to propose that as serotonin levels decline after MDMA, dopamine may still enter into synapses.

In general, reports addressing MDMA neurotoxicity in non-human animals support previously reported conclusions. These include findings of reduced brain serotonin in rats and monkeys and reduced dopamine in mice, the impact of hyperthermia on MDMA neurotoxicity, evidence of a role for oxidative stress, and signs of damaged serotonin axons. However, findings reported since 2002 may alter some conclusions reported then. There is no longer any basis to believe MDMA produces dopamine neurotoxicity in non-human primates, and a study in rodents reported evidence of harm to neuron bodies, though these findings were dependent on dose and presence of hyperthermia. An examination of the brains of monkeys that had self-administered MDMA over an eighteen-month period found no indicators of reduced dopamine function and non-significant declines in brain serotonin, and no signs of axonal damage as assessed through measuring levels of VMAT. Though some findings point to additional routes of neurotoxicity and other studies question the degree or type of neurotoxicity seen after MDMA, an overall evaluation of these findings does not yet change the assessment of safety reached in the IB and the 2002 update to the IB, except with respect to dopamine toxicity. Human participants receiving no more than a cumulative dose of about 2.8 mg/kg on two separate occasions in a normothermic environment should be at minimal risk for potential serotonin neurotoxicity after MDMA, and so far it appears that they do not face any risk of dopamine toxicity.

Effects on Learning and Memory

Non-human animals appear to be less susceptible to impaired learning and memory after MDMA than might be estimated from studies of Ecstasy users (see for example Frederick et al. 1998; and further discussion in the IB). There are only a few reports of impaired learning in rodents (Marston et al. 1999), and none in monkeys, with differences in monkeys only seen after pharmacological challenge (Taffe et al. 2002). Even reports of apparent learning or memory deficits in rodents reviewed in the 2002 update of the IB (Morley et al .2001; Pompei et al. 2002) may be interpreted as reflections of increased anxiety or sociability rather than signs of a learning or memory impairment. While neonatal or young rats may be more susceptible to the effects of MDMA on learning (see Williams et al. 2002), previous research has not detected learning or memory impairments after MDMA, even at doses that reduced brain serotonin. At the time of this review, still remains true for non-human primates (Bowyer et al. 2003; Taffe et al. 2003), but recent reports suggest that this may no longer be true for rats (McGregor et al. 2003a; Sprague et al. 2003A, but see also Timar et al. 2003).

Eleven months after receiving daily doses of 10 mg/kg MDMA or vehicle (no MDMA) for four consecutive days, MDMA-treated rhesus monkeys failed to perform any differently than controls on a test battery designed to measure learning, memory and motivation in non-human primates (Taffe et al. 2003). In controls, tryptophan depletion improved performance on a spatial sequential search task, while MDMA-treated

monkeys did not benefit from tryptophan depletion. Neurochemical analyses were not reported in this study, so presence or degree of reduced brain serotonin in MDMA-treated monkeys is not known, but the doses used appear to be comparable to doses that lower serotonin in the same species. These findings suggest that long-term functional effects in monkeys may only emerge in specific circumstances, as under transient alterations in serotonin function (Taffe et al. 2002). The relevance of these findings to studies of cognitive function in Ecstasy users remains unclear, since an examination of research findings suggests a dissociation between impaired cognitive function and signs of reduced serotonin function (see discussion in "Studies of Ecstasy Users.") These results also indicate that when they can be found, changes in cognitive function appearing after repeated MDMA in nonhuman primates are subtle.

Bowyer and colleagues (2003) assessed performance on a learning and behavioral test battery in male rhesus monkeys given 10 mg/kg S-(+)-MDMA twice daily for four consecutive days. Monkeys with high plasma levels of MDMA took longer to perform the tasks a week after the last MDMA administration, but their performance had returned to normal a month after the final dose of MDMA. The learning task consisted of making the correct sequence of lever presses to earn a reward on an array of six levers. It would appear in this case that the changes in performance were temporary. By contrast, studies in Ecstasy users have not found that impaired memory or executive function dissipates after a period of abstinence, and some studies even found impaired cognitive function only in abstinent Ecstasy users.

A study assessing spatial memory seven days after rats received two 20 mg/kg injections of MDMA given 12 hours apart found that MDMA-treated rats learned to navigate the Morris water maze (test of spatial memory) as well as saline-treated rats, but that they had difficulty recalling or locating the spot where the escape platform had been when it was removed (Sprague et al. 2003A). MDMA-treated rats in this study also had lower levels of serotonin in the hippocampus when assessed 15 days post-drug. It should be noted that since memory was assessed seven days post-drug, and given the transience of the effects found in monkeys, it is not clear if this impairment reflects a long-term effect. An examination of the impact of ambient temperature on long-term effects of MDMA in rats (McGregor et al. 2003a) reported that MDMA (four hourly doses of 5 mg/kg) impaired performance on a test of object memory, assessed by noting time spent exploring a novel versus familiar object, and that performance on this task was further reduced in rats given MDMA in a warm environment (28 C) versus a cooler one (16 C). . In contrast with studies finding impaired learning or memory in rats, a comparison of the effects of single versus multiple doses of S-(+)-MDMA and amphetamine in rats failed to find impaired active or passive learning after four injections of 10 mg/kg S-(-)-MDMA given every two hours (Timar et al. 2003). Timar and associates did not assess brain serotonin or serotonin function, so it is not known whether rats had lower levels of brain serotonin, though the dose the researchers used is known to reduce brain serotonin in rats. Both of the learning tasks in this study rely on fear-based learning, so it is possible that MDMA-associated increases in anxiety made it more likely that MDMA-treated rats would perform well at these tasks.

As was true of research previously reviewed in the 2002 update of the IB, published findings appearing in 2003 concerning the long-term effects of MDMA on learning and memory in non-human animals are inconclusive. Studies in rodents sometimes reported signs of impaired learning or memory after MDMA, while studies in monkeys found impairment or changes in performance that was either temporary or that only appeared under pharmacological challenge.

Behavioral Effects and their Association with Neurotoxicity

Researchers continue to study the behavioral effects of MDMA in rodents, including assessments of anxiety (Clemens et al. 2004; McGregor et al. 2003a; 2003b; Robledo et al. 2003; Thompson et al. 2004), sensitization to other drugs (Cole et al. 2003) or locomotor activity (Itzhak et al. 2003). Interest in the long-term effects of MDMA on anxiety and "depression-like" behavior (performance on the forced swim test, used to assess potential antidepressants) continues to interest researchers, both as a result of findings of reduced psychological well-being in Ecstasy users and because of a presumed relationship between mood or affect and the serotonin system. So far, most studies have found increased anxiety after repeated doses of MDMA (Fone et al. 2002; Gurtman et al. 2002; Morley et al. 2001). However, reduced anxiety has been found on occasion (Mechan et al. 2002), and may be an alternative explanation for some findings described as measures of social memory (Pompei et al. 2002), as discussed in the 2002 update to the IB. Researchers also reported that MDMA increased sensitivity to other stimulants (Fone et al. 2002).

Most recent publications reported increased anxiety in rodents after MDMA, as measured in the emergence test (Clemens et al. 2003; McGregor et al. 2003a; 2003b; Morley et al. 2003; Thompson et al. 2004) and in the open field test (McGregor et al. 2003a). Studies found increased anxiety after dose regimens not known to reduce brain serotonin, and not just after doses that usually reduce brain serotonin, suggesting that changes in anxiety do not represent a marker for MDMA neurotoxicity. Repeated doses of MDMA also reduced social interactions between pairs of novel rats (Clemens et al. 2003; Morley et al. 2003; McGregor et al. 2003a; 2003b; Thompson et al. 2004). It is notable that in some studies, neuroprotective treatments, such as fluoxetine (Thompson et al. 2004) or THC, or a cannabinoid CB1 agonist (Morley et al. 2003) did not attenuate MDMA-associated reductions in social interaction, even when (in the case of THC), the treatment attenuated anxiety after MDMA (Morley et al. 2003).

Anxiety-increasing doses of MDMA in studies ranged from four 5 mg/kg injections every 2 hours (Clemens et al. 2003) to four 10 mg/kg every two hours for one day (Timar et al. 2003), with most studies administering four hourly doses of 5 mg/kg for two consecutive days (McGregor et al. 2003a; 2003b; Morley et al. 2003; Thompson et al. 2004). Researchers assessed anxiety as early as four weeks post-MDMA (Clemens et al. 2003), and as late as 12 to 15 weeks post-MDMA (Thompson et al. 2004). In most cases, MDMA increased both social and non-social anxiety. Administering MDMA in a cooler environment (16 degrees C versus 28 C) did not reduce the appearance of anxiety afterwards (McGregor et al. 2003a).

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While four injections of 2.5 mg/kg MDMA did not reduce brain serotonin and 5HIAA to the same degree as 5 mg/kg (Clemens et al. 2003), the lower dose increased anxiety as assessed via emergence test, while there was only a trend for increased anxiety, measured 11 weeks post-drug, after the higher dose. By contrast, the higher dose, and combinations of MDMA and methamphetamine, reduced social interactions, whereas the low dose did not. Another study found that even a single 5 mg/kg injection increased anxiety without any significant changes in brain serotonin or 5HIAA (McGregor et al. 2003b). Taken together, examining all studies assessing anxiety after MDMA suggest MDMA is more likely to increase anxiety in rodents, and that increased anxiety after MDMA is not caused or produced by lower brain serotonin, and may instead be the result of some other as yet unmeasured change in brain function or structure. One possibility is that changes in receptor activity, such as changes in 5HT2A receptors, result in these and other behavioral changes.

Two studies reported on the effects of MDMA on the "forced swim" test, considered a measure of depression-like behavior in rats (McGregor et al. 2003a; Thompson et al. 2004). Sixteen to 18 weeks after receiving four hourly doses of 5 mg/kg MDMA for two days in a row in either 16 or 28 C environments, rats showed increased immobility and reduced escape attempts during the forced swim test (McGregor et al. 2003). Rats in another study that received the same MDMA regimen (four hourly doses of 5 mg/kg given for two days) also showed increased immobility and decreased active response on the forced swim test (Thompson et al. 2004). A five week course of fluoxetine administered in drinking water (with rats ingesting approximately 6.2 mg/kg fluoxetine per day) attenuated MDMA-associated reductions in forced swim performance, even though this dose of fluoxetine surprisingly did not improve forced swim performance in saline-treated rats. Furthermore, fluoxetine had very little effect on serotonin levels in MDMA-treated rats, though it did decrease 5HIAA levels. The authors propose that fluoxetine ameliorated anxiety and depression-like effects by acting on serotonin receptors and not through neuroprotection.

Since many studies now find that changes in psychological well-being in Ecstasy users are liable to be related to variables other than Ecstasy use (see discussion in "Studies in Ecstasy Users" and in the 2002 update to the IB), the relevance of increased anxiety in MDMA-treated rodents remains unclear, but supports the possibility of an association between MDMA and anxiousness. However, because these effects are seen both after neurotoxic and non-neurotoxic dose regimens, increased anxiety cannot be treated as an indicator of reduced serotonin function. Given that findings from human studies do not assign a strong or unique association between MDMA and anxiety or depression, and given that humans, these findings in no way increase the estimation of potential risk of increased anxiety in human participants receiving MDMA.

Developmental Toxicity

In the IB and especially in the 2002 update to the IB, it was noted that exposing rats to MDMA either prior to birth or shortly after birth altered brain chemistry and sometimes

produced impaired learning and memory. There has been controversy concerning studies describing developmental toxicity in humans (see for example McElhatton et al. 1999), but researchers continue to examine the effects of prenatal (Kelly et al. 2002; Koprich et al. 2003A), neonatal (Kelly et al. 2002; Koprich et al. 2003B; Williams et al. 2003), or early "youth" (Bull et al. 2004) exposure to MDMA in rats. So far, these studies have detected changes in brain neurochemistry and behavior.

Rat pups whose mothers had received twice-daily injections of 15 mg/kg MDMA on gestational days 14 through 20 were more active in a novel cage three days after birth compared to pups born to saline-treated rats (Koprich et al. 2003A), but fine motor activity was unaffected by MDMA exposure. Twenty-one days after birth, MDMA-treated rats had lower levels of serotonin and dopamine metabolites, possibly implying slower neurotransmitter turnover, since there were no differences in brain serotonin or dopamine content. By contrast, another research team (Kelly et al. 2002) reported that brain serotonin levels were not lower in rats born to mothers given 20 mg/kg MDMA twice daily over four consecutive days and starting on gestational day 15. Differences in research findings may be due to different dosing regimens, or to using different means of assessing brain serotonin levels, as Koprich and colleagues used high performance liquid chromatography (HPLC) whereas Kelly and colleagues assessed serotonin transporter binding with radioactively labeled paroxetine.

Neonatal rats exposed to high, frequent doses of MDMA (twice-daily injections 20 mg/kg for 10 days, beginning on postnatal day 11) performed less well than controls on water maze tasks that assessed spatial memory (Williams et al. 2003). Another study employing the same dosing regimen and time of dosing in rats found reduced serotonin and dopamine content in specific brain areas (Koprich et al. 2003B). Contradictory findings are reported in a study that varied time of neonatal exposure, and only administered twice-daily injections of 20 mg/kg MDMA for four days (Kelly et al. 2002). No differences were seen in serotonin levels (measured by paroxetine binding) when MDMA exposure occurred prior to postnatal day 25, but brain serotonin levels were presumably reduced in rats given a first dose of MDMA on postnatal day 25 or 30. Kelly and colleagues found even greater reduction in brain serotonin when MDMA was begun on postnatal day 90. Differences in findings may be the result of differences in length of dose regimen (four versus ten days) and differences in assessment of brain serotonin. In reviewing these studies, it is important to note that most researchers believe that rat neonates are analogous to human fetuses in the third trimester of pregnancy, and so these findings would reflect a window of vulnerability occurring at the third trimester.

Young rats given four hourly doses of 5 mg/kg MDMA on two consecutive days exhibited increased anxiety and decreased social interaction (Bull et al. 2004), and brain serotonin and 5-hydroxyindoleacetic acid (5-HIAA) was lower. However, serotonin transporter density was apparently unchanged, leading the authors to conclude that behavioral changes were associated with changes in number or sensitivity of receptors, though changes in serotonin function could also be involved.

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As was the case with previously reviewed research, these studies support the existence of one or more critical periods when exposure to high or repeated doses of MDMA could alter brain development, impair specific forms of learning and increase anxiety, though it may be the case that MDMA must be administered for longer than four days for this effect to occur. Though doses used in these studies remain high, the findings continue to support the exclusion of pregnant women and women who are not using an effective means of contraception. Because MDMA-assisted therapy is not treating an acutely life-threatening illness, this restriction seems appropriate even if the high and repeated doses used in rodent studies may be overestimating the risk of developmental toxicity.

Other Possibly Related Effects

An investigation into the effects of MDMA on regulation of an area of the brain related to circadian rhythm (Dafters and Biello 2003) found that when the dopamine synthesis inhibitor AMPT or the D2 antagonist haloperidol were administered along with daily doses of 20 mg/kg MDMA injected on three consecutive days, they reduced MDMA-associated hyperthermia. However, these drugs did not alter the effects of MDMA on suprachiasmatic nucleus (SCN) neuron response to the 5HT1A receptor agonist 5-OHDPAT. The authors conclude that alterations in the SCN must be the result of MDMA metabolites, and not body temperature or dopamine presence per se, but they did not assess brain serotonin levels. The significance of these findings for understanding MDMA effects in humans is not clear.

Toxicity

Cardiotoxicity

Unpublished research finding that MDMA was an agonist at the 5HT2B receptor was reported to institutional review boards in the 2002 update to the IB. After the recent discovery that fenfluramine, an anorectant taken off the market in part because of its association with valvular heart disease (VHD), acted on the newly discovered 5HT2B receptor, it was suggested that drugs activating this receptor may increase the likelihood of VHD (Rothman and Baumann 2002). A receptor activity assay demonstrated that MDMA is a 5HT2B agonist, and incubation with the fairly large dose of 10 mM MDMA stimulated heart valve cell growth, as did identical concentrations of fenfluramine, dexfenfluramine and MDA. However, only fenfluramine and dexfenfluramine produced statistically significant increases in heart valve cell growth. VHD is even rare after chronic fenfluramine use (Davidoff et al. 2001; Rothman and Baumann 2002), and there are no medical reports of VHD appearing in an Ecstasy user. These findings do not suggest any increased risk of VHD after intermittent administration of MDMA.

Thermoregulation

Researchers continue to be interested in MDMA effects on body temperature, its mechanisms of action and the relationship between body temperature and neurotoxicity. To date, all recently performed studies have been performed in rodents. Recent

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publications examined possible neurochemical mechanisms (Fantegrossi et al. 2004B; Fantegrossi et al. 2003) and involvement of skeletal muscle thermoregulation, or "non-shivering" heat production, in MDMA-induced hyperthermia (Fiege et al. 2004; Mills et al. 2003; Sprague et al. 2003B).

Both racemic and S-(+)-MDMA produced dose-dependent hyperthermia in mice, while R-(-)-MDMA never produced hyperthermia, even at reliably lethal doses (Fantegrossi et al. 2003). This study found that group housing (six or twelve mice per cage) increased MDMA lethality, and that cold ambient temperature (a room kept at 4 C, or 39 F) reduced lethality for group-housed mice, suggesting a role for hyperthermia in aggregate (crowd or group related) toxicity of MDMA. Further investigations by the same author in mice found that both alpha1 adrenergic and 5HT2A antagonists reduced hyperthermia (Fantegrossi et al. 2004A), but only nantenine, a novel plant-based compound bearing some structural resemblance to MDMA, reduced MDMA-induced hyperthermia 30 minutes after MDMA administration.

Two studies in mice published by the same research team found relationships between MDMA-induced changes in body temperature and non-shivering heat production (Mills et al. 2003; Sprague et al. 2003B). One study found that thyroid hormones and presence of intact thyroid or hypophyseal area were associated with elevated body temperature after a single dose of 40 mg/kg MDMA in rats. Intact rats had elevated core and skeletal temperature after MDMA (Sprague et al. 2003B), but hypothermia was seen after the same dose of MDMA in hypophysiectomized and thyroparathyroidectomized rats. Transgenic mice lacking the gene for the uncoupling protein 3 (or UNCP3) had lower elevations in body temperature than normal mice after 10 to 40 mg/kg MDMA, and were more likely to survive after receiving 50 mg/kg MDMA (Mills et al. 2003). It is notable that doses of MDMA in these studies were high; lower doses may not trigger non-shivering heat production in rodents or humans. While the significance of these findings to humans is somewhat unclear, especially given the high doses used to elicit hyperthermia in these studies, these findings do offer another explanation for elevated body temperature after MDMA.

Swine susceptible to malignant hyperthermia, a genetic disorder probably related to abnormal calcium metabolism in skeletal muscles, had higher body temperatures than non-susceptible swine after receiving 8 mg/kg and 12 mg/kg MDMA, though non-susceptible animals showed temperature increases after 12 mg/kg MDMA (Fiege et al. 2003). The researchers successfully reduced hyperthermia in malignant hyperthermia susceptible swine by administering the muscle relaxant dantrolene. These findings suggest that humans susceptible to the same disorder may respond similarly to MDMA. Though findings suggest that people possessing the genetic disorder that causes malignant hyperthermia would experience hyperthermia after MDMA, the rarity of the condition makes it an unlikely explanation for most cases of hyperthermia in Ecstasy users.

No cases of significantly elevated body temperature or clinically significant hyperthermia have occurred during any human trials of MDMA. The lack of any such occurrences

continues to demonstrate the minimal risk of administering 1 to 2.5 mg/kg MDMA to humans in controlled, normothermic settings. As discussed earlier in this review, human volunteers given MDMA in clinical trials sometimes experienced a slight elevation in body temperature, and even this elevation was not always detected. The effects of MDMA on body temperature appear to be dose dependent (Greene et al. 2003), but also appear to be related to ambient temperature and activity. These studies in non-human animals do not alter our original estimation that human volunteers taking part in clinical trials of MDMA are very unlikely to experience hyperthermia.

Liver Toxicity

As discussed in the IB, there have been sporadic reports of liver problems in Ecstasy users. While their etiology is not fully understood, high ambient or body temperature may be involved (see for example Andreu et al. 1998; Caballero et al. 2002; Henry et al. 1992). One researcher posited that liver problems may arise from impurities in illicit Ecstasy (Green et al. 2003B), though without presenting supportive evidence for the claim. In vivo and in vitro investigations of MDMA effects on the liver have been discussed in the IB and in the 2002 update of the IB. These investigations have found that MDMA seemed to impair liver function in cells when given at very high doses, and that these effects appear to be temperature-dependent (see Carvalho et al. 2002; Montiel-Duarte et al. 2002), As noted in the previous review of the literature, the doses used are probably not relevant either to doses taken by Ecstasy users or to doses administered in clinical trials.

One of the research teams responsible for several previous investigations performed another study investigating the effects of the MDMA metabolite MDA, and a putative metabolite alpha-methyl-dopamine (or Alpha-MeDA) on rat hepatocytes (Carvalho et al. 2003). 0.2, 0.4, 0.8, and 1.6 mM MDA, incubated with cells for 3 hours at 37 deg C (human body temperature), failed to impair rat liver cell function or reduce viability at any dose tested, while the highest dose of Alpha-MeDA reduced cell viability and increased some signs of impaired liver function (such as reduced glutathione content, without increasing signs of lipid peroxidation, a marker of oxidative stress. MDA is only a minor metabolite of MDMA in humans (de la Torre et al. 2001; Pizarro et al. 2002; Segura et al. 2001), and the concentration of alpha-MeDA that altered liver function is probably much greater than that expected in humans, assuming that levels of alpha-MeDA will always be lower than those of MDMA. Study findings do not alter earlier risk estimations related to liver toxicity. To date, no liver problems have been reported in human volunteers enrolled in clinical trials of MDMA.

Self-administration and Reward Value

Studies in rats (Cole et al. 20003; Cornish et al. 2003; Schenk et al. 2003; Wakonigg et al. 2003) and monkeys (Fantegrossi et al. 2004B) continue to find that non-human animals find MDMA rewarding. Two of four studies examined self-administration or reward value in animals already familiar with self-administering cocaine (Fantegrossi et al. 2004A), two others involved drug-naïve animals (Cornish et al. 2003; Wakonigg et al.

2003), and one study compared both cocaine-trained and drug-naïve rats (Cole et al. 2003; Schenk et al. 2003).

One study assessed reward value by first associating arrival at the end of a "runway" (an alley) with an injection of 1 mg/kg MDMA or saline (Wakonigg et al. 2003). The speed at which the rat arrived at the alley was considered an indicator of reward value. Researchers found more rapid arrival times after MDMA than after saline in two strains of rat (Long Evans and Sprague Dawley). While cocaine-trained rats learned to self-administer MDMA more readily than drug-naïve rats (Schenk et al. 2003), rats in both conditions worked to receive 0.1 to 2 mg/kg MDMA. Rats made more frequent lever presses when the dose of MDMA they received was low (e.g. 0.5 mg/kg), and stopped responding when only saline was available. Cornish and colleagues (2003) found that rats learned to self-administer a range of doses of MDMA (0.1 to 1 mg/kg), and that rats worked harder for all doses of MDMA when in a warm room (30 C, or 86 F) versus in a 21 C (70 F) "room temperature" setting, suggesting that the rewarding properties of MDMA increase with increasing ambient temperature, at least in rats. Cornish and colleagues also found that rats given MDMA in a warm environment were more likely to engage in social interactions than rats given MDMA in the cooler environment. A study in rhesus monkeys experienced in self-administering other drugs found that they also self-administered MDMA (Fantegrossi et al. 2004A). This study probably examined the same sample first described in a previous paper by the same team (Fantegrossi et al. 2002) reviewed in the 2002 update to the IB. Monkeys already maintaining self-administration of cocaine were presented with MDMA, as racemate and as R-(-)- and S-(+) forms, approximately three times a week, and number of self-administrations was catalogued over an eighteen-month period. Monkeys generally self-administered between 2 and 4 mg/kg MDMA per session, as discussed above in "Neurotoxicity." All forms of MDMA were self-administered at the start of the study, but by the end of the study, monkeys self-administered less racemic and R-(-)-MDMA, suggesting a use pattern analogous to the "loss of magic" reported by Ecstasy users. (Self-administration of S-(+)-MDMA declined over time in one monkey, while another self-administered more of this enantiomer.)

Conditioned place preference, or the tendency to remain in a place associated with a previous drug administration, was used in a study in rats (Cole et al. 2003) and a study in mice (Robledo et al. 2003), though neither of the two studies were focused on the reinforcing effects of MDMA. In one case, the authors investigated the possibility that rats previously given three injections of 10 mg/kg MDMA every 2 hours increased the reinforcing effects of other drugs, including a second dose of MDMA (Cole et al. 2003). They did not find any increased conditioned place preference for any of the drugs tested, MDMA amongst them, and instead found that ethanol produced less conditioned place preference in rats previously given MDMA. These results stand in contrast to an earlier report of increased conditioned place preference for cocaine after previous exposure to MDMA (Fone et al. 2002). The other study sought to establish whether MDMA produced a "withdrawal syndrome" or any signs of an aversive experience after MDMA discontinuation in mice (Robledo et al. 2003). Though the authors reported that administering a serotonin antagonist (metergoline) and a beta adrenergic antagonist

(timolol) a day after MDMA administration produced some somatic effects in MDMA treated mice only, metergoline did not reduce MDMA-associated conditioned place preference, and only the highest dose of timolol reduced conditioned place preference. The researchers also failed to find any signs of reduced efforts in working for food reward or any signs of conditioned place aversion for a location previously associated with time after a 10 mg/kg injection of MDMA, indicating that the period when all MDMA effects are gone is not experienced as aversive. How these findings relate to reported sub-acute effects in humans and their relation to drug dependence remains unclear. Humans experience sub-acute effects of MDMA, but as discussed in the IB, most Ecstasy users take the drug on a weekly to monthly basis rather than taking more Ecstasy to avoid sub-acute effects.

Altogether, study findings suggest that rodents and monkeys will self-administer MDMA at doses that are similar to or not much higher than those taken human Ecstasy users. Findings of self-administration and reward value in non-human animals confirm earlier reports of the reinforcing effects of MDMA in non-human animals, and findings concerning rewarding dose range also suggest that dose equivalents calculated through interspecies scaling do not appropriately reflect doses used by humans. It also appears that warm ambient temperature may increase the reinforcing effects of MDMA. None of the findings provides a basis for either increasing or decreasing estimated risk of abuse liability for clinical trials with MDMA.

Conclusion

Recent examinations of MDMA toxicity in heart, liver, and thermoregulatory system report findings similar to those reviewed in the previous update to the IB. Likewise, evidence of MDMA self-administration has already been noted in previous reviews of the literature. Subjects in clinical trials of MDMA are carefully screened for the presence of cardiovascular and hepatic (liver) disease, and to date, clinical trials have not reported heart or liver problems in volunteers. Volunteers are also screened for recent substance abuse or dependence disorders, thus reducing the chance that MDMA will be given to people who will then seek to self-administer Ecstasy. None of the research findings reviewed have given any cause for revising risk estimates associated with participating in clinical trials of MDMA.

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