Louisa Degenhardt and
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The health and psychological effects of "ecstasy" (MDMA) use

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THE HEALTH AND PSYCHOLOGICAL EFFECTS OF "ECSTASY (MDMA) USE"

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Acknowledgements

This work arose out of the increasing perception that there needed to be a summary of existing research on the epidemiology and possible effects of "ecstasy" (MDMA) use, given its increasing prevalence among young adults, and understandable concerns about studies reporting on various putative adverse consequences of this use.

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Many people assisted with aspects of the work conducted for this monograph. Natasha Sindicich was extremely dedicated to the task of helping to assemble some of the literature for chapters in addition to her work on some chapters. Eva Congreve provided important advice on literature search strategies and was always on hand to help locate less accessible journals and reports. Ed Silins was a blessing to the project.

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[1] See http://ndarc.med.unsw.edu.au/NDARCWeb.nsf/page/EDRS

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Glossary

Term	Definition
Acute effects	The immediate, short-term effects of using a drug
AIDS	Acquired Immune Deficiency Syndrome
Allogenic lymphocytes	Cell types that induce distinct immune responses from an organism
Analgesic	A drug which reduces pain
Anorexia	Significant loss of weight, which can affect HIV patients
Antagonist	A substance that blocks the positive effects of a drug
Asphyxiation	Choking, suffocation
Autocrine	Within cells of the same type
BMA	British Medical Association
Burden of disease	The effect that a disorder has upon society measured by the years of life lost and amount of disability it causes
Cannabinoids	Chemicals that act upon the same receptor sites in the brain as THC
Cannabis	All forms of the product of the *cannabis sativa* plant
Carcinogen	A substance that causes cancer
Cardiac arrhythmias	Irregular heart rhythms that can be fatal
Cardiomyopathy	General term for diseases of the heart muscle
CD&SA	The Canadian Controlled Drug and Substances Act
Cerebrovascular disease	Atherosclerosis of the arteries in the brain that can lead to stroke: damage caused in the brain by blood clot or other obstruction interrupting the flow of blood and hence of oxygen to the brain
Chronic effects	The longer-term effects of drug use that may occur if drug use is continued over months or years
Cohort	Any designated group of persons who have been exposed to some event (e.g. use of cannabis)
Cohort study	A study design in which people who have and have not been exposed (e.g. to cannabis) are followed up to see how many develop a disease
Concanavalin A (ConA)	An extract from the jackbean plant *Canavalia ensiformis* . It is a potent T cell activator. ConA stimulation is a classical test for measuring the ability of an animal's T cells to respond.
Coronary atherosclerosis	A disease in which deposits of cholesterol and fats form block the arteries that supply the heart muscle. It may lead to a "heart attack"
Cross-over study design	Study in which participants received two or more treatments without

Term	Definition
	their knowledge to see whether they respond differently to them
Cross-sectional study	A study design in which the health status and risk factors of a sample are assessed at one point in time e.g. a survey
DAWN	The US Drug Abuse Warning Network
DEA	The US Drug Enforcement Administration
Dependence (drug)	A disorder in which persons experience loss of control over drug use, and continue to use the drug despite the problems it causes them (see Chapter 8 for criteria)
DHHS	The US Department of Health and Human Services
Dopamine	A chemical that acts as a neurotransmitter in the brain
Double blind study	A study in which neither the patient nor the treating physician know whether the patient is receiving an active or placebo drug
Dysphoria	Unhappy mood (as opposed to euphoria)
Endocrine	affecting different organs (systemic)
Epidemiological research	Research that studies the occurrence of disease or risk factors for disease in the general population
Epilepsy	A disorder in which abnormal brain electrical activity causes seizures
Experimental study	A study design in which exposure to a key factor is under the researcher's control, e.g. when two groups of people are randomly assigned to receive a drug or a placebo
Glaucoma	A disease caused by raised intra-ocular pressure that, if untreated, can cause blindness
Histopathological	Abnormality of the structure of bodily tissues
HIV	The Human Immunodeficiency Virus which causes AIDS
Humoral	Pertaining to the blood or the fluids of the body
Huntington's disease	A movement disorder caused by a dominant gene, producing pathological brain changes, including in areas controlling movement
Hypertension	High blood pressure
Hypomania	A condition in which people are energetic and have elevated mood
IFN-γ	Is produced by T cells and NK cells, usually following sensitization with viral antigens. It has multiple actions including anti viral and anti tumour, and immunoregulatory functions.
IL-1β	One of the primary cytokines produced by activated monoctes/macrophages and dendritic cells. This cytokine has multiple actions on a number of different cell and organ types. It can

Term	Definition
	re-set the hypothalamus thermoregulatory center, which results in an increased body temperature which expresses itself as fever. IL-1 has previously been called endogenous pyrogen
IL-2	A T cell derived cytokine that has potent T & B cell growth activity, vital for T cell differentiation. IL-2 stimulation of activated B cells results in immunoglobulin secretion. IL-2 promotes moncyte cytolytic activity.
IL-4	Required for the stimulation of both B and T cells. For T cell differentiation.
IL-6	Has many actions, including an important role in inflammation. In vitro IL-6 is secreted by many cell types.
IL-10	Primarily a monocyte derived anti inflammatory cytokine able to inhibit the production of numerous proinflammatory cytokines. Paradoxicly IL-10 can also be proinflammatory.
IL-12	Predominantly an activated macrophage derived cytokine, IL-12 acts synergistically with IL-2 in the generation of lymphokine activated killer cells and enhances the activity of NK cells and T cell differentiation.
IL-15	Secreted by activated monocytes and macrophages following sensitization to viral antigens. IL-15 is required for NK cell development.
	TGF-β family of proteins controlling proliferation and differentiation of many cell types, along with many other functions.
Illicit drugs	Drugs which adults are prohibited from using by law
Immunosuppressive	Anything (e.g. a drug, radiation, viral infection) that suppresses the functioning of the body's immune system
INCB	The United Nations' International Narcotics Control Board
IND	A program of the FDA that allows patients with serious or life-threatening diseases to use experimental drugs

Term	Definition
IOM	Institute of Medicine, US
IOP	Intra-ocular pressure; pressure within the eyeball
Lipopolysaccharide	(LPS, [a surface molecule of Gram-negative bacteria.LPS binds to cells possessing the CD14 receptor. CD14 +ve cells include macrophage/monocyte/dendritic cells. A soluble form of CD14 exists that *can* confer LPS responsiveness to otherwise non CD14+ve cells. LPS binding to CD14+ve cells typically results in a strong immune response in normal animals. LPS stimulation is a classical in vitro measure of the ability of an animal's immune system to respond.
Leucocyte trafficking	including blood and lymphoid tissue.
Longitudinal study	A synonym for a cohort study
Lower brainstem	Areas of the brain including the cerebellum that control movement and respiration
Marijuana	Leaves and flowering tops of the *cannabis sativa* plant
Marinol	The trade name for dronabinol
MHC	Major histocompatability complex
Metabolites	Chemical products of a drug that are produced when it is processed in the body
Mitogens	Substances that induce cell transformations
MS	multiple sclerosis
mutagen	an agent or substance that induces genetic mutation in cells
Nabilone	A synthetic drug that has similar effects to THC
Naldolol	Is a beta-blocker which non-selectively blocks beta adrenergic receptors which amongst other things inhibits the effects of the catecholamines epinephrine and norepinephrine
Narcotic	A legal term for drugs prohibited by international drug treaties that includes opioids, cocaine and cannabis
NCR	The Canadian Narcotic Control Regulations
NDA	An investigational New Drug Application, one step in the process in the US for approving drugs for medical use
Negative symptom	In schizophrenia, absence of a behaviour ordinarily seen in "normal" people, such as initiative
NIDA	The US National Institute on Drug Abuse

Term	Definition
n-of-1 clinical trial	Trial in which a single patient receives a drug and a placebo and their behaviour is measured under double blind conditions
NORML	The US National Organization for Reform of Marijuana Legislation
Odds ratio	A ratio of the odds of disease in persons who are and are not exposed to some factor. It measures the strength of the association between the factor and the disease
ONDCP	The US Office of National Drug Control Policy
Organic symptoms	Symptoms that are ascribed to physical (organic) causes
Pancreatitis	Acute or chronic inflammation of the pancreas
Paracrine	Affects local cells of differing types
Parkinson's disease	A movement disorder that results from damage to area of the brain involved in movement control
Phytohaemaglutinin (PHA)	An extract from the red kidney bean *Phaseolus vulgaris*. Belongs to the class of substances called mitogens. A potent T cell activator.
Phagocyte	Typically comprise macrophages/monocytes, granulocytes and dendritic cells
Phagocytosis	In the context of the immune system, this process refers to the engulfment and destruction (and removal) of particles (eg bacteria).
Pharmacopeia	A book containing a list of products used in medicine, with descriptions, tests for purity and identity, and dosages
Placebo	An inactive drug that is indistinguishable in appearance from the active drug with which it is being compared
PLWHA	Association for People Living With HIV/AIDS
Positive symptoms	In schizophrenia, presence of a behaviour not seen in "normal" people, such as hallucinations and delusions
Premorbid	A person's behaviour or personality prior to the onset of an illness
Prevalence	The number of cases of an illness or disease that are present in the total population in a specified period of time e.g. a year
Prodromal	In schizophrenia, symptoms that precede the onset of the illness
Prospective study	A synonym for a cohort study
Psychoactive drug	A drug that affects feeling, memory and thinking
Psychomotor	Having to do with voluntary movement
Psychostimulants	Drugs that have stimulating effects and increase psychomotor activity
Psychotomimetic drugs	Drugs that produce symptoms of psychosis, such as visual

Term	Definition
	hallucinations, delusions and distorted perception
R&D	Research and development
RACP	Royal Australian College of Physicians
Rhabdomyolysis	Rapid breakdown of muscle fibres resulting in the release of toxins in to the bloodstream which can result in kindney and other organ failure
Randomised controlled trial	A clinical trial to evaluate a treatment in which participants are randomly assigned to receive an active drug or a placebo
RCT	Randomised controlled trial
Relative risk	A ratio of the rate of disease among persons exposed to a factor (e.g. cannabis use) and the rate among those who are not exposed
Resorption	To absorb again (from the Latin meaning "to suck back")
Retrospective study	A study design in which exposure to a risk factor (e.g. drug use in adolescence) is determined retrospectively (e.g. by asking an adult about their drug use in early adolescence)
SAP	The Canadian Special Access Program
SCOST	House of Lords Select Committee on Science and Technology
Serotonin Transporter (SERT)	A monoamine transporter protein which allows cells to accumulate serotonin
Stress-diathesis model	A model of schizophrenia in the disorder is precipitated among vulnerable individuals (those with the diathesis) by life stressors
Temporal lobe	An area on either side of the brain that is involved in memory and emotion
Teratogen	A substance that produces abnormalities in a foetus during its development in the uterus
TGA	The Australian Therapeutic Goods Administration
THC	Delta-9-tetrahydrocannabinol, the principal psychoactive ingredient of cannabis
Titrate	To measure the dose of a drug against its effects
TNF-α	Is primarily a macrophage derived cytokine, with multiple proinflammatory actions. (IL-1β and TNF-α are the two main cytokines involved in primary inflammatory responses -"acute response")
Tourette's syndrome	A movement disorder that results from damage to area of the brain involved in movement control

Term	Definition
Toxic psychotic disorder	A psychosis caused by high doses of a drug or other substance
TPP	The Canadian Therapeutic Products Programme
Viscous	A substance that is sticky or glutinous

1. Introduction

Louisa Degenhardt and Wayne Hall

MDMA under the name of "ecstasy" was first noted in the nightclub scene in the 1980s in the UK, US, Europe, and Australia in the late 1980s and early 1990s [1] [2]. For the first decade of use when the prevalence of use was low, MDMA was regarded as a relatively benign "party drug". This perception gradually changed for a number of reasons.

First, in the mid-1990s, there were some widely publicised deaths attributed to ecstasy use in Australia and the UK[3]. One case in Australia in particular received huge media attention (that of Anna Wood). An attractive young girl from a middle-class family in Sydney died after taking MDMA and the girl's parents became very active in efforts to promote awareness of the risks of ecstasy's use.

Second, in 2002, a study funded by the United States National Institute on Drug Abuse (NIDA) was published in *Science* that reported apparently devastating effects of "recreational" levels of MDMA on serotonergic neurons in the brains of monkeys[4]. This study was very heavily promoted, and led to understandable concerns in the community about impacts that using this drug would have upon the brains of the millions of young adults. The study was later retracted following the discovery that the monkeys had in fact been mistakenly given a different drug (methamphetamine). The retraction[5] received much less community attention than the original study.

Third, a number of studies have found that regular ecstasy use was associated with subtle impairments in cognitive functioning such as verbal memory. These studies typically compared ecstasy users with non-users on standardised psychological tests of cognitive functioning, and found that ecstasy users performed less well on some tests than non-users.

This monograph arose out of the need for a synthetic review of the existing evidence on the epidemiology of "ecstasy" (MDMA) use and its putative adverse health and psychological **consequences**.

In assessing the adverse effects of using any drug we must first consider whether an association exists between using the drug and the adverse health outcome of interest. Then, we must

examine alternative explanations for the association, that is, generate a list of other factors might explain the relationship and generate evidence to exclude them. We must also attempt to estimate the magnitude of any increase in risk that users have of experiencing that outcome. All of these steps require studies that have used appropriate methodological designs.

In this monograph, a number of possible consequences of ecstasy use are considered. In each chapter, evidence on the association between ecstasy and the outcome of interest is presented, with critical evaluation of the evidence that can be brought to bear on the nature of the relationship.

The logic underlying this monograph is similar to that of the monographs on *The health and psychological consequences of cannabis use* written by Hall and colleagues in 1994[6] and updated in 2001[7]. The guiding principles underlying an examination of the evidence on the effects of ecstasy are outlined by Hall in Chapter 2.

Chapter 3 provides a very brief overview of the history of use of MDMA and a summary of the characteristics of the illicit "ecstasy" market. As will be clear from that Chapter, some of those characteristics (e.g. lack of quality control over production) make it more difficult to infer whether "ecstasy" is causally related to the adverse health outcomes of interest; whether MDMA is involved in those outcomes; and how much of the associations may also reflect other factors. Evidence on the epidemiology of ecstasy use in Australia and elsewhere is discussed in Chapter 4.

In Chapter 5, Iain McGregor, Murray Thompson and Paul Callaghan review research on the psychopharmacology of MDMA. This evidence is drawn largely from carefully conducted laboratory studies with both animal and humans. It provides a reasonable degree of confidence in our understanding of the acute effects of the drug on the brain and behaviour.

The acute adverse health effects of ecstasy (MDMA) use are reviewed by Edmund Silins in Chapter 6. The possibility that MDMA has effects upon the reproductive and immunological systems is reviewed by Ross Beck in Chapter 7.

Chapter 8, with contributions from Libby Topp and Raimondo Bruno, reviews the animal and human evidence that can be brought to bear on the question of whether ecstasy (MDMA) users can develop dependence on the drug. Chapter 9 reviews the evidence on the association between ecstasy use, other drug use and mental health problems. Edmund Silins and Richard Mattick review evidence on the possible cognitive effects of ecstasy (MDMA) use in Chapter 10. Edmund

SiIins also reviews the mechanisms of ecstasy-related mortality in Chapter 11, including the evidence on the magnitude of risk for mortality related to this drug.

In Chapter 12, Natasha Sindicich and colleagues summarise the literature on the putative therapeutic uses of MDMA for the treatment of psychological disorders.

As will become clear, the state of the evidence in many areas has not yet moved beyond documenting **associations** between MDMA use and adverse outcomes. This monograph therefore identifies what research needs to be done to more definitively answer questions about whether ecstasy has adverse **effects** on health of type reviewed. These suggestions are provided in Chapter 13.

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2. Assessing the adverse health and psychological effects of MDMA ("ecstasy") use

Wayne Hall

2.1. Introduction

As discussed in greater detail in Chapter 5, MDMA (3,4-methylenedioxymethamphetamine) is an amphetamine analogue that produces euphoric and stimulant effects and a feeling of closeness towards others [2 8]. MDMA use has increased over the past two decades among young Australian adults[9] (see Chapter 4).

MDMA has been perceived by some (but not all[10]) users to be a relatively "safe" illicit drug, and widely used as a "dance party" drug[2], but a number of concerns have been raised about potentially adverse effects of its use. First, deaths have been reported among previously healthy young MDMA users who have died from malignant hyperthermia and hypernatreamia and rarer, possibly idiosyncractic, reactions to the drug [11 12]. Second, animal studies indicate that MDMA may be neurotoxic to serotonergic neurons in the brain [13]. Third, the prevalence of hazardous patterns of MDMA use has probably increased, with some users using it more frequently, using multiple doses over a 24-28 hour period, and injecting it [14 15] (see also Chapters 4 and 8). Fourth, neuropsychological studies of regular MDMA users have reported suggestive evidence of neurotoxicity in the form of impaired memory and cognitive performance [15] (see Chapter 10).

This chapter discusses the major challenges in interpreting this evidence and outlines the types of research that is needed to reduce the uncertainties that remain about the adverse health effects that MDMA produces and the magnitude of the risks that MDMA users run of experiencing them.

2.2. Making Causal Inferences about the Adverse Effects of MDMA Use

There are two major types of technical challenge in assessing the impact that MDMA use has the health of users that are shared with assessments of the adverse effects of other illicit drug such as cannabis [16]. These include: uncertainties in deciding whether MDMA use is a contributory cause of various acute and chronic adverse health and psychological effects that have been attributed to its use: and challenges in quantifying the magnitude of the risk that users have of experiencing any of these adverse health effects.

Before a claim can be accepted that MDMA causes an adverse health outcome there must be evidence: that there is an association between its use and the health outcome; the association is not due to chance; that MDMA use preceded this outcome; and that alternative, non-causal explanations of the association are implausible [16 17].

Evidence of an association between MDMA use and a health outcome (e.g. death from hyperthermia) is provided by comparing rates of the health outcome in MDMA users and non-users in case-control, cross-sectional, cohort, or experimental studies. In case control and cross-sectional studies, we compare rates of MDMA use among persons who do and do not report an adverse effect. In cohort studies we identify large representative samples of young adults and compare rates of adverse outcomes in persons who subsequently do or do not use MDMA. In experiments we randomly assign young adults to use MDMA or a placebo and we compare the rates of various adverse events in the two groups.

Evidence that chance is an unlikely explanation of any relationship observed in any of these types of study is provided by constructing a confidence interval around the measure of association in the sample. If the confidence interval does not include the value that is consistent with no relationship, we infer that chance is an implausible explanation. The width of the confidence interval provides an indication of the degree of uncertainty surrounding the inference, while its upper limit indicates how large an association may have gone undetected [18].

If MDMA use is the cause of an adverse health outcome, then its use should precede the effect. The strongest evidence that MDMA use precedes adverse health outcomes comes from cohort studies and experiments. In a cohort study the researcher is able to observe individuals before

they use MDMA and hence is able to ensure that MDMA use precedes any adverse health effects. In an experiment, the experimenter ensures by design that MDMA use precedes any adverse health outcomes.

The criterion for causal inference that is the most difficult to satisfy is excluding the possibility that any relationship between MDMA use and an adverse health outcome is due to an unmeasured third variable, which increases the risk of both using MDMA use and of experiencing the adverse health outcome [16 17]. In surveys of young adults, for example, MDMA users often report more impulsive behaviour than non-users (e.g. [19]). This may be because MDMA use increases impulsivity but an equally plausible hypothesis is that more impulsive young people are more likely to use MDMA [20].

Experimental evidence provides what is often regarded as the "gold standard" for ruling out common causal explanations [21-23]. If, for example, we randomly assign young adults to use MDMA or not, we ensure that the two groups are equivalent in all respects before using MDMA. Hence, any subsequent differences in adverse health outcomes can be confidently attributed to MDMA use. When studying anything other than acute and innocuous health effects, it is impossible for ethical and practical reasons to randomly assign young adults to use MDMA or not. It would be unethical, for example, to force some young adults to use MDMA, and impracticable, even if ethical, to prevent those assigned not to use MDMA from doing so.

2.3. The Role of Animal Experimentation

Experimentation on laboratory animals is often used to assess the harms of drug use when human experimentation is ethically unacceptable. For example, when MDMA is administered to rodents and non-human primates it produces damage that may be permanent to axons and axon terminal fibres containing serotonin in the cortex, hippocampus and striatum of the brain [24] [25]. Decreases in the density of brain serotonin axons have been observed in squirrel monkeys, for example, more than seven years after MDMA administration. [24]

A major limitation of animal studies of MDMA is that they have maximized their chances of detecting effects by administering high doses (e.g. 5 mg/kg of MDMA) repetitively (twice daily for four consecutive days) [20]. These doses are much higher and more frequent than has been typical in human users, and MDMA has often been injected, a route that is two to three times more neurotoxic in monkeys than the oral route primarily used by human users [26].

Because of these differences in dose and route of administration, some authors have argued that the animal evidence is of no relevance to human users. [8] This argument ignores two key points. First, larger animals appear to be more susceptible to the toxic effects of a given mg/kg dose of a drug than are smaller animals. [27] In the case of MDMA, for example, primates are more susceptible to MDMA neurotoxicity than rats, [25] that are in turn more susceptible than mice. [28] Second, surveys indicate that a substantial minority of MDMA users take the drug in ways that may produce similar risks of neurotoxicity [15]. For example, in Australia in 1999, 1 in 6 of regular MDMA users reported injecting MDMA at some time, 42% reported using MDMA for 48 hours or more in the past six months [14], and many reported taking multiple tablets in a single episode of use [14]. MDMA is also typically used in environments that are hot and crowded with limited access to drinking water, all conditions that are known to increase neurotoxicity in rats. [29]

Experimental animal studies are probably most useful in studying the acute adverse effects of known doses of MDMA on biological functioning, e.g. its effects on temperature regulation. Such studies have proven less useful in assessing the adverse effects of chronic MDMA use in humans, namely, the effects of regular sustained use on human mood and cognitive performance. The animal evidence suggests that such effects may occur in some human users but confirmation depends on observational evidence on the effects of MDMA use on the mood, cognitive performance and memory of human users.

2.4. The Role of Epidemiological Research

When a suitable animal model does not exist, and randomisation of human subjects to MDMA use is unethical, observational epidemiological and clinical studies are the only way of assessing the effects of human MDMA use. In these studies statistical methods are used to address the problems solved by randomisation in experiments. These methods adjust for the effects of pre-existing differences in risk of adverse outcomes between MDMA users and non-users and control for the effects of other illicit drug use on outcomes. If the relationship between MDMA and the outcome persists after statistical adjustment for pre-existing differences and other drug use, then confidence is increased that the relationship is not attributable to the effects of the variables for which statistical adjustment has been made [30]. This type of statistical control has been used, for example, in longitudinal studies of the effects of adolescent cannabis use and psychosis (e.g. [31-33]). The approach has only recently begun to be used to study the effects of MDMA use on mental health because rates of MDMA use are much lower in representative samples of young adults than is cannabis use (e.g. 12% lifetime use of MDMA vs 50% for cannabis among young Australians aged 20 to 29 years) [9].

There are several limitations to the use of statistical methods of adjustment in observational studies. First, we often either have not been able to measure all of the important potential confounding variables (e.g. cognitive performance or memory prior to MDMA use), or we may not know what the important variables are to measure. Second, measurement error in the potentially confounding variables may limit the capacity of statistical methods of adjustment to fully control for the effects of confounding variables [30]. Third, the relative rarity of MDMA use in the population, and its strong association with the use of other drugs, may limit the ability of statistical methods to adequately control for the effects of other drug use and pre-existing differences in cognitive ability or memory.

2.5. An Overall Appraisal of Causal Hypotheses

Causal inferences are made in the light of a research literature by assessing the body of evidence against criteria for causal inference such as those of Hill [34]. These criteria are not sufficient for establishing that an association is a token of a causal relationship since the criteria may be met and yet we may be mistaken in making a causal inference. The more of the criteria that are met, however, the more likely it is that the association is a token of a causal relationship [16].

2.5.1. Strength of association

Relationships that are stronger indicate that if MDMA is used there is a high likelihood that the health effect will also occur. Stronger relationships are generally more deserving of trust than weaker ones because the latter are more easily explained by measurement or sampling biases.

2.5.2. Consistency of relationship

Relationships between MDMA use and a health outcome that are consistently observed by different investigators, studying different populations, using varied measures, and research designs are generally more credible than relationships which are not. This is because a relationship that persists despite differences in sampling and research methods is less unlikely to be explained by sampling, measurement, or other biases.

2.5.3. Specificity

Specificity is a desirable but not a necessary condition. It exists when MDMA use is strongly associated with a health outcome that is rare in the absence of MDMA use. Specificity is desirable in that if it exists we can be more confident that there is a relatively simple and direct causal relationship but its absence does not exclude the possibility of a more complex causal relationship (e.g. in which the effect is conditional on the presence other factors such as personal vulnerability).

2.5.4. Biological gradient

This refers to the existence of a dose-response relationship between cannabis use and the health outcome: the more heavily and the longer that MDMA has been used, the greater the likelihood of the health outcome. Satisfaction of this criterion is also desirable but not necessary since there may be other patterns of relationship between exposure and disease, e.g. a threshold effect, an "all or none", or a curvilinear relationship.

2.5.5. Biological plausibility

This refers to the consistency of the relationship with other biological knowledge. If we can think of no conceivable mechanism whereby MDMA can produce such an effect, then we may have grounds for skepticism. But in the face of compelling evidence of association from well-controlled studies implausibility may be a signal that existing theories are wrong, or that we need to develop new theories that explain previously unknown phenomena.

2.5.6. Coherence

This means that the relationship coheres with, or makes sense given, other information about the natural history and biology of the health outcome. This too is desirable but not necessary: it is desirable if we have independent information that we can trust but its absence is not fatal since the other information with which it is inconsistent may be in error.

2.6. Assessing the Magnitude of Risk

The standard epidemiological measures of risk are **relative risk** and **population attributable risk**. Relative risk assesses the increase in the chance of experiencing an adverse health outcome in those who use MDMA compared to those who do not. It can also assess dose response relationships between the frequency and duration of MDMA use and the risk of experiencing any of these adverse outcomes. The population attributable risk represents the proportion of cases with an adverse outcome (e.g. impaired memory) that can be attributed to MDMA use, *if* the relationship is causal.

Relative risk is most relevant measure for individuals who want to know how much they increase their risk of experiencing an adverse outcome if they use MDMA. Attributable risk is of more relevance from a societal perspective on the harms of MDMA use. The importance of each depends upon how common MDMA use is and the increase in the risk of adverse outcome occurs among people who do use MDMA. An exposure with a low relative risk (say 2) may have a modest personal significance but major health significance if a large proportion of the population is exposed (e.g. as is the case for cigarette smoking and heart disease). Conversely, an exposure with a high relative risk (e.g. that between benzene and leukemia) may have modest public health significance because very few people are exposed but it has major significance for those individuals who are exposed.

It is difficult to estimate either the relative or attributable risk of any of the outcomes currently attributed to MDMA. Some guesstimates of the risk of fatality from MDMA use have been made [35] that illustrate the high degree of uncertainty around the estimates because of poor data on deaths attributed to MDMA and limitations in data on the number of persons in the population who have been exposed to MDMA. Better estimates will require epidemiological studies of large samples of MDMA users with good toxicological data on deaths.

2.7. Conclusions

Causal inferences about the adverse health effects of MDMA are complicated by: a dearth of good studies of relationships between MDMA use and health outcomes; uncertainty in some cases about which came first, the MDMA use or the health effect; difficulties in excluding plausible alternative explanations of associations that have been observed in observational studies; and in the case of null findings, uncertainty as to whether they provide reasonable evidence for the absence of effects. An estimation of the magnitude of the health risks of cannabis is handicapped by the absence of epidemiological studies that provide quantitative estimates of the risks in representative samples of users controlling for the effects of pre-existing differences in personal characteristics and the effects of other illicit drug use.

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3. What is "ecstasy"?

Louisa Degenhardt and Natasha Sindicich

3.1. Introduction

In this Chapter some of the important characteristics of MDMA and the "ecstasy" market are noted, because they have implications for research evaluating the effects that ecstasy/MDMA has those who use it.

"Ecstasy" is the most widely used street name for pills that are sold on the black market purportedly containing MDMA. In this monograph we will use that name in preference to other less common names. This includes a wide range of names for drugs sold illicitly as MDMA, including: Adam, X, E, XTC, eccy, pills, lover's speed, and the love drug.

In this monograph we will make clear when we are referring to laboratory research that examines the effects of the drug MDMA, and when we are discussing epidemiological and clinical research involves studies of people using the illicit drug "ecstasy". This distinction is an important one because of the varying purity and content of "ecstasy" tablets, as we discuss in this Chapter.

3.2. The development of MDMA

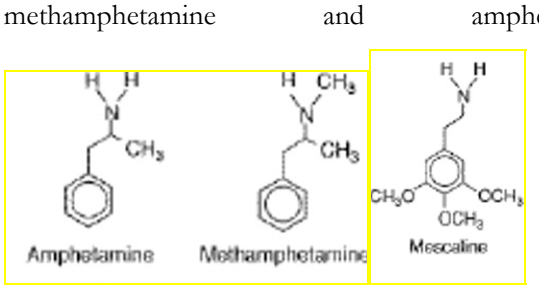
The substance 3, 4- methylenedioxymethamphetamine (MDMA) was first synthesised by Merck, a German pharmaceutical company, in 1912. The discovery of MDMA came about in an effort to exploit a novel chemical pathway to produce new blood clotting agents (haemostatic substances)[36].

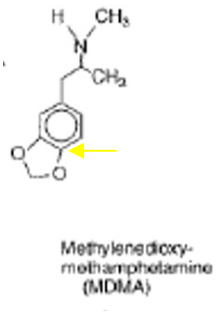
Many published reports in the MDMA literature have erroneously stated that MDMA was developed as an appetite suppressant[37] [38] [39] [40] [41] [42] [43]. Reasons for this error in the literature may be linked to the structural relationship between MDMA and its structurally similar analogue MDA (methylenedioxymethamphetamine), which was evaluated by Smith, Kline and French between 1949 and 1957 as a potential appetite suppressant and antidepressant[36].

Between 1953-54, the University of Michigan was contracted by the Army Chemical Center to conduct the first thorough toxicity and behavioural pharmacology study of MDMA[36]. This assessed the potential use of MDMA as a chemical warfare agent. Seven other drugs were also evaluated at this time, on five animal species. MDMA was found to be less toxic than MDA but more toxic than mescaline. These results remained classified until 1969 and were only published in 1973 (see [44]).

3.3. MDMA the drug

Methylenedioxy-methamphetamine (MDMA) is a derivative of the compounds methamphetamine and amphetamine.





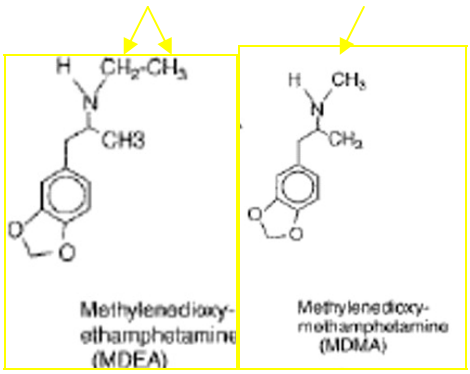
MDMA differs from amphetamine and methamphetamine in one important respect; it has a methylenedioxy (-0-CH_2-O-) group attached to the positions 3 and 4 of the aromatic ring of the amphetamine molecule (i.e. "it is ring-substituted"). In this respect its structure resembles that of mescaline, which has hallucinogenic properties. The pharmacological effects of MDMA are a blend of the amphetamines' stimulant and mescaline's hallucinogenic properties.

MDMA is an indirect monoaminergic agonist and reuptake inhibitor[45] that boosts the release of the neurotransmitters, serotonin, dopamine, noradrenaline, acetylcholine and histamine[46] [47] [48]. Serotonin has effects on the regulation of mood, aggression, sexual activity, sleep and sensitivity to pain[49]. The ability of MDMA to increase the concentration of serotonin explains the common effects reported by users of improved mood[50], a marked increase in wakefulness, endurance and sense of energy, sexual arousal and postponement of fatigue (see chapters 5 and 6). It was the psychological effects of MDMA that lead to its use in therapy (see chapter 12 for further discussion).

3.3.1. MDMA derivatives and related drugs

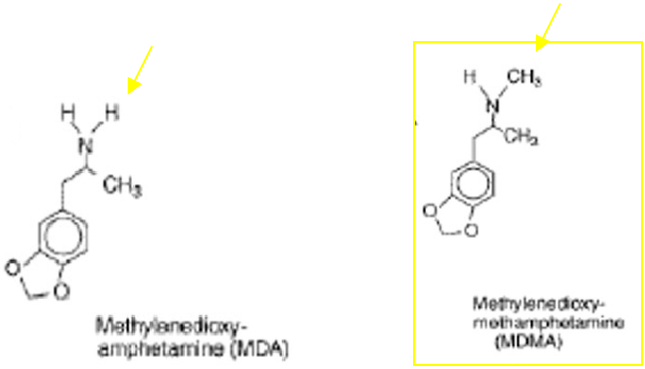
MDMA, MDEA and to an extent MDA, are closely related in terms of their chemistry and biological effects while differing in their potency, time of onset and duration of action[12].

- 3,4-methylenedioxyethylamphetamine (MDEA)



MDEA often referred to as 'eve' or MDE, is a closely related compound differing from MDMA in having a 2-carbon ethyl group, rather than a 1-carbon methyl group attached to the nitrogen atom of the amphetamine structure. The effects of MDEA are extremely similar to those of MDMA except that a larger dose of MDEA is needed to achieve the same effects (100-200mg). MDEA also has a shorter duration effect (3-5 hours) than MDMA (4-5 hours), does not contain its "communicative" qualities and has a mildly hallucinogenic effect[8].

- 3,4-methylenedioxyamphetamine (MDA)



The only molecular difference is the absence of the methyl group in MDA, which is attached to the nitrogen atom. The addition of the methyl group to the nitrogen atom in MDMA makes the molecule more lipid (fat) soluble. Since the brain is largely made of lipids, MDMA has greater solubility in brain tissue. In general, drugs that have greater solubility in lipids and act in the brain also have a *faster onset* and a *shorter duration* of action. As expected, MDMA has a faster onset of effect, but a shorter duration of effect than MDA (8-12 hours). MDA also has more of an amphetamine- and hallucinogenic effect[8]; MDMA is, however, metabolised into MDA in the body.

MDA was first synthesized in 1910, by the same Merck researchers who went on to create MDMA. It was patented as a cough suppressant in 1956, as a tranquilizer in 1960, and as an appetite inhibitor in 1961. It was not marketed for any of these purposes, however[38].

- Para-methoxymethamphetamine (PMA)

PMA is a synthetic hallucinogen sometimes packaged as ecstasy and mistakenly assumed to be a by-product in the synthesis of MDMA[51]. PMA shares the stimulant and hallucinogenic effects of MDMA, with doses of less than 50mg (usually one pill). However, dosages over 60-80 mg (lower than those used regularly for Ecstasy) are potentially lethal. They can cause cardiac arrhythmia and arrest, breathing problems, pulmonary congestion, kidney failure, hypothermia, vomiting, convulsions, coma and death[52]. The toxicity of PMA is related to excessive central nervous system stimulation. PMA does not appear to have any medical use.

- Hallucinogens

Hallucinogens significantly alter perception, mood and thought by distorting all senses. This can result in the user experiencing distortions in their sense of reality, time and emotions. The most common hallucinogen is a synthetic hallucinogen known as LSD (Lysergic acid diethylamide). Only a small amount is needed to cause visual hallucinations and distortions. These experiences are known as "trips". Psilocybin is converted to psilocin in the body. Effects of hallucinogens include: euphoria and well-being, auditory and visual hallucinogens, distortions in perception of reality, time and space, nausea and dizziness, poor coordination and paranoia. Changes in body temperature may also occur, either an increase in heat causing sweating, or a decrease in temperature causing chills and shivering [53].

3.4. A very brief history of recreational "ecstasy" (MDMA) use

MDMA was rediscovered by Alexander Shulgin in the 1970s and used therapeutically in the United States by a small number of psychotherapists with selected clients (see Chapter 12). Inevitably, as the use of MDMA increased in therapy, word spread about its effects and began to be used as a recreational drug.

In 1981 the universal brand name of MDMA 'ecstasy' was coined, by a member of the Los Angeles distribution network, in the hopes that 'it would sell better than calling it 'empathy', although 'empathy' would be arguably more appropriate[54]. Demand for ecstasy in the 1980s increased exponentially with the ready availability of the drug. Because it was not yet illegal, ecstasy was freely and openly available in many bars and nightclubs around the United States[55].

Ecstasy use soon came to the attention of the DEA (Drug Enforcement Agency), which took action in 1985 to have MDMA classified as a Schedule One prohibited substance. This meant that the manufacture and sale of the drug was illegal and with severe restrictions placed on its use in research and medicine (see [56]).

While the ban on MDMA dampened use in the United States, by this time the reputation of 'ecstasy' had spread across the Atlantic. It was first introduced into Europe in two ways: the followers of Bhagwan Rajneesh, the Indian guru, brought it to Europe when they moved out of their ashram in Oregon and spread its use as a means of enlightenment[8]; and around the same time, British pleasure-seekers in Ibiza discovered it and brought it back to England.

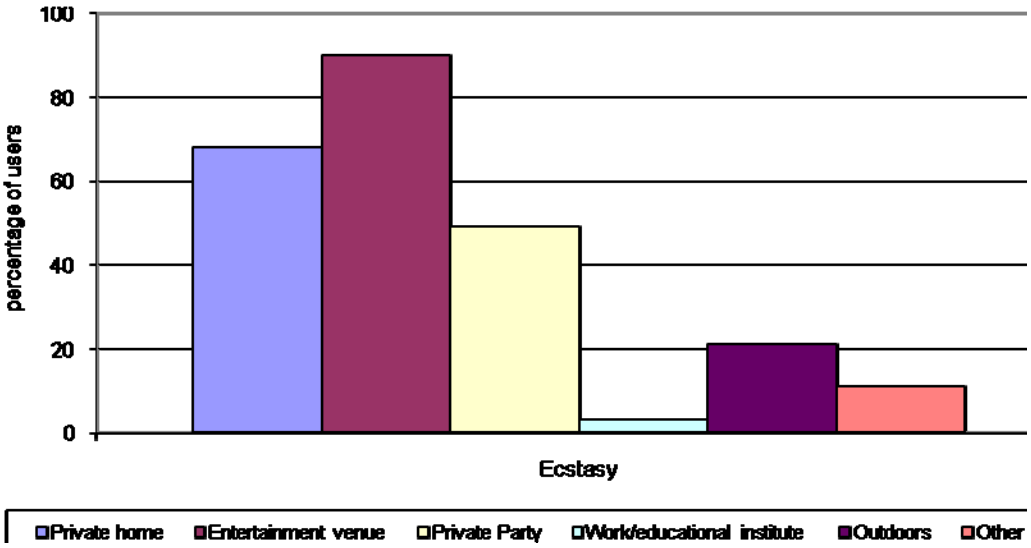
Extensive media coverage of MDMA use may also have inadvertently contributed to the rapid increase in numbers of people experimenting with it[57] [58]. Ecstasy became highly concentrated in the dance party and night club scene where its use was associated with the trance music and dance movement of the late eighties to early nineties. Ecstasy came full circle when the English rave goers went to San Francisco in the winter of 1991 and brought both their trance music and dance party patterns of ecstasy use.

As ecstasy use has become more established in the illicit drug market, the contexts in which it is used have changed. The groups, social contexts and ages[59] of those using ecstasy have all broadened in recent years. The original association with "rave" cultures in North America, the UK and Europe and Australia is still present (e.g. [60] [61]), but use also occurs in a range of settings

with a wider range of users [62-67]. Some have suggested that this might reflect the "normalisation" of ecstasy use as an accepted part of young adult recreational culture[68 69].

In 2007, regular ecstasy users interviewed across capital cities in Australia reported using ecstasy in a wide range of contexts in the past six months (Figure 3.1). Notably, the use in private locations such as people's own homes was extremely common[70]. Although ecstasy use continues to be highly associated with the dance party and nightclub scenes, it is increasingly used in a wide range of settings on a variety of recreational occasions.

Figure 3.1: Usual locations of ecstasy use among regular ecstasy users in Australia, 2007



Source: EDRS interviews 2007[70]

3.5. The "Ecstasy" market

3.5.1. Content of drugs sold as "ecstasy"

As with many illicit drugs, the content of pills that are sold as "ecstasy" can vary greatly[56]. The composition and purity of tablets sold as ecstasy are important issues to consider when discussing ecstasy markets. There is evidence of changes across historical time in the extent to which tablets sold as ecstasy contain MDMA, the nature of other psychoactive drugs found in such tablets, and the purity of those tablets that do contain MDMA[56].

A recent study examining historical data in the UK across the 1980s and 1990s suggested that during the 1980s and early 1990s tablets nearly always contained MDMA[56]. During the mid-1990s, the chances increased that tablets contained MDA, MDEA, amphetamines, or other drugs. This changed once again in the late 1990s when the proportion of ecstasy tablets containing MDMA increased to around 80-90%. The latest available data in the UK suggested that tablets almost always now contained MDMA and that purity levels were around 90-100% [56].

Similar analyses have been conducted more recently in Victoria, Australia[71] [72]. In Victoria, every illicit drug seized is submitted for analysis, allowing for complete ascertainment of the content and purity of all illicit drug seizures in that jurisdiction. Data from 2003-2007 suggest that "ecstasy" tablet seizures accounted for around 40% of all non-plant illicit drug seizures by weight[72]. Across time, there were changes in the proportion of tablets containing MDMA; in 2007 around 60% of tablets contained MDMA, with the remainder most likely to contain no active drug (around 25%), or MDA/MDEA (around 10%)[72]. In 2007, the average purity of tablets in Victoria that contained MDMA was 25% and around half of tablets where MDMA was detected also contain another psychoactive drug (usually MDA or MDEA)[72].

Many regular ecstasy users acknowledge that the unknown content of the tablet is a risk associated with the use of ecstasy[73] [74], yet many nonetheless rely on anecdotal evidence from friends and dealers as to the content and purity of what they purchase[61]. This is despite many indicating that they would not consume pills if they contained other substances such as methamphetamine and ketamine[73].

There has been considerable debate about the use of pill "testing kits" that allow users to establish if the drugs they purchase contain MDMA. Systems have been in place in the Netherlands to allow users to submit tablets for forensic analysis[75] but no such system exists in other countries. Some organisations in Australia and the United States have provided pill testing

kits on-site at raves and outdoor dance parties in an attempt to allow users to make more informed decisions about their ecstasy use.

3.5.2. Ecstasy tablet logos and branding

One of the notable features of the ecstasy tablet market is the extent to which branding and logos have been used by drug distributors. Figure 3.2 shows a few examples. Tablets sold as ecstasy vary in shape, size, colour and in the logo or "brand" that is imprinted onto the tablet. The colour and logo of pills is often used as a marketing tool or "brand name" In the late 1990s and early 2000s, for example, "Mitsubishis" (pills with the logo for the car brand) were very well known and often sought after by users because they were thought to be a quality product. Analyses of a range of "Mitsubishis" have found that the logo and appearance bore no relationship to pill content, purity or weight.

Figure 3.2: Tablets sold as "ecstasy"

3.6. Dose and routes of administration

3.6.1. Amounts taken

The dose of MDMA contained within a tablet of "ecstasy" can vary greatly across "batches", locations and time. A typical rule of thumb used to be that a desired dose of MDMA was 100mg, but it is difficult to make such approximations when the content of MDMA in tablets is so variable. Some UK research has suggested that an "average" dose of MDMA might be 75mg in

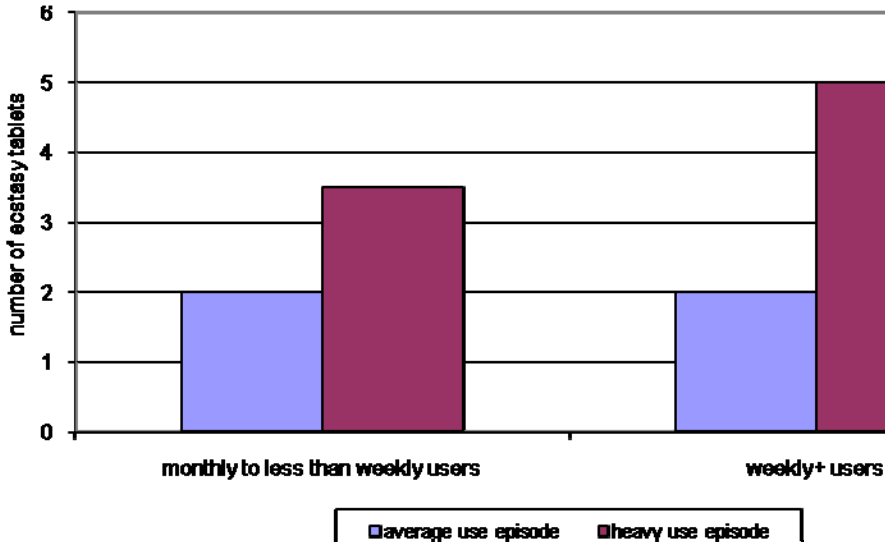
that country[76]. In the absence of accurate data on dose, however, ecstasy consumption is typically measured by the number of tablets taken and the frequency of their use.

Tolerance to the more euphoric effects of MDMA develops both within and across use episodes [1 15 58 77 78]. There is some evidence that users escalate their levels of ecstasy use in search of the euphoric effects experienced on their first use, with some evidence that the likelihood of more severe aversive effects increases with dose used [1 15 58 77 78].

Ecstasy users in Australia typically take one or two tablets over a typical "session" of use[70] (see Figure 3.3), which may last from the evening until the next morning. Some users do report using much large numbers of tablets[79]. There may also be differences across different countries: in the UK, some studies have reported users typically taking as many as six tablets[80].

For heavier use episodes that span longer periods of time, sometimes referred to as a "binge" session of use that lasts for 48 hours or more. Such users typically take larger amounts, often twice the number used in a typical use episode[61]. More frequent users also report heavier ecstasy use (Figure 3.3), and are also more likely to report more frequent "binge" ecstasy use than less frequent ecstasy users[70].

Figure 3.3: Median number of pills typically taken in "average" and "heavy" use episodes by frequency of ecstasy use in the past six months among regular ecstasy users in Australia, 2007



Source: EDRS interviews 2007[70]

3.6.2. Routes of administration

The most common way that ecstasy is taken is by swallowing it. This is true even among regular users who take the drug on an extremely frequent basis and in large amounts[61 81]. Some more frequent users report that they have experimented with using other ways, such as by injection or "snorting" (intranasal)[61], but these are almost never the way users generally to take the drug.

This pattern of use contrasts sharply with users of other powder-based drugs. For users of methamphetamine, cocaine and heroin, snorting is often the typical route of first use but heavier and dependent users often progress to injection or smoking to maximise their dose [82-85]. Little research has examined the reasons why ecstasy users prefer to swallow the drug but anecdotal evidence suggests that the speed of onset and peak of effects may be difficult to judge for MDMA when it is smoked, snorted or injected and the effects of using it in these ways can be aversive given the unknown MDMA and other content of ecstasy tablets.

3.7. Summary

The substance MDMA was first synthesised by a pharmaceutical company in Germany in 1912 for the purposes of a being used as a blood clotting agent. MDMA was rediscovered by a chemist in the United States, Alexander Shulgin in the 1970s. He was responsible for introducing its use into psychotherapy, where it was used to treat clients until the DEA classified it as a Schedule One substance in 1985. Recreationally, MDMA use spread from the United States to Europe and abroad and later became associated with the "rave" dance party culture.

Structurally and chemically, MDMA shares properties with methamphetamine, amphetamine and mescaline. The physical effects of increased concentration, higher level of energy and improved mood can be explained by the increased concentration of serotonin produced by MDMA. The physiological effects of MDEA and MDA are similar to MDMA with the exception of shorter duration of onset and effect and lower potency.

Regular ecstasy users interviewed in 2007, across all Australian capital cities, suggest that the context of ecstasy use now includes private homes and private parties, as well as the more usual entertainment venues.

One of the primary risks associated with ecstasy use is to assess the MDMA or other content of each ecstasy tablet (pill). Anecdotal reports from friends and dealers are the most usual ways in which REU assess the content of their pills. In 2007, illicit drug analyses in Victoria of ecstasy tablet seizures found that 25% of tablets contained MDMA, with other psychoactive substances such as MDEA and MDA detected in 50% of cases.

The predominant route of ecstasy use is oral. Dose is usually measure by the number of pills taken in one episode. This averages 1-2 pills in Australia. Tolerance to its effects develops with users increasing their dosage in an attempt to achieve the original euphoric effect. This situation increases the likelihood of experiencing negative acute effects such as nausea or a stimulant overdose, as well as to more chronic effects. It may also be related to the severity of the aversive effects during the recovery period.

3.8. References

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4. The epidemiology of ecstasy use

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4.1. Studying ecstasy use

4.1.1. How is "ecstasy" use measured?

Most research with illicit drug users involves surveying them about their drug use. Community surveys often ask participants whether they have ever used the drug ("lifetime" use), and if so whether they have used in the past year, the past month and the past week. More detailed assessments of the self-reported patterns and context of ecstasy use are typically undertaken when targeted samples of more frequent ecstasy users are accessed.

Although there is rarely any validation of these self-reports with other sources of information, research has been conducted on the validity of self-reported illicit drug use in surveys. This work suggests that individuals' self-reports of substance use in surveys are both consistent across time and valid unless they have some motivation (e.g. avoiding arrest) to be misleading[86-88].

A major challenge that confronts research on the possible consequences of illicit MDMA use is quantifying use when the content of pills sold as "ecstasy" can vary so widely. Even if users have bought pills with the desire to take MDMA, they are often sold a tablet containing any one of a number of related drug types (Chapter 2). This makes attempts to detect specific consequences of MDMA use more difficult because ecstasy users in some countries such as Australia are often not taking MDMA or only MDMA. In many European countries, however, this appears to be less of an issue[56], with seizure data now suggesting that tablets sold as ecstasy are more likely to contain MDMA of a more consistent strength[56] than seen in Australia.

Unfortunately, better methods of quantifying use are difficult to undertake. For example, although we could in principle chemically test illicit ecstasy for its MDMA content, there are major ethical, logistical and legal issues in conducting such research. Testing of urine or hair can

provide some evidence that a drug has been taken but these assessment methods provide limited information on the timing, frequency and amounts of the drug that have been taken[89].

4.1.2. Methods used to access ecstasy users

A range of methods are used to access ecstasy users. When conducting population-level research of drug use (including ecstasy), the traditional approach is to select a random samples of individuals from households. This method allows estimates of the size of the ecstasy using population in Australia to be made. Such methods probably yield reasonably accurate estimates of population size for a drug such as ecstasy, which appears to be used by many different types of people across the community[90 91]. It is less appropriate method for surveying much less more commonly used, more socially stigmatised and geographically concentrated drugs such as heroin[92].

Population surveys are more limited in their capacity to undertake detailed examination of the context and nature of ecstasy use and possible consequences. This is primarily because of the cost involved in obtaining a large enough sample of users, and because of the multiple competing demands on the time of interviewees when general drug use surveys are undertaken. More detailed assessments are typically made using face-to-face interviews involving samples recruited by "purposive" sampling methods (in which the researchers intentionally target certain populations of users in order to gain sufficient numbers of them to provide detailed information on patterns of drug use and their correlates) (e.g. [93 94]).

Many samples of ecstasy users are "convenience" samples. That is, they use a range of recruitment methods to obtain a sample at minimal cost in time and resources. These can include: "snowball" methods where participants refer drug using peers to the researchers[95]; "respondent-driven sampling" (RDS) [96] that documents the initial "seeds" and tracks subsequent participants with the aim of minimising the bias caused by the non-random selection of initial "seeds" (participants) in snowball sampling methods and bias due to volunteerism and masking. An evaluation of this method when used to recruit ecstasy users concluded that the method yielded samples that were representative of the broader ecstasy user population, with few sources of bias[96].

More recently, surveys administered to volunteer samples via the internet have been used as an additional, very inexpensive way of recruiting ecstasy users. Respondents in these studies self-complete a survey that is typically of a more limited length[97-101].

There has been limited comparison of results using these very different sampling methods. Topp and colleagues examined the similarity of a purposive sample of ecstasy users (who had been recruited to provide detail about ecstasy and related drug markets) with a household survey sample[102]. The demographic characteristics of ecstasy users in the two samples were broadly similar, but levels of some drug use were higher among the sample purposively recruited (who had been selected because they were frequent ecstasy users)[102].

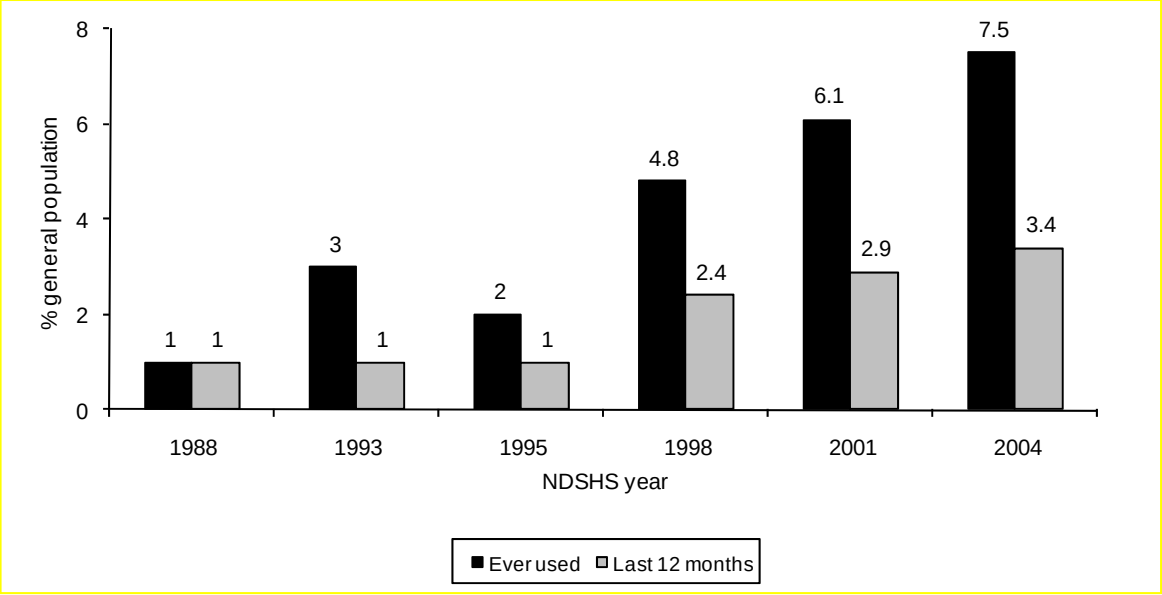
More recently, Miller and colleagues extended this work to compare a purposive, a household survey sample and an Internet sample[103]. The three samples were comparable in demographics, reporting a mean age in their mid-20s, with similar proportions being male. The majority were from an English speaking background and most had completed secondary education[103]. The majority of participants in all samples were currently employed, but the purposive sample was more likely to be unemployed than the Internet and household samples. Small differences were noted in other drugs taken, levels of polydrug use and the locations in which drugs were used[103].

In summary, different methods may be used to recruit ecstasy user and study patterns of use and associated variables. The use of a particular method is affected by the primary aims of the research, as well as other important logistical issues. It is important to remember that recruitment methods may affect the prevalence and patterns of ecstasy and other drug use found. They may also affect other variables such as the frequency of depression and problems related to use in the sample.

4.2. Ecstasy use in Australia

"Ecstasy" use was first assessed in the Australian National Drug Strategy Household Survey (NDSHS) in 1988. In that year, it was estimated that 1% of the general population aged 14 years and over had ever used ecstasy (Figure 4.1). The levels of lifetime use reported in surveys since then have increased to 7.5% of those aged 14 years and above who were estimated to ever have used ecstasy in 2004?[104]. The prevalence of past year ecstasy use also increased, from 1% in 1988 to 3.4% in 2004[104].

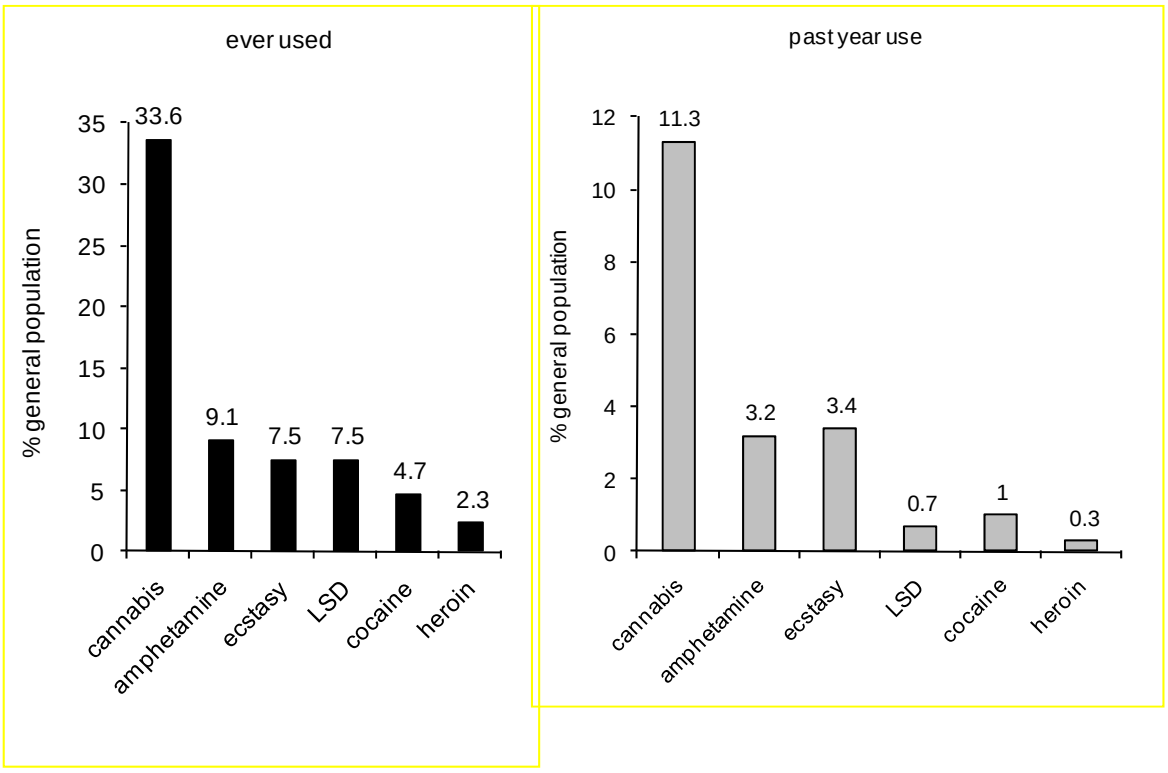
Figure 4.1: Prevalence of ecstasy use in Australia, 1988-2004



Source: Australian National Drug Strategy Household Surveys 1988-2004

Ecstasy is the only illicit drug for which the estimated levels of use in Australia have increased in prevalence in every survey from 1998 to 2004 – all other illicit drugs have remained at similar levels or apparently decreased[104]. Figure 4.2 shows the estimated prevalence of ever and past year ecstasy use compared to other drugs in Australia[105].

Figure 4.2: Prevalence of ecstasy use relative to other illicit drugs, Australia, 2004

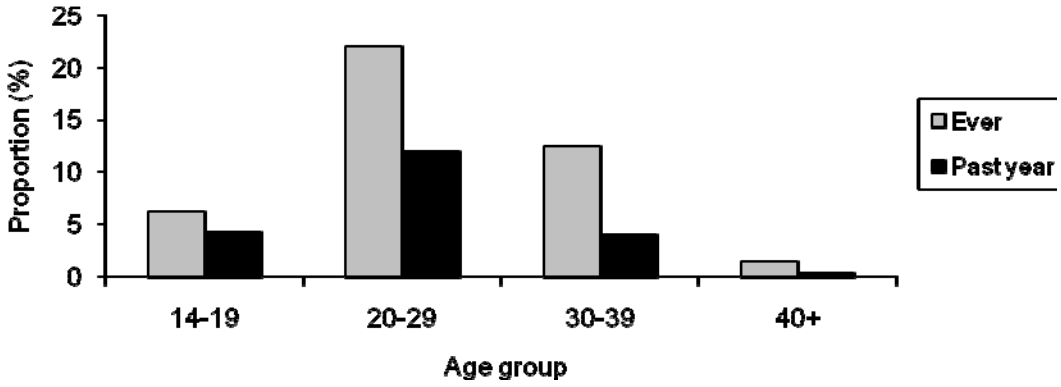


Source: Australian National Drug Strategy Household Survey, 2004

The prevalence of ecstasy use varies slightly according to sex, although differences are more modest compared to other drugs[106-108]. In 2004, 9.1% of males and 6% of females in Australia reported that they had ever used ecstasy.

Ecstasy use is most commonly reported by young adults in Australia. In 2004, both lifetime (22%) and past year use (12%) of ecstasy were most common among those aged 20-29 years (Figure 4.3). Again, more males than females in this age group reported lifetime use (25.8% vs. 18.2%) and past year use (15.1% vs. 8.8%). Those aged 30-39 years reported lifetime use of 12.5% and a recent use of 4%. Those aged 14-19 reported a lifetime use of 6.2% and recent use of 4.3% [104].

Figure 4.3: Prevalence of lifetime and past year ecstasy use by age, Australia, 2004



Source: Australian National Drug Strategy Household Survey, 2004

4.3. Ecstasy use in other countries

Table 4.1 presents some comparative estimates of the prevalence of ecstasy use in the general population of different countries, and Table 4.2 displays the results of surveys of use among school students or young adults. The countries with highest rates of recent (past year) use among these countries are Australia, New Zealand and the United Kingdom.

To use these figures as good indicators of harm or problems would be mistaken. A recent United Nations report discussed the fact that "prevalence rates for ecstasy are still highest in Oceania" (p. 152) [109] . An over-reliance reliance on these estimates of "any past year use" ignores what might be considered more important measures of use and of harm. Rates of frequent or heavy use, and indicators of harm related to this pattern of use, are more important measures from both a public health and clinical perspective. There is evidence, for example, that ecstasy users in the United Kingdom consume drugs of a much higher MDMA purity[56], in much greater amounts per session[80], than users in Australia[61 72].

Table 4.1: Prevalence of ecstasy use across countries

	% ever used	% used past year	Age range
Australia[1]	8.9	3.5	14 + years
Canada[2]	4.1	1.1	15-64 years
France[3]	0.9	0.3	15-64 years
Ireland[4]	3.8	1.1	15-64 years
Netherlands[5]	3.6	1.5	15-64 years
New Zealand[6]	5.5	2.9	13-45 years
Spain[7]	4.2	1.4	15-64 years
United Kingdom[8]	5.9	1.9	15-59 years
United States[9]	4.6	0.9	12+ years

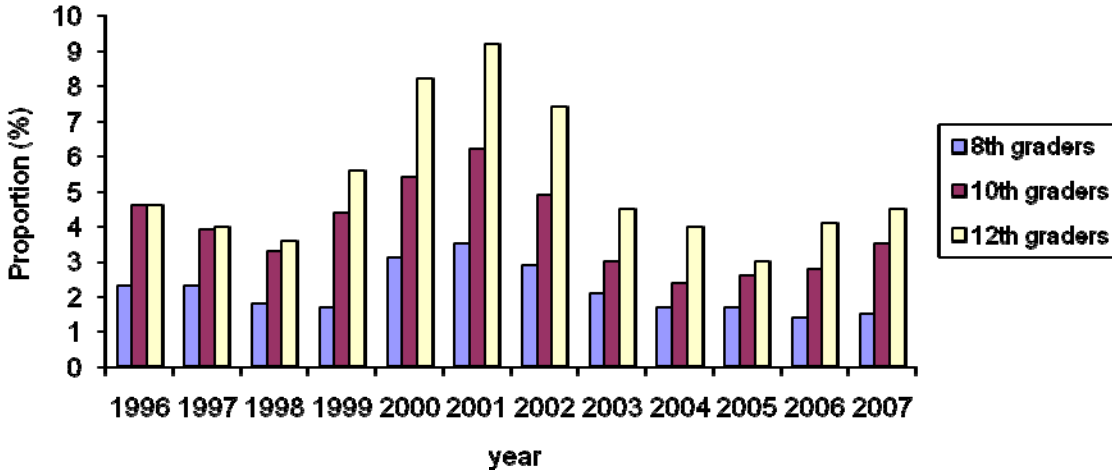
1. Australian National Drug Strategy Household Survey 2007[110]
2. 2004 Canadian addiction survey[111]
3. EROPP 2002[112]
4. Drug use in Ireland and Northern Ireland: First results from the 2002/2003 drug prevalence survey[113]
5. Licit and illicit drug use in the Netherlands 2001[114]
6. 2005 New Zealand Illicit Drug Monitoring System (IDMS)[115]
7. Spanish Household Survey on Drugs 2001[116]
8. British Crime Survey 2001/2[117]
9. US National Survey on Drug Use and Health 2006[118]

Table 4.2: Prevalence of ecstasy use among young people across countries

	Ever used	Past year	Age range
Australia[1]	17.0	8.5	15-34
Canada[2]	5.2	4.5	7-12th Grades
France[3]	3.7	1.0	15-34
Ireland[4]	7.1	2.3	15-34
Netherlands[5]	8.1	2.7	15-34
New Zealand[6]	7.5	--	13-45
Spain[7]	7.0	2.1	15-34
United Kingdom[8]	13.4	4.1	16-34
United States[9]	13.7	3.1	18-25 years
	1.6	1.0	12-17 years
United States[10]	2.3	1.5	8th Grade
	5.2	3.5	10th Grade
	6.5	4.5	12th Grade

1. National Drug Strategy Household Survey 2004[110]
2. Drug Use Among Ontario Students 2005 [119]
3. EROPP 2002[112]
4. Drug use in Ireland and Northern Ireland: First results from the 2002/2003 drug prevalence survey[113]
5. Licit and illicit drug use in the Netherlands 2001[114]
6. 2005 New Zealand Illicit Drug Monitoring System (IDMS)[115]
7. Household Survey on Drugs 2001[116]
8. British Crime Survey 2001/2[117]
9. SAMHSA 2005 National Survey on Drug Use and Mental Health[118]
10. US Monitoring The Future survey 2007[120]

Figure 4.4: Prevalence of past year ecstasy use among high school students, United States, 1996-2006

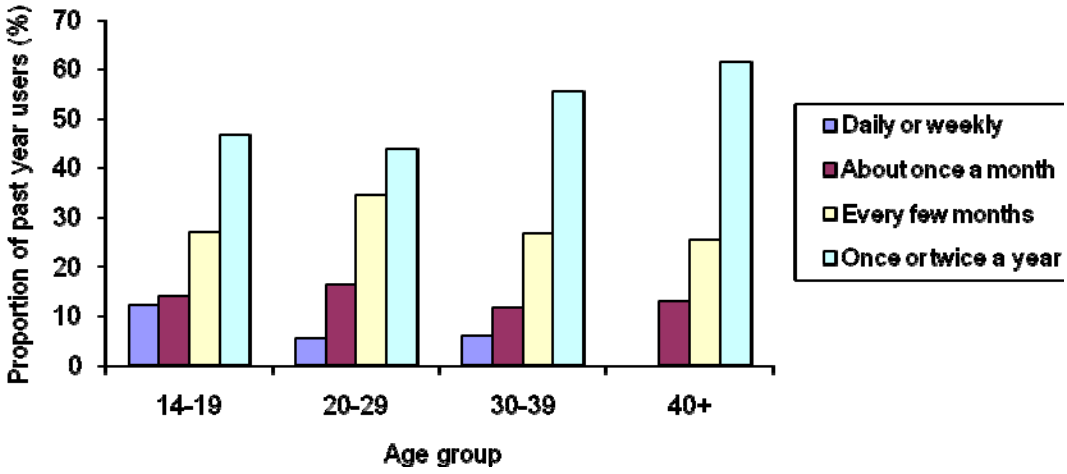


Source: US Monitoring the Future Survey, 1996-2007

4.4. Patterns of ecstasy use

Most people who use ecstasy do so infrequently. Figure 4.5 shows the patterns of ecstasy use among those in the general population who reported past year use in the 2004 NDSHS. The most common pattern of use is once or twice per year, with between 40-60% of users in each age group reporting that frequency of use. The next most common pattern of use was between three to 12 times a year. Around one quarter of ecstasy users aged between 14-29 years report using the drug at least monthly. These findings are consistent with other population studies of ecstasy users, which typically find a very occasional pattern of use of the drug for most users (e.g.[121]). Nonetheless, a minority of users do use more frequently. Among 14-19 year old users, one in ten used the drug at least weekly, with around 5% of users aged 20-39 doing so.

Figure 4.5: Frequency of ecstasy use among past year users in Australia, 2004



Source: Australian National Drug Strategy Household Survey, 2004

4.4.1. Use among sentinel groups of ecstasy users

More frequent use of ecstasy raises more concerns about the possibility of users experiencing drug-related problems and mental health problems (e.g. [122]). Since 2000, "sentinel" groups of ecstasy users have been recruited in Australian capital cities who use ecstasy at least monthly and hence, have regular involvement in the illicit drug market[123]. Annual cross-sectional surveys of these users have provided useful information on more prevalent emerging patterns of ecstasy and related drug use among regular users (e.g.[73 74 124-127]).

Among those interviewed in 2007, the median age of first ecstasy use was 18 years (range 12-45) (Table 4.3). This was much older than the age at which the group had begun using alcohol and illicit drugs such as cannabis. At least monthly use had begun at age 19 years (range 12-50) and had continued for a median of 3 years (range 1-23 years). There were no sex differences in any of these patterns of use. Participants had used ecstasy on a median of 12 days in the past six months (range 2-145 days). Three in ten (28%) used ecstasy between fortnightly and weekly, and 14% used more than once per week (Table 4.3).

Table 4.3: Patterns of use in regular ecstasy users in Australia, 2007

	n=741
Median age first used ecstasy (years)	18
Median age first used ecstasy at least monthly (years)	19
Ever injected ecstasy (%)	10
Median days used ecstasy in the last 6 months#	12
Used ecstasy more than weekly in the last 6 months (%)	14
Median tablets in a 'typical' session of use	2
Typically use >1 tablet (%)	71
Mainly use ecstasy tablets (%)	100
Usually swallowed ecstasy (%)	93
"Binged" on ecstasy (used 48hrs or more) last 6 months (%)	40
Typically use other drugs with ecstasy (%)	94
Typically use other drugs to "come down" from ecstasy (%)	82

Source: **EDRS REU interviews 2007**

4.5. Natural history of ecstasy use

We know very little about the natural history of ecstasy use because very little prospective research has been conducted in which patterns of ecstasy use have been examined over time. The only population-based follow up study has been conducted in Germany[128]. In this study a sample of young people aged 14-24 years 4.7% had used ecstasy, hallucinogens or amphetamines at baseline [128]. At a follow up around three years later (mean follow up 42 months), 9.1% had used these drugs, with a further 0.6% having developed "ecstasy dependence" (see Chapter 8 for more discussion of this issue). There was a birth cohort effect, with those born in the more recent cohort were more likely to begin use at an earlier age. Initiation of ecstasy use was associated with increased levels of other legal and illegal drug use[128]. Interestingly many of those who had used ecstasy or related drugs at baseline (amphetamines or hallucinogens) had ceased or reduced their use at follow-up, and only 2.8% of the sample used these drugs at follow-up[128]. The authors suggested that use and problematic use of these drugs was a "transient phenomenon"[128].

The only other prospective study of ecstasy use is being carried out in the Netherlands. The Netherlands XTC Toxicity (NeXT) study was designed to examine the causality, course, and clinical relevance of possible ecstasy (MDMA) related neurotoxicity[129], rather than the natural history of ecstasy use per se. It comprises three sub-studies: (1) a cross-sectional sub-study of heavy ecstasy users and controls with variation in other drug use; (2) a prospective cohort sub-study among ecstasy-naïve participants with high risk of future ecstasy use (as indicated by their self-reported intention to begin using ecstasy), and (3) a retrospective cohort sub-study involving ecstasy users and matched controls from an existing general population sample[129]. Recently published work involving the prospective study baseline ecstasy-naïve participants indicated that depression, impulsivity, and sensation seeking did not predict first time ecstasy use[130]. As all of these young people were recruited *because* they were at high risk of starting ecstasy use, we do not know whether this group differed from young people who did not intend to use ecstasy.

No Australian research has examined patterns of initiation, progression or cessation of ecstasy use. Given the lack of other studies of this sort, there is little by way of comparison. Cross-sectional studies of ecstasy users certainly suggest that some users continue to use the drug for many years[61], but these samples have been recruited *because* they still use ecstasy so it is difficult to know how this compares to other more typical users. There is agreement among researchers that studies of the natural history of ecstasy use are needed (e.g. [131]) because most of what we know is based upon the retrospective accounts of people who still use the drug, making it difficult to say much about those who cease their use, or about the factors that predict risk of initiating or escalating use.

4.6. Correlates of ecstasy use

Age: Ecstasy use typically begins in the late teens or early twenties. Levels of use are highest among young adults aged between 20 and 30 years.

Sex: As with many drugs, males are more likely than females to use ecstasy, but quite a number of studies have noted that the sex difference for this type of drug use is less marked than for other illicit drugs. Convenience samples of ecstasy users often have a larger proportion of females than convenience samples of other illicit drug users.

Education: In contrast to other types of drug use, many studies have reported that ecstasy users are educated and often attending (or having completed) tertiary education. There does not appear to be a strong link between ecstasy use and educational attainment in the way that there is for cannabis. This also applies to **income** and **socioeconomic status**[90]. In general, ecstasy use does not appear to be very strongly linked with these demographic characteristics.

4.7. Summary

Ecstasy use has increased over the past few decades in Australia and is now one of the most commonly used illicit drugs in the general population (albeit used on an infrequent basis). Despite this, extremely limited population-based research has been conducted on the patterns of use, correlates and natural history of this drug use. Ecstasy use appears to be more generalised across social strata – on average, those who us ecstasy may be better educated and less socially disadvantaged than the users of most other illicit drugs.

Most ecstasy use is intermittent and time limited, but a minority of users use the drug frequently (for example, once a week). Perhaps 5-10% of current ecstasy users aged 14-39 years in a given year might use weekly (around 25-55,000 young Australians in that age range). This is the user group most likely to experience any adverse effects from using the drug.

4.8. References

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5. The Psychopharmacology of MDMA

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5.1. Introduction

The psychoactive drug 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy, E, XTC) has an interesting history and a fascinating pharmacology. As discussed in Chapter 2, MDMA was first synthesised in 1912 and patented by the company E. Merck in 1914[1]. Although commonly thought to have been designed as an appetite suppressant, the original patent bears no record of this and simply states that MDMA was deemed to contain primary constituents for therapeutically active compounds[2]. The first reported pharmacological study involving MDMA occurred in 1927 although it was of limited scope[2] and basic toxicology studies were not undertaken until the 1950s[1]. Toxicology studies by Merck in 1952 provided little insight into the pharmacology of MDMA focusing on its effects on flies[2]. Further studies at the University of Michigan, supported by the US Army, reported LD_{50} values for five different species, the lowest LD_{50} value being found in dogs, the highest in mice[3].

As mentioned in Chapters 3 and 13, the first systematic use of MDMA was as an adjunct to insight-oriented psychotherapy[4], with administration of MDMA producing an easily controllable altered state of consciousness with positive emotional and sensual overtones[5]. The colloquial term for MDMA changed from "Empathy" as had been used by therapists in the 1970s, to "Ecstasy", emphasising the drug's euphoric effects[6] [7]. Heavy media attention in 1985 sensationalised Ecstasy's euphoric effects[5]. Despite this surge in popularity, the settings in which Ecstasy was used in the middle of the 1980's typically involved two individuals or a small and intimate group[5]. This was soon to change with the emergence of the "rave" scene.

In 1986, MDMA became a Schedule 1 drug in the USA, deemed to possess no recognised therapeutic value despite claims to the contrary[1]. By the 1990s, ecstasy had became intrinsically linked to the club and rave culture[8], with use by groups of young people attending all-night dance parties where vigorous dancing occurred to highly repetitive and hypnotic "techno" music. This was thought to have originated in Europe in the late 1980s[9] [10]. Patterns of use in Australia largely mimicked those seen abroad, with dance parties, private parties and nightclubs listed as the most

popular venues for use[11]. Its popularity has continued to grow, and the contexts of use broadened [11-16].

5.2. The Basic Pharmacology of MDMA

MDMA is a ring-substituted amphetamine, with a methylenedioxy group attached to the aromatic ring of amphetamine[17]. The most important pharmacological property of MDMA is to potently release serotonin (5-HT) from axon terminals into the synapse and to inhibit 5-HT reuptake. To a lesser extent, it also releases dopamine, noradrenaline and acetylcholine[18 19].

The action of MDMA in increasing synaptic neurotransmitter levels has been attributed to a number of direct and indirect processes, some of which differentiate MDMA from both the parent compound amphetamine and other substituted amphetamines [20]. All ring-substituted amphetamines cause greater 5-HT release than amphetamine itself [21] and MDMA's ability to do this involves a specific interaction with the serotonin transporter (SERT, see Figure 1) [22 23]. This mode of action contrasts with hallucinogenic ring substituted amphetamines such as mescaline and LSD that directly activate postsynaptic 5-HT receptors and not the SERT [21].

MDMA possesses two stereoisomers: (-)-MDMA has a higher affinity for postsynaptic 5-HT receptors while (+)-MDMA has a higher affinity for the SERT [23 24]. The two isomers differ in their behavioural effects in rhesus monkeys [25] and subjective effects in humans [26]. These two isomers also differ in the rate in which they are metabolised across individuals which may result in large inter-individual differences in the overall response to MDMA [17].

5.2.1. Serotonergic Effects of MDMA

MDMA reverses the action of the SERT, so that instead of transporting 5-HT from the synapse back into the presynaptic neuron, 5-HT stores from the neuron are pumped into the synapse [27 28]. This results in a rapid depletion of up to 80% of neuronal 5-HT stores [29]. An additional related action is to block the reuptake of 5-HT, which further increases synaptic 5-HT concentrations [30]. Pre-treatment with SERT ligands including reuptake blockers (e.g. fluoxetine or imipramine) prevents MDMA-induced 5-HT release in brain slices [31 32], and *in vivo* [33]. In addition to these effects on 5-HT efflux, MDMA-mediated inhibition of monoamine oxidase prevents the breakdown of 5-HT and other monoamines such as dopamine, further contributing to elevated monoamine levels [34]. A further effect of MDMA is to inhibit tryptophan hydroxylase (the rate-

limiting enzyme for 5-HT synthesis). This effect may contribute to depletion of 5-HT stores in the days following MDMA use [35].

MDMA also binds to various 5-HT receptors with moderate to high affinity [22] [23]. Receptor binding studies indicate that MDMA possesses a high affinity for the 5-HT_2 family of receptors and a moderate affinity for 5-HT_1 type receptors [23]. Direct activation of these receptors by MDMA may affect synaptic concentrations of other neurotransmitters such as dopamine (see below). Activation of 5-HT_{1A} receptors largely acts to inhibit serotonergic cell firing [36] although the resultant inhibitory effects on 5-HT release are overridden through MDMA-induced effects at the SERT in forebrain brain regions [20].

5.2.2. Dopaminergic Effects of MDMA

MDMA increases synaptic dopamine levels, but these increases are generally smaller than that the increases in 5-HT in any given region [24]. MDMA-induced dopamine release was initially attributed to a 5-HT_2 receptor mediated secondary process because 5-$HT_{2A/2C}$ agonists are able to augment MDMA-induced dopamine release. [37] This effect can be attenuated with tetrodotoxin (TTX) which binds to voltage-gated sodium channels, ketanserin, a 5-$HT_{2A/2C}$ antagonist [38] or the 5-HT_{2A} antagonist MDL 100,907 [39]. However, there is growing evidence that MDMA exerts its own direct effects upon the dopamine terminal to enhance dopamine release. While initial reports suggested that MDMA had low affinity for the dopamine transporter (DAT) [23], it is now known to increase dopamine efflux via the DAT, albeit far less potently than either amphetamine or methamphetamine [24] [40]. Dopamine levels are also augmented by an action of MDMA on the vesicular monoamine transporter (VMAT2). MDMA acts as a substrate at the VMAT2, causing dopamine efflux from vesicular stores via carrier-mediated exchange in a similar, but less potent, manner than amphetamine or amphetamine-like derivatives [41].

5.2.3. Other Neurotransmitter Systems

Effects of MDMA on other neurotransmitter systems are only occasionally described. MDMA causes significant release of noradrenaline via an interaction with the noradrenaline transporter (NET) [42]. Acetylcholine release occurs in the prefrontal cortex and dorsal hippocampus following MDMA administration [43]. Additional modulation of acetylcholine efflux has been hypothesised to be a result of an interaction with histamine [19] [44]. Evidence has also arisen for involvement of the GABA [38] [45] [46], glutamate [47-49], nitrergic [50] and sigma systems [51] in the effects of MDMA. Overall, however, it appears MDMA's primary action is upon 5-HT and dopaminergic neurons.

This has been largely confirmed in functional pharmacological studies of MDMA using behavioural and other models.

5.3. Acute Effects of MDMA in Humans

5.3.1. Pharmacokinetics and Metabolism

Several studies have administered MDMA to human subjects in controlled laboratory settings e.g. [52] [53-56]. These show that MDMA's distinctive effects occur at doses of 1 mg/kg or above [57]. Peak MDMA serum concentrations are observed 2 hours post administration, a time that coincides with reported peak psychological effects [58] [59]. Low doses in humans have a half life of 8-9 hours, with a 30-60 minute delay in the onset of notable effects [58], and a duration of action of 3-4 hours [60].

MDMA has non-linear pharmacokinetics, with increasing doses resulting in blood/body concentrations of drug that cannot easily be predicted [55] [58]. There is still conjecture over what blood concentrations are considered to be toxic. Most pharmacokinetic studies in humans have used low concentrations, to minimise ethical concerns relating to possible MDMA neurotoxicity [58] [61-63]. A recent study taking samples from users at a dance party in South Australia indicated that the blood concentrations were higher than predicted from pharmacokinetic studies [64].

Like most other psychoactive drugs, MDMA is primarily metabolised by the liver via the cytochrome P450 family of enzymes. MDMA has a very complex metabolic pathway in comparison to other amphetamine analogues such as methamphetamine or p-methoxyamphetamine. This complexity is thought to provide an explanation for the lack of an apparent dose-response relationship between ecstasy tablet intake and the development of side effects and acute adverse events. The complication is that many of the metabolites of MDMA including the initial metabolite of MDMA, MDA, are active psychoactive substances in their own right [65] [66].

Metabolites of MDMA are generated via 5 main biosynthetic pathways. The two most important of these, N-demethylation and O-demethylenation, play a primary role in rodents, non-human primates and humans [59] [67]. Of the many P450 enzyme isoforms present in the liver, the 2D6 isozyme (or its analogue in the rat, CYP2D1) mediates the O-demethylenation of MDMA in rats (with N-demethylation) and humans. Polymorphisms of the CYP2D6 gene are found in humans,

[68] with about 7 % of the Caucasian population having a deficiency in the CYP2D6 gene, leading to a decreased ability to metabolise MDMA. About 3% of the population are extensive metabolisers of MDMA.

The primary metabolites of MDMA in humans, HHMA and HMMA, are readily broken down in the body to ortho-quinones, highly reactive compounds that may lead to free-radical-induced brain injury. Interestingly, recent studies have shown that a single dose of MDMA in humans alters its own metabolism via inhibition of the CYP2D6 isozyme for 10 days [69]. This means that further doses of MDMA taken within that period of time can lead to unpredictably significantly higher concentrations of MDMA in plasma (as well as higher levels of putatively neurotoxic metabolites). This provides a plausible hypothesis for why doses of MDMA that have been previously taken safely by users can later produce acute adverse responses.

5.3.2. Physiological and Endocrine Effects

MDMA affects a range of physiological measures in humans. An increase in heart rate and blood pressure are commonly observed [56 64]. Despite well publicised reports of hospital presentations in ecstasy users for severe hyperthermia[70], MDMA at the doses administered to humans in laboratory settings produces only marginal effects on body temperature[57]. Factors like excessive MDMA consumption, drug interactions or an interaction with environmental factors (e.g. high ambient temperatures and vigorous exercise) may underlie the severe hypthermic effects of MDMA observed in clinical cases [71]. MDMA can also cause endocrine changes in humans including an increase in plasma oxytocin, vasopressin, cortisol and prolactin [72 73], effects which may be potentiated in a dance club environment [74].

5.3.3. Positive Psychological Effects

MDMA is sometimes termed an "entactogen", that is, a substance that produces empathy, well-being and insightfulness but with distinct subjective effects similar to hallucinogens[75]. MDMA induces a positive mood state [11] along with increased energy and euphoria[76], positive effects that have been observed across many drug types, particularly amphetamine derivatives[16]. In addition to general mood enhancement, MDMA users regularly report a sense of intimacy and empathy [8 13] coupled with an increased feeling of closeness to others [77]. Such effects have been observed in a double-blind placebo-controlled study [56].

These feelings of empathy and increased sociability differentiate MDMA from other drugs. Of ecstasy/MDMA's ten most frequently reported acute psychological effects, closeness to others,

happiness, feeling more easy going, accepting, sensual and euphoric were all seen to distinguish MDMA from both amphetamines and LSD [11]. In addition, MDMA also enhances perceptions and sensations [56 78-80]. Users report heightened responses to both touch and music, although these experiences differ from that of the classic hallucinogens such as mescaline or LSD [81].

Consistent with its primary action on the SERT, the SSRIs fluoxetine and citalopram attenuate many of the acute psychological effects of MDMA in human volunteers [53 81]. In addition, pre-treatment with citalopram prevents MDMA-induced blood pressure increases [53 82] while fluoxetine acted without any discernible effects on MDMA-induced changes in blood pressure [81]. Both drugs reduced MDMA-induced heart rate changes [81 82]. Further studies by the Vollenweider group showed that MDMA-induced perceptual changes and emotional excitation are partially mediated by post-synaptic 5-$HT_{2A/2C}$ receptors since these effects can be attenuated by ketanserin [83]. Furthermore meta-chlorophenylpiperazine (mCPP), a serotonin releasing drug with 5-HT_{2C} agonist properties has some similar perceptual effects to MDMA [52].

The positive acute effects of MDMA in humans do not appear to be purely serotonergic in nature. Thus, the DA antagonist haloperidol was able to partially antagonise positive and mania-like mood states induced by MDMA [78]. MDMA also possesses rewarding effects similar to dopaminergic drugs (e.g. amphetamine) that are not observed in other purely serotonergic agents such as mCPP [79]. In a forced choice paradigm where participants who were previously trained to discriminate d-amphetamine and mCPP were administered MDMA under double-blind control conditions there was no clear consensus as to whether MDMA more resembled a serotonergic or dopaminergic agent [84]. Some 25% of experienced drug users claimed that MDMA was unlike any other drug they had experienced [11]. It has also recently been suggested that the neuropeptide oxytocin, which plays a key role in social and affiliatve processes in many mammalian species, may play a key role in the positive social effects of MDMA [85-87].

5.3.4. Adverse Acute Psychological Effects of MDMA

A number of acute adverse psychological effects have been reported in the literature. Cohen[88], in a survey of 500 ecstasy users, reported that 20% of participants had suffered from paranoia and 16% from anxiety as an acute result of ectsasy use. These perceptions contrast with the positive effects upon mood, but as all mood states and cognitions tend to be accentuated by MDMA [89], anxiety can occur in conjunction with otherwise positive mood effects[57 90]. Case studies of more severe panic disorders following ecstasy use have also been reported in the literature although these appear to be rare [91-93].

Ecstasy may also cause confusion in users [88] although the extent of this confusion and its relation to interference with cognitive tasks is debatable. Only a limited number of studies have investigated the acute effects of MDMA upon cognitive function in human users. Parrott and Lasky [94] found impairment in verbal recall and visual scanning during acute MDMA intoxication. Similar cognitive impairment has been reported in some more recent studies [95] [96].

5.4. Acute Effects of MDMA in Laboratory Animals

The acute effects of MDMA have been investigated in a diverse range of animal species, with the vast majority of studies using either mice or rats. A smaller number of studies have utilised non-human primates. A key consideration in utilising animal models is in establishing appropriate animal dosing levels to model human MDMA use. This issue is far from resolved. It is complicated by the facts that plasma MDMA levels are affected by differences in drug metabolism (both within and between species), age, sex and time between repeated doses[97]. Unfortunately, many studies with laboratory animals have utilised MDMA dose regimes that are at the extreme range of those seen in humans [24].

5.4.1. Physiological and Endocrine Effects

In rats, as in humans, MDMA increases blood pressure [98], heart rate [99] [100] and elevates levels of cortisol and prolactin [101]. MDMA can also cause release of the neurohypophyseal hormones oxytocin and vasopressin [102] [103]. It also exerts a powerful influence on body temperature in laboratory rats, with the direction of change (hyperthermia or hypothermia) dependent upon the ambient temperature of the environment. Moderate to high doses of MDMA administered at standard room temperature (21-24ºC) produce a marked hyperthermic response in rats and rhesus monkeys [104] [105]. The hyperthermic response to MDMA appears in part to be reliant upon the mitochondrial uncoupling protein 3 (UCP-3) which initiates a process in striated myocytes that uncouples free energy stores in the mitochondria causing heat production [106] [107]. Hyperthermia can also be related to MDMA's ability to produce peripheral vasoconstriction, further preventing heat loss [100].

At lower ambient temperatures (less than 17ºC), MDMA reliably decreases body temperature [108-110]. With a high enough dose hypothermia can be observed even when the ambient temperature is as high as 22ºC [111]. The hyperthermic and hypothermic effects of MDMA may be caused by

distinct neural mechanisms. Hyperthermia can be prevented by the D_1 receptor antagonist SCH 23390 but not fluoxetine [112]. In contrast, the hypothermic response to MDMA seen in cool environments may be under the control of the D_2 or D_3 receptors [113].

5.4.2. Reinforcing Properties

MDMA self-administration has now been reported in a range of species including mice [114], rats [115-118] and non-human primates [25] [119-122]. Rats will show a conditioned place preference to MDMA, an effect that involves dopamine, opioid and endocannabiniod systems [123] systems. Overall, MDMA's reinforcing qualities are significantly less than that of other abused drugs such as cocaine and methamphetamine [115] [117]. Dopamine D_1-like antagonists can attenuate MDMA self-administration in rats [118]. Of further interest is that self-administration rates of MDMA are increased at high ambient temperatures [117] [124]. This effect may be in part due to augmentation of MDMA-stimulated increases in dopamine and neuronal activation in the nucleus accumbens following ambient temperature increases [125] [126].

5.4.3. Effects on Learning and Memory

The acute effects of MDMA on learning and memory in laboratory animals appear rather subtle. The anorexic effects of MDMA can present a major confound in food-motivated learning tasks, while the stereotypy induced by higher doses of the drug may render the animal incapable of co-ordinated responses. MDMA interferes with response acquisition in rats. [127] [128] Learning and retention difficulties are observed in rats during passive avoidance tasks [129] [130] and in non-human primates tested on a complex four lever response task [131-133] although see [134] for contrasting results. By contrast, specific MDMA-induced memory deficits appear rather difficult to observe [131-133] [135] [136]. When acute memory impairment is observed, these effects appear marginal even at the highest doses tested [137]. It remains possible that MDMA serves to alter time estimation [133] and/or between trial discrimination processes [138] while memory processes are relatively unaffected.

5.4.4. Effects on Anxiety-like Behaviours

Modulation of anxiety-like behaviours by MDMA is seen in rodents across a variety of tests. In the elevated plus maze, MDMA has been reported to produce an anxiogenic-like effect when administered at low or moderate doses in both mice and rats [139-143]. In contrast, an anxiolytic effect was observed at the highest dose administered in the elevated plus maze in both mice (20

mg/kg) [139], and rats (15 mg/kg) [144], indicating that MDMA may have biphasic effects upon anxiety.

In the emergence test, where rats are tested on their willingness to leave a small hide box to enter a large open field, MDMA-treated rats show increased anxiety [142] [145]. Additionally, MDMA-treated rats showed increased immobility, decreased rearing and decreased locomotor activity in the open field test, presenting a behavioural profile similar to that of the anxiogenic drug yohimbine [141]. MDMA also reduced exploratory behaviour in the light/dark test in mice but did not modify the total time spent in the light and dark compartments [146]. Overall then, MDMA appears to have an anxiogenic effect in rodents in tests of generalised anxiety.

5.4.5. Effects on Social and Aggressive Behaviour

In line with its characteristic effects in humans, MDMA reduces aggression in mice [147] [148] and increased social interaction has been observed in rats. Detailed observation of rats and fish has revealed that both species spend increased times in adjacent contact following acute MDMA treatment [145] [149] [150]. Adjacent lying or huddling is, however, an important social behaviour of rats that is common in young littermates but is also maintained during adulthood [145]. Interestingly, the increase in adjacent lying in rats is even greater when MDMA is given at high ambient temperatures [117]. This reinforces the assumption that this is a specific prosocial behaviour elicited by MDMA and not simply a thermoregulatory response to perceived cold. Moreover, MDMA-treated rats will voluntarily move to a cooler environment following MDMA administration if one is available [151].

Morley *et al.* [145] report that the 5-HT_{1A} receptor antagonist WAY 100,635 attenuated MDMA-induced social interaction by reducing adjacent lying times. The oxytocin receptor antagonist tocinoic acid also reduced MDMA-induced adjacent lying suggesting a key role for this neuropeptide in MDMA's prosocial effects [87].

5.5. The 5-HT Depleting Effects of MDMA

5.5.1. Animal studies

Exposure to relatively high doses of MDMA reduces brain monoamine levels in a variety of animal species [18]. While rats and primates show a primary reduction in brain 5-HT, mice show

primary reductions in brain dopamine [152]. Long lasting reductions in SERT density in cortical, limbic and striatal regions following MDMA has been reported in many studies with rats and primates [108 153-157]. Given that the SERT protein is primarily located in 5-HT axons, MDMA-induced axotomy has been invoked as the primary reason for this effect. This has been confirmed in histological studies [158-163].

A reduction in 5-HT levels and SERT density is not sufficient evidence to establish that MDMA has neurotoxic effects. However, the argument for its neurotoxicity is strengthened when this is combined with evidence from histochemical studies showing MDMA-specific cell damage. MDMA produces a selective loss of fine 5-HT axon terminals while sparing the thicker axons that are found in deep layers of the cortex and the medial forebrain bundle [158]. This pattern of MDMA-induced axonal degeneration is site specific, with changes in axonal density most prominently displayed in the neocortex, striatum and thalamus.

As with reductions in 5-HT content, axonal damage is long lasting. Hatzidimitriou *et al.,* [163] report abnormal 5-HT axonal immunoreactivity 7 years post MDMA treatment in squirrel monkeys. Furthermore, reinnervation of brain regions such as the hypothalamus following MDMA treatment also appear abnormal with proximal targets hyperinnervated while distant targets remain denervated [164].

Again however, these indicators of reduced 5-HT axonal projections following MDMA treatment do not fully confirm a neurotoxic effect in the classic sense. Gliosis is not typically observed following MDMA administration, nor is there any damage to serotonergic cell bodies observed [24]. The widely discussed notion of MDMA-induced neurotoxicity therefore remains controversial.

In addition to global SERT changes, alterations in the density of specific 5-HT receptor subpopulations can be seen following MDMA administration. McGregor *et al*., [155] in an extensive study of rats given MDMA 3 months previously, reported significant reductions in 5-$HT_{2A/2C}$ receptor density in cortical, striatal, thalamic and hypothalamic regions. 5-HT_{1B} receptor density was also reduced in the globus pallidus, hippocampus and medial thalamus but increased in the nucleus accumbens and lateral septum.

High temperatures at the time of dosing may exacerbate MDMA-induced 5-HT depletion. [111 165]. Moreover, a protective effect of co-administered drugs (e.g. haloperidol, ketanserin and pentobarbitone) may result from an induction of hypothermia or by preventing the hyperthermic effects of MDMA [165-169]. Indirect studies that aim to reduce the peripheral metabolism of MDMA and subsequent conjugation of metabolites with glutathione have also found that these protective

effects are a result of reductions in hyperthermia [170]. Although hyperthermia is not essential to induce MDMA-mediated 5-HT depletions [108 171] and some drugs are protective without affecting body temperature [165], hyperthermia does appear to facilitate MDMA's long-term 5-HT depleting effects. It appears that free radical formation may be increased by hyperthermia in MDMA-treated animals because a variety of free radical scavengers have been shown to attenuate MDMA's 5-HT depleting effects [18].

5.5.2. Assessment of 5-HT systems in human "ecstasy" users

Ecstasy users differ from controls on a range of neurochemical and neuroendocrine measures related to 5-HT. For example, McCann *et al.,* [172] demonstrated a reduction of cerebrospinal 5-HIAA levels. A single human autopsy study of brain neurotransmitter levels found striatal levels of serotonin and its metabolite 5-HIAA decreased by between 50 and 80% [173]. While post-mortem studies such as this provide a good direct method for investigating the effects of MDMA on 5-HT systems, the difficulty of obtaining suitable post-mortem brains makes it impractical to study large sample sizes.

Decreased global and regional SERT density in ecstasy users was first reported by McCann *et al.,* [174] but this study has since been heavily criticised [175]. However, reduced SERT density in ecstasy users has since been replicated and extended albeit with far more modest results [176-178]. In contrast to their earlier study, McCann *et al.,* [176] found no differences in SERT densities in the midbrain or putamen in MDMA users. Prolonged abstinence was correlated with higher SERT density, suggesting a recovery of SERT function with abstinence.

MDMA users also differ from controls in the density of 5-HT_{2A} receptors. Reneman *et al.,* [179] found decreased 5-HT_{2A} binding levels in recent MDMA users whereas an increase in 5-HT_{2A} binding levels was observed in now-abstinent MDMA users. This result, which is opposite to findings from animal studies (e.g. [155]) might be explained by an upregulation of 5-HT_{2A} receptors in abstinent users to compensate for reduced synaptic levels of 5-HT [179].

Although there has been some success in identifying 5-HT related deficits in ecstasy users using neuroimaging, results from other studies utilising markers of neuronal viability and brain activation have been less definitive. Investigations of N-acetylaspartic acid (NAA), a nonspecific marker of neuronal dysfunction or loss, and myo-inositol (MI), a marker of glial activity in ecstasy users, have provided largely inconsistent results [180-182]. This may be due to differences in participants' age between these studies, or questionable data analysis techniques[183]. Results from

functional imaging studies utilising either PET or fMRI suffer a similar pattern of inconsistencies, with reports of brain activity increases, decreases and occasionally even a lack of effect in ecstasy users undertaking attention and memory tasks [177].

As a more indirect marker of 5-HT depletion, experienced ecstasy users consistently use more Ecstasy in a single session than novice users [184]. Given increased experience and knowledge of the drug, this dose escalation is not in itself surprising or unique to ecstasy. Of greater concern is that many experienced users report either tolerance or sub-sensitivity to the effects of ecstasy[185] [186] that may manifest itself after as few as 6 or 7 uses [11] [187]. Recent study in rats showed that rats displayed decreased sensitivity to the prosocial effects of acute MDMA following pre-exposure to a dose regime that caused a lasting (albeit modest) depletion of brain 5-HT [188].

5.6. Long-term effects of ecstasy use in humans

The continued popularity of ecstasy, and its possible neurotoxicity, has produced a strong research focus on long-term cognitive or behavioural deficits that might arise from MDMA use. Many studies have now linked ecstasy use to long-term adverse psychological effects including mood changes, anxiety, depression, learning and memory problems.

While the number of adverse findings may be taken to provide evidence for an adverse effect of MDMA on mood and cognition, many of these studies have been criticised for poor methodology. A high proportion of ecstasy users also use other substances, raising the possibility that any observed differences may not be specifically related to ecstasy use. Coincident cannabis use can be a particularly troublesome confound which appears to compromise neuroendocrine function [189] as well as cognitive measures [190-192], although the possibility remains likely that the effects of MDMA and cannabis could be additive [89].

Because of such inconsistencies in the literature, there is a need for longitudinal studies to control for pre-morbid psychiatric and cognitive problems that may co-exist with ecstasy use [193-195]. However, the reality remains that determining directions of causality in human studies is very tricky. Preclinical studies thus become vitally important in cleanly addressing the issue of whether MDMA exposure has lasting adverse cognitive and emotional consequences.

5.7. Long-term Effects of MDMA In Laboratory Animals

A large body of evidence highlights the lasting functional consequences of MDMA exposure in rats, mice and primates. Unfortunately, as noted above, many of these studies have used doses that are both short-term and excessive and therefore provide a very poor simulation of typical human use. For example, early studies such as that of Battaglia *et al.*, [153] which investigated the neurotoxic effects of MDMA, used cumulative doses of 80 mg/kg MDMA or higher over 2-4 days [24]. More recent studies have used more modest dosing regimes [155] [196], and sometimes given MDMA weekly over several months [197], to better represent human use.

5.7.1. Operant Behaviour, Learning and Memory

Early studies such as those of Slikker *et al.,* [198] and Ricaurte *et al.,* [199] found no significant differences in maze behaviours despite MDMA-induced 5-HT depletion in rats. Similarly, LeSage *et al.,* [136] reported no long-term memory impairments in pigeons. In addition, prenatal exposure to MDMA failed to affect passive avoidance learning when rats were tested on post-natal day 95 [200]. This result was confirmed by Broening *et al.,* [201] who demonstrated that learning and memory deficits are only observed when neonatal rats were administered MDMA after day 21.

More recently, MDMA-induced learning and memory deficits have been revealed in rats using more sophisticated tests of spatial learning and memory such as the Morris or Cincinnati water maze [201-205]. The novel object recognition task has also been used to detect memory deficits resulting from MDMA pre-treatment [171] [206] [207]. Marston *et al.,* [208] showed impairment in a delayed non-matching to sample working memory task in rats pre-exposed to MDMA. Few other studies involving learning and memory paradigms have found long-term effects of MDMA treatment [127] [209-211] suggesting that MDMA may only have effects on a subset of learning and memory systems.

Despite using an extensive battery of tests, repeated MDMA exposure appeared to have surprisingly few long-term cognitive consequences in non-human primates [131] [133] [212-214]. Some subtle long-term effects of MDMA upon cognitive performance in primates can be unmasked when they are challenged with serotonergic agents such as the 5-HT releaser mCPP, antagonists of 5-HT_{1A} or $5\text{-HT}_{2A/2C}$ receptors or through tryptophan depletion [212] [213]. A lack of marked MDMA-induced long-term effects upon learning and memory in primates is observed, despite significant reductions in brain 5-HT and 5-HIAA levels [131] [212] [214].

5.7.2. Anxiety and Depressive-Like Symptoms

Consistent residual effects of prior MDMA treatment have been observed in a number of tests of anxiety-like behaviour in rodents. These include an increase in anxiety as assessed in the emergence test in Wistar rats up to 3 months after brief exposure to MDMA [155 171 206 215-217] and the elevated plus maze in both Wistar [206 216] and Sprague-Dawley rats [218]. Interestingly these long-term anxiogenic effects are seen both with high dose MDMA dosing regimes that deplete brain 5-HT and low dose regimes that do not affect brain 5-HT levels. MDMA pre-treatment can also cause depressive like symptoms in rats with decreased climbing times and increased immobility in the forced swim test [171].

In contrast to consistent findings in Wistar rats, MDMA pre-treatment had no significant anxiogenic effects upon the emergence test [198 219] or elevated plus maze using Sprague-Dawley rats [219]. Sumnall *et al.,* [220] found no significant effects on the plus maze using Lister hooded rats. This raises the important possibility that genetic differences may be a key determinant of the lasting adverse effects of MDMA [221] a theme that is also emerging in the human literature [222].

Interestingly, co-administration of □□-THC with MDMA was successful in preventing lasting adverse effects of MDMA in the emergence test in rats. It also partly attenuated 5-HT and 5-HIAA tissue reductions caused by MDMA treatment [215]. This effect was attributed to the free-radical scavenging qualities of □ ^{9}-THC and was not reliant upon CB_1 receptors. This surprising result indicated that concomitant cannabis use may confer neuroprotection against MDMA-induced monoamine depletion.

5.7.3. Social Behaviour and Aggression

Morley *et al.* [206] were the first to report a deficiency in social behaviour in Wistar rats 3 months following exposure to either low or high dose MDMA treatment. Since this time, these results have been extensively replicated using a number of different dosing regimes [155 171 197 215-217 223-226] revealing the social interaction model to be particularly sensitive to detecting lasting adverse effects of MDMA exposure.

In other models of social function, subchronic MDMA treatment was found to disrupt isolation-induced pup ultrasonic vocalisation [227] and sexual behaviour in rats [228]. Additionally, using the resident-intruder model of aggression, rats treated with MDMA 3 weeks previously exhibited reductions in social interaction, while aggressive behaviours were not affected [229].

To date, a number of authors have commented upon the dissociation between MDMA-induced social interaction deficits and long-term 5-HT and 5-HIAA depletion in brain tissue levels [149] [155] [171] [226]. Thus significant reductions in social interaction have been observed in the absence of any changes in tissue 5-HT levels [197] [223] [225]. The lasting social deficits caused by MDMA and other drugs in animal models have recently been hypothesised to reflect lasting neuroadaptations in brain oxytocin systems [86].

5.8. Conclusions

MDMA is a drug with a unique, complex and controversial pharmacology. No other drug, with the possible exception of GHB, has the capacity to produce such marked facilitatory effects on social behaviour in humans and other animal species, as encapsulated in the colloquial names for MDMA that include "The Love Drug" or "The Hug Drug".

Until recently, however, the majority of psychopharmacological studies of MDMA have tended to shy away from exploring the mechanisms underlying these fundamental prosocial effects of the drug, focusing instead on the possible harmful effects of MDMA and particularly its capacity to cause serotonergic neurotoxicity. Yet even here, despite a plethora of human and animal studies spanning more than two decades, experts in psychopharmacology cannot reach consensus, with some recently claiming MDMA to be largely innocuous[230] and others proclaiming a clear link between MDMA use and psychopathology[89].

The one constant factor is that our overall knowledge of MDMA psychopharmacology continues to grow, as research studies involving both human ecstasy users and laboratory animals administered MDMA continue to increase in sophistication, scope and power. Perhaps given another decade of research, a greater consensus will emerge, and we will understand not only how MDMA acts in the brain to produce "chemical love" but also whether this is a good or bad thing for the health of the individual.

5.9. References

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6. The acute effects of ecstasy (MDMA) use

Edmund Silins

6.1. Introduction

This chapter primarily focuses on the acute effects of MDMA use. 'Acute' refers to the effect of MDMA shortly after ingestion or during the acute stage of intoxication. In humans, serum levels of MDMA peak approximately 2 hours after administration[1-8] and the elimination half-life of the drug is about 6-8 hours[5,7]. The majority of ecstasy users swallow the drug[9] and the primary acute effects usually last for between 2 to 12 hours[10-12]. The non-linearity of MDMA pharmacokinetics suggest that relatively small increases in the amount of MDMA administered are likely to produce disproportionate increases in the concentration of MDMA in blood, which partly explains why acute toxicity may develop[3-5,7].

The characteristic psychological effects of ecstasy are thought to be caused by enhanced serotonin neurotransmission[11,13]. The drug also has arousing effects which are likely to be induced by the release of dopamine and/or noradrenaline[13-16]. A review of placebo-controlled studies which administered oral MDMA to healthy volunteers, found that MDMA displayed all its prominent features at doses of 1.0 mg/kg and above[17]. This is in line with the typical doses used by recreational users[18,19] to experience the drug's euphoric and stimulant properties. For interested readers, the acute neuro-endocrine effects of MDMA are described more fully in Chapter 5.

6.2. Acute psychological effects

The vast majority of studies which have investigated the acute psychological effects of ecstasy use have reported on the subjective experiences of users. Ecstasy users frequently report an overall sense of well-being, improved mood and euphoria shortly after taking the drug[20-27]. Other relatively common acute emotional experiences reported by ecstasy users include an increased sense of closeness and unity with others, and a greater sense of warmth and intimacy toward anyone present[20-24,26,28,29]. A substantial proportion of users report feeling relaxed, calm and serene whilst under the influence of ecstasy[20,23,24,26,29]. Greater open-mindedness and decreased defensiveness have also been described as acute emotive effects of ecstasy[20,23,28].

A range of negative acute psychological effects of ecstasy use have also been reported. These appear to be experienced less frequently than the desirable acute emotional effects but the proportions experiencing them are meaningful[10]. It is not uncommon for ecstasy users to report feelings of anxiety[20,21,24-26,28,30-33], depressed mood[22,25,26,28,30,32,34], irritability[26,30-32] and fear/paranoia[25,26,30,21,24,28,32]. A handful of case reports have noted delirium as a clinical feature of acute ecstasy intoxication[35,36], which may be due to MDMA.

Relatively few placebo controlled studies have investigated the acute psychological effects of ecstasy use. Using mood and consciousness rating scales, studies in a controlled medical setting have found that during the peak effects of MDMA participants report significantly enhanced mood, a greater sense of well-being and thought disorder[13,37,38]. Lietchi et al (2001) has summarized these findings[31]. Self-reported feelings of sedation among MDMA users have been found to increase compared with amphetamine, but not with placebo[39]. Other studies using standardized instruments have reported a lack of anxiety during acute MDMA intoxication[40,41]. To date, increases in empathy or feelings of closeness to others associated with ecstasy use have not been formally measured in controlled clinical studies.

6.3. Acute physiological effects

When human volunteers were given MDMA in doses equivalent to those used in a recreational setting (i.e. 0.25-1.9 mg/kg), cardiovascular activity increases, peaking 1 to 2 hours after administration[3,5,7,13,37,41-46]. Increases have been observed in heart rate[31,43], blood pressure[31,43] and cardiac output[43]. One study found that MDMA-induced increases in blood pressure were more pronounced in males than in females[31]. Another study found a dose-response relationship for acute MDMA-induced cardiovascular effects: at doses below 1.0 mg/kg, no change was observed relative to placebo while above this dose all studies reported significant increases[17].

Elevated body temperature has also been observed after exposure to MDMA. Whilst in the laboratory setting increases in body temperature have been modest, not exceeding 0.4C[3,5,7,13,31,37,41,47], in the setting of recreational use, there have been a handful of case reports published which describe serious, acute ecstasy-related hyperthermia[48-53]. A recent study measured a range of physiological parameters in 27 subjects in the 'real life setting' of ecstasy use (i.e. before and after attending a dance party)[54]. The study found small but significant increases in blood pressure and heart rate after drug intake. Although subjects with the highest plasma concentrations of MDMA tended to have elevated temperatures a few hours after drug ingestion, differences did not reach significance.

Numerous other acute physiological effects following MDMA use have been reported in controlled studies. These include: trismus (jaw clenching), thirst, heart palpitations, sweating, pupil dilation, nausea and vomiting[31,37,42].

Reports from large numbers of ecstasy users of the acute subjective effects of MDMA generally support laboratory findings in regard to the physiological effects of the drug. Users have reported experiencing a wide range of somatic effects[20,24-26,30,34,55-58]. A recent comprehensive review by Baylen et al (2006) identified a subset of subjective physiological effects reported repeatedly by large proportions of participants across multiple investigations[10]. The twelve most common acute subjective physiological effects were: nausea and/or vomiting, bruxism (teeth grinding)/teeth problems, headache, body temperature changes, accelerated heart/heartbeat, muscle aches or tightness, fatigue, dizziness, dry mouth/thirst, increased energy, sweating and numbness/tingling. Other acute physiological effects have included: tremor/shakes, inability to urinate, blurred vision, nystagmus (rapid, involuntary eye movement), stomach pains, diarrhoea and memory lapse[21,24,30,31,55].

6.3.1. Acute MDMA toxicity

Whilst acute ecstasy toxicity is rare[59], it can result in serious medical complications. Hyperthermia (i.e. body temperature above 38 C) is one of the major symptoms of acute ecstasy-related toxicity that can lead to other often fatal conditions such as rhabdomyolysis, disseminated intravascular coagulation, renal failure and liver damage[48-53]. The impairment of temperature regulation among ecstasy users is likely to be a result of the combined direct effects of MDMA, high ambient temperature, prolonged physical activity and insufficient fluid replacement[50,51].

Disturbances in salt and water balance can also occur in ecstasy users[59]. Symptoms include confusion, reduced consciousness, seizures and convulsions. In the majority of cases, recovery is achieved once sodium levels are returned to normal. However, fatalities have occurred which generally were caused by cerebral oedema from over-hydration[60-62].

MDMA may produce in users a clinical picture resembling mild serotonin toxicity. Whilst this is generally transient, there is potential for serious, acute toxicity[63-68]. Liver damage, or liver failure, associated with the use of ecstasy has also been reported[49,69-71]. Evidence suggests that MDMA may have cardio-toxic properties[60,72-75], and pre-existing cardiac disease is likely to increase vulnerability[76-78]. Several case reports have linked the use of ecstasy with cerebrovascular accidents (e.g. intracerebral and subarachnoid haemorrhage)[79-81] and respiratory complications[82-84].

6.4. Other acute effects

A range of other acute effects have been reported. Baylen et al (2006) found that the some changes in sensory perception were reported by substantial proportions of participants in multiple investigations. These were primarily visual effects or changes in visual perception, and sound hallucinations or altered sound perception. Large numbers of users have also reported an enhanced sense of touch[10]. Other changes in sensory perception which have been recorded include heightened awareness[21,24] and altered time perception[28].

Cognitive acute subjective effects reported by ecstasy users include increased alertness[10] and enhanced 'presence of mind'[29]. Confused thought[24,30], memory problems[30] and difficulty concentrating[31] have also been reported by some users.

A study which assessed simulated driving performance found that vehicle control was partly affected after MDMA and deteriorated further after multiple drug use. Furthermore, both after MDMA and after multiple drug use, there was a tendency toward risky and unsafe driving practices[85].

Although a proportion of users report sexual arousal[25,42,86], improved sex[86,87] and enhanced lubrication in women[86] as acute effects of ecstasy, the inhibition of sexual arousal is also reported[20,37,87]. Among a sample of 100 ecstasy users, most described the drug as providing a sensual rather than a sexual experience[88]. In an early study, Buffum et al (1986) found that increased receptivity to sexual behaviour was commonly reported amongst ecstasy users, but that the drug affected male erection and inhibited orgasm in both men and women[89]. The study also found that a proportion of subjects who engaged in sexual activity while intoxicated were more likely to participate in activities that were not part of their usual sexual repertoire (e.g. group sex, anal sex, homosexual sex). Ecstasy also lowered inhibitions among users[87,88], making sexual risk-taking more likely while using the drug. Topp et al (1999) found that there was less condoms use with casual sexual partners when users were acutely intoxicated on ecstasy[87].

Other acute subjective effects of ecstasy intoxication include increased talkativeness[21,26], changes in appetite[24] and sleeplessness[31,37].

6.5. Sub-acute effects

Although the primary focus of this chapter is on the effects of ecstasy shortly after ingestion or during the acute stage of intoxication, a range of physiological and psychological effects are generally experienced by users in the days following ecstasy use. The residual effects of ecstasy intoxication are experienced in the 24-48 hours *after* ecstasy use. This is commonly referred to as the 'come-down'. Whereas the effects which tend to be reported by ecstasy users as 'positive' are generally experienced in the initial 24 hour period, the 'negative' effects are mainly experienced in this sub-acute phase (e.g. 24-48 hours after ingestion)[24].

Common symptoms reported while coming down are low mood and/or poor concentration[24,27,37,90]. A study of 430 regular ecstasy users found that participants who reported low mood during the sub-acute period tended to be older than those who did not. In addition, men who reported low mood had been using ecstasy for longer, and using it less frequently, than those who did not report low mood. Female users who reported impaired concentration during the sub-acute period were found to be older than those who did not report this effect[24]. One study reported that 8% (n=26 is this the total sample or the number reporting suicidal thoughts?) of subjects, suicidal thoughts were experienced as a sub-acute effect of ecstasy use[30]. Other sub-acute effects experienced by users include energy loss, irritability, muscle aches, loss of appetite and trouble sleeping[24,30,37].

6.6. The role of drug dose and other factors

A range of drug and non-drug factors have been found to influence the effects of ecstasy.

6.6.1. Ecstasy dose and previous ecstasy use

Larger doses of ecstasy have generally been found to be associated with additional and more intense adverse effects. Compared to the effects of a 'usual' dose of ecstasy, Zervogiannis et al (2003) reported that larger doses were associated with additional unique effects such as nystagmus, confused thought, panic attacks and memory loss[21]. Larger doses produced more reports of hallucinatory effects, disorientation and adverse side-effects[34].

Users have reported that multiple or successive doses of ecstasy produce less intense effects of shorter duration than the initial dose[34]. In addition, subsequent doses are associated with reduced pleasurable effects and increased side-effects[34]. In keeping with this finding, binge use of ecstasy (e.g. using the drug on a continuous basis without sleep for 48 hours or more) was associated with a greater number of negative effects than non-binge use[30].

Studies investigating the association between ecstasy use history and acute drug effects have revealed mixed results. Solowij et al (1992) found that participants who had used ecstasy 3 or more times were more likely than novice users to experience the reportedly positive effects of activation and insight, although there was no difference between these groups on measures of positive/negative mood and intimacy[34]. In the study, the severity of physical and mental effects correlated positively with the total number of ecstasy doses consumed and the frequency of use. On the other hand, another study found that participants with a longer history of ecstasy use reported health problems less often and were sick at parties less often than those with a shorter history of use[22]. Other studies have found no relationship between ecstasy use history and the acute effects experienced by users[24,28,33].

Recently, an abundance of studies have investigated the effect of acute and lifetime ecstasy use on cognitive function[24,91,92]. Although subtle cognitive deficits have been demonstrated among ecstasy users reporting occasional use or a low cumulative dose, there is a growing body of evidence which suggests that it is chronic, heavy use of ecstasy that is associated with cognitive impairment, the severity of which is related to the level of lifetime exposure to ecstasy[93-96].

6.6.2. The physical environment

One hypothesis is that MDMA produces stronger acute effects when it is used in stimulatory conditions (e.g. dance parties and raves)[97-99]. The implications of taking ecstasy at dance parties were explored in a recent review[98]. Whilst emphasising that there is little supporting empirical data, Parrott (2004) noted that if ecstasy is used in a calm and neutral physical environment, the drug tends to display a general 'releasing' function, boosting positive and negative mood states[98].

By contrast, the subjective experience of ecstasy users, who often use the drug in hot environments (e.g. nightclubs), is generally more intense and euphoric. This difference may partly be explained by the findings of animal research, which suggests that hot and stimulating conditions boost the acute drug response, and also increase the potential for adverse effects. There is extensive animal literature on the contributory roles of environmental (i.e. 'non-drug') factors in the effects of MDMA, and these studies are described in detail elsewhere[98,99]. The contributory roles of environmental factors as they relate to humans are summarised here.

As mentioned earlier, one acute physiological effect of ecstasy use is increased body temperature. Ambient temperature has been shown to influence the effect that MDMA has on body temperature. Studies have reported that the hyperthermic response in MDMA-treated rats tends to be more acute when the ambient temperature is higher[100-103]. In humans, MDMA increases body temperature[104], and under hot conditions the increase in metabolic activity is even greater[105].

In a field study, dancing clubbers who had taken ecstasy had significantly higher temperatures than other dancers at the same venue[106]. Subjective feelings of being hot were also more common among this group and these were correlated with objective temperature measurements. In contrast, among nightclub attendees, Cole et al (2005) found that both ecstasy polydrug users and non-psychostimulant users had normal oral temperatures despite increases in environmental temperature and periods of dancing[107]. Similarly, another study of dance party attendees found that although ecstasy users with high plasma concentrations of MDMA had elevated temperatures a few hours after ingestion, differences did not reach significance and were not clinically significance[54]. Whilst research in animals and laboratory studies in humans tends to suggest that ambient temperature may be a factor contributing to the acute hyperthermic effect of ecstasy, findings from field studies do not always support this hypothesis.

It has also been hypothesized that prolonged exertion (i.e. dancing for long periods) might exacerbate the effects of ecstasy in elevating body temperature[99]. The effect of physical activity when on ecstasy was assessed in an internet study of 206 ecstasy users. Preliminary results suggest

that prolonged dancing on ecstasy was related to more reports of depression, poorer concentration and organizational difficulties in the sub-acute period (i.e. the 'come-down'). It was also associated with more prospective memory problems in the long-term[97].

Fluid intake and level of dehydration are also thought to be factors which may influence the hyperthermic effect of ecstasy in humans because water deprivation acutely increases the hyperthermic response of MDMA-treated rats in high ambient temperatures[108]. Recent research has also found that loud music/noise exacerbates the stimulatory effects of amphetamine in mice[109], and potentiates the (electrocortical) effects of MDMA in rats[110]. It has therefore been suggested that loud music played at dance parties may heighten the acute and long-term effects of ecstasy in humans[99,109,110].

6.6.3. Social setting and user expectancies

The relationship between social setting and expectation have also been explored in relation to the drug experience of MDMA users[111-113]. A qualitative study of 98 current and former ecstasy users found that the social setting in which ecstasy was used influenced the acute subjective effects of the drug[114]. Participants reported that their interaction with others contributed to the drug experience, particularly some of the reportedly negative subjective effects of ecstasy use. For example, the negative experiences of others, especially friends, were seen to adversely affect their own experience.

Additionally, the capacity of ecstasy to deliver its purported pleasurable effects is related to a combination of social setting and positive preconceived expectations about the experience. As with users of alcohol[111], ecstasy users have a range of pharmacological and social expectations about the effects of the drug[114]. Ecstasy users expected to feel 'loved up', sociable and confident, and the ways in which these feelings are manifest appear to be in users' interactions with others[114].

Some users report experiencing positive *and* negative psychological effects during a single episode of MDMA use[14,115]. This tends to support the important role setting and expectancy have in generating a positive (or negative) experience among MDMA users[20]. Furthermore, a positive setting can be important in the absence of an active drug. Parrott and Lasky (1998) found the mood of ecstasy users at a dance club were very positive, but so too were the moods of non-users[90].

6.6.4. Age and sex

Relatively few studies have addressed whether age and sex are factors which may influence the acute effects of ecstasy. Some studies have reported that younger ecstasy users experience more negative physical effects[30], whereas others have found that age was not related to acute subjective effects[24].

There is mounting evidence that sex may influence the subjective effects of ecstasy, with females tending to be more prone to the adverse effects of the drug. In a study of 329 ecstasy users, females were more likely than males to experience adverse physical and psychological effects related to ecstasy use[30]. In keeping with this finding, women were found to report more acute negative effects of ecstasy use than men[116], and females were more frequently ill during or shortly after parties where they had used ecstasy[22].

An analysis of pooled data from 3 controlled studies revealed that the psychoactive effects of MDMA were more intense in women than in men[31]. Women had higher scores for MDMA-induced hallucinogenic-like perceptual changes, thought disturbances, and fear of loss of body control. Furthermore, in women the dose of MDMA positively correlated with the intensity of perceptual changes. The authors concluded that equal doses of MDMA per kilogram of body weight produced stronger subjective effects in women than men. This is consistent with an increased susceptibility of women to the serotonin-releasing effects of MDMA. The study also found that MDMA-induced increases in blood pressure were more pronounced in males than in females[31].

With regard to the sub-acute effects of ecstasy, Verheyden et al (2002) found that females tended to report mid-week depressed mood following weekend use of ecstasy, whereas males were more likely to experience aggression in the days after ecstasy use[117]. These differences are likely to have a biological basis. One review concluded there were sex differences in drug sensitivity in laboratory animals, and that males and females differed in their behavioural, neurological and pharmacological response to drugs[118].

6.6.5. Other factors

A range of other factors may also modulate the physiological and psychological effects of ecstasy. Co-use of other stimulants (e.g. amphetamine, cocaine, nicotine) and/or depressants (e.g.

cannabis, alcohol) are likely to increase the likelihood of cumulatively detrimental acute effects[92,116,119-121].

Premorbid characteristics, such as a predisposition towards anxiety, stress or depression, may increase the likelihood of acute or chronic adverse effects to psychoactive drugs, including ecstasy[24,91,122-124]. One researcher speculated that 'robust' personality types may be better able to handle the effects of repeated psychoactive drug use because of individual differences in cellular metabolism and other mechanisms (the complexities of this possibility were acknowledged)[99].

Circadian aspects (sleep/wake cycles) are affected by MDMA in rats and humans[125], and MDMA-induced impairment in psychomotor performance among night club attendees has been found to be compounded by sleep loss[126]. This suggests that lack of sleep or inadequate rest may be factors that directly or indirectly contribute to the adverse sub-acute effects of ecstasy use.

Nutritional factors may also have a role. Ecstasy use can reduce appetite and lead to weight loss[24,127] which may exacerbate the effects of the drug[99]. MDMA can also reduce immune competence in humans[128,129], potentially decreasing the ability to process any psychoactive drug and contributing to impaired general health[99].

The multiple influences of drug and non-drug factors which modulate the neuropsychobiological effects of MDMA are considered in detail in a bioenergetic stress model described by Parrott (2006)[99]. Interested readers are encouraged to consult this paper.

6.7. Summary

The primary reason many people use ecstasy is to experience its euphoric and stimulant effects. Users frequently report an overall sense of well-being, improved mood and increased closeness with others.

Significant proportions of ecstasy users also experience undesirable effects such as anxiety, irritability and depressed mood. These are particularly common in the sub-acute phase or 'come-down' period following use. Commonly reported physiological effects of ecstasy use are nausea, teeth problems, headache, body temperature changes, accelerated heart beat, increased energy and sweating. Although acute MDMA toxicity is rare, it can result in serious medical complications.

The acute effects of ecstasy depend on a range of drug and non-drug factors which include the dose received, the environmental and social setting in which the drug is used, and the user's expectations. The variability in these factors may contribute to difficulties in effectively titrating doses that produce the desired positive effects while minimising the occurrence of adverse acute effects.

6.8. References

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7. Does MDMA use affect the immune and reproductive systems?

Ross Beck

7.1. Introduction

This chapter examines possible effects that MDMA use has on the immune and reproductive systems of users. In the context of this Chapter, the term MDMA refers specifically to 3,4-methylenedioxy-N-methylamphetamine because much of the research on these topics has been conducted to date using MDMA in animals, both *in vitro* and *in vivo*. There has been almost no research on the effects of 'ecstasy' (which may or may not contain MDMA and adulterants) on human immune and reproductive system functioning.

7.2. Possible effects upon the immune system

7.2.1. The nature of the immune system

The immune system is divided into two different, yet linked, components. The **innate** ("non-specific" or "non-adaptive") system is the body's frontline immune defence. This system comprises a range of defensive mechanisms that are present prior to exposure to an infectious organism or other foreign substance and are not enhanced by re-exposure to the same organism. The range of systems include various blood borne cells and molecules along with physical barriers (such as skin).[1]

Cells of the innate system also provide priming and presentation functions for the **specific** (or acquired) immunity. This amplifies the response of natural immune mechanisms, and direct these responses to sites of entry. In addition acquired immunity provides immunologic memory, so that subsequent encounters with an infectious organism result in rapid, specific and effective defence mechanisms. That is, re-exposure to the same organism results in an enhanced immune response.[1] Together, the innate and adaptive components form a complementary system, comprising numerous cells and molecules, for dealing with the majority of infective agents which can infect an organism.[1]

Innate immunity

There are a number of components of the innate system. *Lysozyme* is found in tears and saliva. Its degrades bacterial cell walls and it also aids in phagocytosis (ingestion of the bacteria by body's cells), in conjunction with components of the innate immune system such as macrophages or neutrophils.[1] *Complements* are a series of proteins normally found in inactive form in the blood. On encountering a pathogen, these form an amplifying cascade, resulting in pathogen lysis or phagocytosis.[1]

Monocytes/Macrophages: this is a mono-nuclear family of phagocytes that are potent cytokine secretors. Monocytes are blood-borne, whereas macrophages migrate outside the vascular system.[1] The **natural killer (NK) cell**: this is a mononuclear cell capable of recognising and lysing virally infected or tumour host cells that have lost their self identifying (MHC) molecules.[1] The **mast cell** is found in mucous membranes and connective tissue releases chemicals that aid in inflammation. It is also associated with allergic responses.[1] **Neutrophil** is the most plentiful phagocyte of the vascular system. Neutrophils engulf foreign bodies and digest them.[1] The **Basophil/Eosinophil** cell aids in killing parasites through the release of toxic chemicals. It also

can play a role in allergic reactions.[1] The innate system is not always successful in controlling an invading organism. Even when unsuccessful in controlling such an 'invasion', innate components initiate signalling, and interact with the adaptive arm of the immune system which may better deal with the organism.

Specific or adaptive immune system

The specific arm of the immune system is triggered when components of the innate system interact with it. The main cellular components are lymphocytes. **B lymphocytes** are involved in the humoral or antibody-based specific responses against infectious agents. Antibodies aid in the clearance of an infectious organism by binding to the infectious agent or its toxin, thereby neutralising it, or allowing other components of the immune system to better deal with the infectious agent.[1] **T lymphocytes** are comprised of a range of functionally diverse sub-groups. These subgroups are responsible for many functions of the adaptive immune response including up-regulation (activation) following infection, the destruction of infected cells, down-regulation post infection and the maintenance of immunologic memory.

Cytokines are a group of hormone-like substances that are used for signalling between cells.[1] Cytokines have very important roles in both the innate and adaptive arms of the immune system, turning "on" and "off" components of the immune system.[1] Cytokines that are produced by the innate system after it encounters a pathogen also act as stimuli in activating components of the adaptive immune system. There are over thirty known types of cytokines. These include the interleukins, tumour necrosis factors, interferons and chemokines.[2] The cytokine network shows great *redundancy* and *pleiotropism*.[2] The functions of some cytokines can be performed by other different cytokines (redundancy), and a single cytokine can have many different functional effects, either on different cell types or even on the same cell (pleiotropism). This means that the over-expression of a single cytokine may have multiple effects, and the under-expression of a single cytokine may not have an adverse effect.[3]

Stimuli that turn on the immune system are generally viewed as *activating*, whilst stimuli that turn off immune components are viewed as *suppressive*.[2] If an organism has an infection/tumour, the up-regulation (activation) of immune cells and functions to combat it produce a positive functional response of the immune system, as does the timely suppression of those components once the infection or tumour has been defeated.[3] Premature suppression of the immune response would be a negative functional response. So would the inappropriate activation of the immune system, as occurs in an autoimmune disease where the immune system mistakenly attacks the body's own cells.

7.2.2. Immunological effects of MDMA

A range of possible immunological effects of MDMA have been studied in both human and rodent immune systems, including both innate and adaptive components of the immune system. Not all findings in animal models mirror those observed in humans. *In vitro* culture methods are helpful in assessing whether the drug has direct effects on immune cells in isolation from other systems in the body which may affect the immune system. *In vivo* testing involves the sympathetic and neuroendocrine systems within the body.

Animal studies

An early experiment using mice found that 0.0001μM concentrations of MDMA following 24 hour in vitro culture increased IL-2 production in mouse T cells[4]. At the same concentration NK cell activity was mildly elevated (attributed to the IL-2). Concentrations between 0.001 and 1.0 μM had essentially no effect, 10μM was mildly suppressive and 100μM was markedly suppressive. B cell function was unaffected at any concentration, whilst macrophage production of TNF was decreased, IL-6 production following LPS stimulation was unaffected. No mechanisms were suggested[4].

In that study, acute MDMA exposure led to short term *increases* in NK cell numbers and activity. Conversely, (in humans) chronic MDMA consumption has been reported to *decrease* NK cell numbers[5]. One possible explanation is that the increased IL-10 production noted following MDMA exposure was responsible for suppressing IL-12 and IL-15 production, two cytokines crucial for NK cell maturation and activation.

The blocking of IL-10 production in mice with the beta blocker nadolol suggests that IL-10 production may be stimulated by beta-adreno receptor-mediated mechanisms that are not yet fully understood. They are possibly linked to catecholamine release that is induced by MDMA.[6]

In rodents, MDMA decreased neutrophil phagocytosis and the secretion of IL-1β and TNF-α following LPS challenge while increasing IL-10 production. Lymphocyte function as measured by response to the T cell mitogen ConA was also reduced[7 8]. Also of note was that the finding that MDA (methylenedioxyamphetamine), a metabolite of MDMA, has similar immunosuppressive effects in rats to MDMA[9].

Antibody switching is a normal event whereby antibodies produced to initially fight an infection are replaced by a second type that provide long term protection and immunity against subsequent

infection. Usually the first antibody type produced in response to infection is IgM. After a period of time (usually within days) production starts switching to another antibody type IgG. [1]

Abnormalities in antibody switching have been reported in rats acutely administered MDMA[10]. One subclass, IgG2a which is dependent on IFN-γ, has been reported decreased in rats after challenge via a unique antigen[10] . The authors hypothesized that this could be due of the critical role attributed to that subtype in both an antiviral response and the complement cascade.[10]

Similar findings have been reported after chronic exposure of mice to amphetamine[11]. Amphetamine sulphate 0.4 mg/kg administered chronically resulted in a significant decrease in both circulating and splenic lymphocyte numbers and in the mitogenic response. Unfortunately the time points were in increments of four days, so even though a marked lymphocytosis was noted at the first time point, it was not clear whether this occurred earlier than four days[11]. MDMA can exert similar in vivo effects within 30 minutes of exposure (at higher does of 20mg/kg)[7].

Human studies

Trials in humans have produced similar but not identical effects to those seen in animals. The decrease in circulating lymphocytes noted in rats and mice has not been observed after acute MDMA administration in humans. There is a decrease in the number of T4 lymphocytes, with a matching increase in NK cells following acute exposure to MDMA.

Increases in the anti inflammatory cytokines TGF-β and IL-10, a decrease in lymphocyte response to mitogen stimulation have also been observed after acute MDMA consumption.[12] Chronic MDMA use might also decrease NK cell numbers. In one of the few trials of its nature, a small follow-up of study of 8 MDMA users over a two year period suggested that NK cells, CD4+ T cells and B cells were decreased[13]. The researchers suggested that these alterations may be permanent[13]. The small numbers of people in this study preclude strong statements being made about these findings.

Most observational studies of immune functioning in ecstasy users have been cross-sectional. One study found that MDMA/cannabis users had significantly higher rates of mild infections (identified as common cold, acute pharyngitis and sinusitis and uncomplicated urine infections) compared with cannabis only users or normal controls[5]. An earlier study examining MDMA/ecstasy use linked increased use with increased numbers of infections[14]. Further, other lifestyle features associated with problem ecstasy use may include poor nutrition and disturbed

sleep patterns (circadian rhythm), and these may also potentially play a role in immunomodulation[15] [16]. Parrott and colleagues investigated perceived ecstasy-attributed infections in 282 recreational ecstasy users recruited and interviewed via the Internet[17]. Such infections were reported by 5% of novice users (1-9 MDMA occasions lifetime), by 9% of moderate users (10-99 occasions lifetime), but by 35% of heavy ecstasy users (+100 occasions lifetime), with a highly significant group effect ($p<0.001$).

Although the above results are suggestive of an association between ecstasy use and immune function, much more human research is required to investigate these associations further. In particular, there is a clear need to conduct prospective studies and to exclude possibly confounding factors.

7.2.3. Possible mechanisms of MDMA-induced immune modulation

There are a number of possible ways in which MDMA might affect the immune system. Firstly, MDMA might directly affect immune cells. Cells of the immune system are known to possess both dopamine and serotonin receptors[18] [19]. Indeed, serotonin may be required for normal immunological functioning[20]. Other effects may be mediated via the activation of the sympathetic nervous system with resultant release of epinephrine, norepinephrine and dopamine, along with the hypothalamic pituitary axis and its products such as corticosterone.

The mechanisms behind the lymphocytosis observed following acute MDMA administration were initially thought to be glucocorticoid-related, since in at least one experiment[21] an MDMA-induced reduction in circulating lymphocytes was only noted when corticosterone concentrations were elevated. In contrast, the decreased lymphocyte response to mitogen stimulation was observed with doses of MDMA that do not affect corticosterone levels[21]. Some authors have likened a number of MDMA's effects on the immune system to that induced by stress where corticosterone has been implicated[22].

7.2.4. Criticisms of published *in vitro* and *in vivo* tests

One weakness in many of the animal experiments is that small numbers of test animals, typically 6 to 10 animals, are used. Second, in some experiments only male rats or only female rats were used [7] [10] [21] [23-25]. This is a major limitation because there is some evidence of sex differences in

responses to MDMA in both rats and humans[26 27]. The same is the case for human trial data, where males have been used almost exclusively in most studies. In addition, the number of participants in human experimental groups have been as low as n=2, and as high as only 37 participants per group[5 12 28-30].

Polydrug use is another confounding factors affecting human MDMA research, since MDMA users are also likely to be users of other substances that may also affect immune responses (particularly alcohol and cannabis). One report comparing acute MDMA use alone versus MDMA in conjunction with ethanol found that the latter mix resulted in a greater immuno-suppressive effect than MDMA alone[30]. All these limitations mean that conclusions about the possible negative immunological consequences that MDMA may potentiate in humans cannot be made confidently[5].

7.2.5. External validity of MDMA animal models and *in vitro* testing

Multiple biologically active MDMA metabolites exist (resulting from hepatic metabolism), and exert their own influences *in vivo*. MDMA also reaches the circulation and persists for longer than 20 hours.[31] The results derived from *in vitro* testing (where hepatic processing is excluded and there are no metabolites) are therefore still useful, since *in vivo* the immune system is similarly exposed to MDMA.

The validity of animal models such as rats seems sound because similar urinary MDMA metabolites have been identified in rats and humans, suggesting that it is metabolised in similar metabolic pathways in the two species[32]. Despite differences between the immune systems of humans and other mammals, they remain valid test subjects (for an excellent review of this subject see [33]).

MDMA administration in laboratory animals is typically via intra peritoneal (IP) injection, whereas humans tend to ingest MDMA/ecstasy orally. It generally takes longer for a substance to reach the circulation via oral ingestion than by IP injection. Authors have noted this and IP doses of MDMA have been claimed to result in similar plasma concentrations of MDMA as seen in humans.[25]

As mentioned earlier, the studies discussed in this Chapter have all used MDMA. This is in contrast to "ecstasy" tablets used by humans that may contain varying amounts of MDMA along with adulterants such as methamphetamine, ketamine, pseudoephedrine,

paramethoxyamphetamine (PMA), LSD and caffeine (see Chapter 3). For the experiments discussed, 'laboratory grade' 3,4-methylenedioxy-N-methylamphetamine was used, not street derived 'ecstasy'. This limitation to the external validity of laboratory studies has been acknowledged by some authors[4].

7.3. Possible reproductive effects

In experimental studies involving rats, prenatal exposure to methamphetamine has been shown to affect myelination of the axons comprising the optic nerve[34]. It may also affect some aspects of maternal behaviour[35]. In humans, meth/amphetamine use during pregnancy has been associated with obstetric problems for the mothers, and prenatal methamphetamine exposure has been associated with structural and chemical brain abnormalities and decreased birth weight for babies[36 37]. Given the similarities between amphetamines and MDMA, and high rates of use among young women in their reproductive years, it seems reasonable to ask whether MDMA has adverse effects upon reproduction.

7.3.1. Results of animal studies with MDMA

Experiments examining MDMA's effects upon the rat young fall into two categories: research examining the effects of MDMA exposure *in utero* (*prenatal*) where the MDMA is given to the mother and crosses the placenta, and secondly, the effects of exposure after birth (*postnatal).*

There is conflicting evidence on MDMA's ability to affect the developing rat foetus in utero, with some researchers unable to find any effects of *in utero* exposure[38-40]. One hypothesis is that dopamine plays an important role in MDMA-induced neurotoxicity and the undeveloped dopaminergic system in the rat foetus protects it from any adverse effects[38]. Another suggestion is that the metabolism of MDMA differs in adult and foetal brains[40].

Others have documented both short and long term changes in rat offspring following exposure in utero. These include changes to dopaminergic and serotonergic functions that produce transient and long-term neurochemical and behavioural modifications and have significant long-term effects on cerebral function [41-43]. It has also been reported that early exposure *in utero* may result in more serotonergic and dopaminergic neurons being produced [44]. Studies have not suggested any elevation in miscarriage rates after prenatal MDMA exposure in rats[45].

The issue of whether any MDMA induced changes *in utero* are due to MDMA's direct action on the foetus or because of some indirect action MDMA has on the mother has not been concretely addressed. It is known that MDMA from the mother can be found in both the rat amniotic fluid and the brains of the unborn pups[46].

Exposure of newborn rat pups to MDMA in the period from birth till weaning has also been explored. Postnatal exposure to MDMA has been reported to produce behavioural and learning changes in rats[47] [48]. However, one group has reported that MDMA challenge at this stage leads to adult-based changes in thermal regulation and serotonin syndrome responses when challenged again with MDMA[49]. In contrast, differences were noted when MDMA was administered after this time period. Again, results have varied, with some researchers reporting deficits if MDMA was administered from day 11 onwards[50] [51].

7.3.2. Data from human studies

Studies of babies born to women who use MDMA have been inconclusive because of the small number of participants in these studies. Interpretation is complicated further because women who use MDMA during pregnancy also frequently use other drugs and differ from non-users in other important ways (e.g. access to antenatal care and diet during pregnancy), making it difficult to ascribe any observed deficits to MDMA (ecstasy) use specifically.

Data from one UK prospective cohort study was published in 1999 reporting on 127 women who were exposed to ecstasy during pregnancy (71 were exposed to ecstasy alone whilst 56 were polydrug users). It found that of 78 infants born, 12 had congenital abnormalities. This rate of 15.4% compared to the 2-3% usually expected. [45]

From the same study, a congenital deformity of the foot (normally occurring in a 3:1 male female ratio) was observed in 3 female babies, a rate of 38 in 1000 versus 1 in 1000 as would be expected in the general population. Congenital heart defects were observed in 2 babies (a rate of 26 in1000, compared to the normal expected rate of 5-10 in 1000)[45].

A separate prospective study of 49 pregnancies, noted one newborn with a congenital heart defect. The study concluded that the sample size was too small to draw any conclusions. Spontaneous abortions and malformations did not appear more frequently in pregnancies where ecstasy use was reported [52].

7.3.3. Limitations of existing research

Recent reports in this area appear to support the possibility that MDMA exposure results in measurable effects on rats exposed in the prenatal/perinatal/postnatal period[53] [54]. There are

limitations of the extent to which these findings may be extended to humans, however. First is the fact that rat and human foetal development are quite different. For example, rat pups between post natal days 11 to 20 have the equivalent brain development of a *pre natal* third trimester human foetus[55]. Second, there appears to be no universally accepted means of comparing MDMA doses between species[53 56]. Third, it is unclear how comparable the dosing *regimes* are between rat experiments and human studies, given the typically intermittent patterns of use in most human ecstasy users (Chapter 4). Finally, given the variable content of pills sold as ecstasy, young adults taking "ecstasy" may be ingesting varying amounts of MDMA (including none) along with other contaminants and adulterants.

There are also limitations of existing human research. There have been no studies of population based samples of women and no prospective studies assessing ecstasy use and later outcomes. This would be an important addition to the literature.

7.4. Conclusions

Acute MDMA use results in measurable immunological effects in animals and in vitro. Acute exposure to MDMA results in decreased numbers and functioning of circulating monocytes and lymphocytes and decreased/atypical levels of cytokine. Repeated doses over the short term prolong recovery. Given the redundancy of the immune system, and the current patterns of largely occasional use observed for many ecstasy users, the likelihood of serious immune effects from MDMA related-immunomodulation appears low.

The very limited clinical trial data available examining the combined effects of long term MDMA and cannabis use against cannabis or controls alone suggests that MDMA decreases levels of CD-4 T cells, NK cells and the ability to respond to PHA (a measurement of T cell functionality). However, there is insufficient longitudinal data to allow definitive conclusions about the use of MDMA and its immunological consequences in humans. Clearly, however, both *in vitro* and *in vivo* studies suggest that MDMA affects some of the primary and secondary components of the immune system that are involved in the initial response to infection and its longer term control.

With regard to the animal data, the reproductive effects, if any, of prenatal MDMA exposure in rats, are unclear. There is a growing evidence of a link between postnatal MDMA exposure and measurable deficits in the adult animal but the extent to which these effects are generalisable to the human female is uncertain. There is no published evidence that MDMA use effects male fertility either in experimental animals or humans. There is also no evidence that MDMA use affects ovulation or impairs conception in experimental animals or humans. Existing data have limited capacity to predict the *consequences* of MDMA use in humans given the lack of prospective studies and the lack of carefully designed studies of representative studies of females of childbearing age. Further research into these issues should be a priority.

7.5. References

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8. Is there an ecstasy (MDMA) dependence syndrome?

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8.1. Introduction

This chapter considers whether there is sufficient evidence to support the concept of an ecstasy dependence syndrome. Most people who use psychoactive substances do so without experiencing problems, but a minority of users experience difficulties controlling their use. Here, we begin by explaining the requirements for a valid psychiatric diagnosis, and discuss the concept of "drug dependence" and its theoretical basis. We then review the animal and human literature on the topic and discuss the issues arising from this literature.

The evidence for an MDMA dependence syndrome is the subject of debate[1] [2] for reasons that will become clearer in this Chapter. In the following sections, existing evidence on these aspects of the diagnosis of "ecstasy dependence" will be considered. Much of what is known about the natural history and course of ecstasy use careers is derived from cross-sectional convenience samples, and there remains a significant gap in current knowledge of this area.

8.2. What makes a valid psychiatric diagnostic entity?

It is useful to begin by outlining the features of what is considered a "valid" psychiatric diagnostic entity[3]. In most areas of medicine the underlying pathogens of disease are well understood and there are "gold standard" biological tests for the disease. This is not the case in psychiatry, where the mechanisms underlying psychiatric illness, although becoming clearer, are complex and relatively incompletely described and diagnosis depends upon the pattern of symptoms and behaviour reported by and observed in individuals.

A number of features have been proposed to characterise a valid psychiatric diagnosis[3-6]. These include that the diagnostic entity:

a) predicts a patient's prognosis (relative to someone who does not meet such diagnostic criteria);
b) is independent of other diagnoses;
c) predicts treatment response if the patient is treated for the disorder;
d) predicts the course over time; and
e) is related to neurobiology.

There is good evidence to support the validity of dependence syndromes for drugs such as alcohol and heroin. Indeed, the concept of "dependence" was developed from observations made by clinicians treating alcohol users who appeared to be suffering from alcohol-related harms that were related to, but importantly different from, impaired control over alcohol use itself.

8.3. What is "drug dependence"?

Most people who use psychoactive drugs do so without experiencing any problems, but some do develop problems related to their use[7] [8]. The conceptualisation and measurement of these problems has undergone considerable change over the past four decades, with the emergence of the concept of a substance "dependence syndrome", derived from Edwards and colleagues' work on alcohol dependence [9].

In 1977, Edwards and colleagues suggested that alcohol dependence could be conceptualised as a cluster of symptoms occurring in heavy drinkers that were distinguishable from alcohol-related problems[10]. Seven symptoms were regarded as major indicators of the alcohol dependence syndrome:

- Narrowing of the behavioural repertoire surrounding drug use taking behaviours;
- Salience of drinking (alcohol use given priority over other activities);
- Subjective awareness of a compulsion (experiencing loss of control over alcohol use, or an inability to stop using);
- Increased tolerance (using more alcohol to get the same effects, or finding that the same amount of alcohol has less effect);
- Repeated alcohol withdrawal symptoms (such as fatigue, sweating, diarrhoea, anxiety, trouble sleeping, tremors, stomach ache, headache, hallucinations, fever);
- Relief or avoidance of withdrawal symptoms by further drinking; and
- Rapid reinstatement of dependent drinking after abstinence.

These features can be seen to fall into the categories of behavioural indicators (e.g. salience of drinking and awareness of compulsion) and more neurobiological signs (e.g. tolerance and withdrawal). The concept of a dependence syndrome has since been extended to other drugs such as cannabis, tobacco, amphetamines, opioids and sedatives.

These diagnoses have been shown to have good validity in terms of predicting prognosis[11], treatment response and course over time. There is also supporting neurobiological evidence of a dependence syndrome for these drugs.

The most recent operationalisation of the dependence syndromes is in the DSM-IV[12] and ICD-10[13] classification systems[14]. These criteria are summarised in Table 8.1 and 8.2. Both systems

require a cluster of three or more indicators that a person experiences a loss of control over their drug use and/or physical or psychological cravings for a drug to avoid a dysphoric state.

Table 8.1: DSM-IV dependence criteria

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three or more of the following:

1. Tolerance, as defined by either:
    a. a need for markedly increased amounts of the substance to achieve intoxication or the desired effect;
    b. markedly diminished effect with continued use of the same amount of the substance;
2. Withdrawal, as manifested by either of the following:
    a. A characteristic withdrawal syndrome for the substance;
    b. The same or a closely related substance is used to relieve or avoid withdrawal symptoms;
3. the substance is taken in larger amounts of for a longer period than intended;
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use;
5. a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects;
6. important social, occupational or recreational activities are reduced or given up because of substance use;
7. substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

Source: American Psychiatric Association[12]

Table 8.2: Criteria for past year ICD-10 drug dependence

Three or more of the following present together at some time during the previous year:

- A strong desire or sense of compulsion to take the substance;
- Difficulties in controlling drug use in terms of its onset, termination, or levels of use;
- A physiological withdrawal state when substance use has ceased or has been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
- Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses;
- Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects;
- Continued use despite clear evidence of overtly harmful consequences.

Source: World Health Organization [13]

8.4. Theoretical models of drug dependence

Animal models of drug dependence have been developed. Different psychoactive substances certainly act in different ways upon the brain[15-19], but two major pathways in the brain have been implicated as common pathways upon which most drugs of dependence act[18 20 21]. These are the mesolimbic-frontocortical dopaminergic pathway (which extends from the ventral tegmental area (VTA) to the nucleus accumbens and prefrontal cortex) and the endogenous opioid receptor

system. Both acute and chronic use of multiple drugs including alcohol, opiates, nicotine, cannabinoids and amphetamines[22] affect the dopaminergic pathway.

8.4.1. Neuroadaptation

Neuroadaptation refers to changes in the brain that occur after repeated administration that oppose the acute effects of substance use in order to maintain homeostasis in brain systems and thereby maintain a level of brain functioning that is similar to its nondrug state. This may be of two types: *within-system adaptations*, where the changes occur at the site of the substance's action, and *between-system adaptations* which are changes in different mechanisms that are triggered by the substance's action. When substances are repeatedly administered, changes occur in the chemistry of the brain to oppose the substance's effects. When substance use is discontinued, the adaptations are no longer opposed; and hence the brain's homeostasis is disrupted[23 24].

According to this hypothesis, neuroadaptation explains the development of tolerance to the effects of a substance and the experience of withdrawal when substance use abruptly stops[23]. While traditionally, conceptualisations of substance dependence focused on physical withdrawal symptoms, such as diarrhoea or fever, contemporary formulations have emphasised more motivating psychological symptoms, such as dysphoria, depression, irritability and anxiety.

It has been hypothesised that these negative motivational symptoms are manifestations of neurobiological changes that signal "not only…the beginning of the development of dependence, but may also contribute to vulnerability to relapse and may also have motivational significance" (p.53)[18]. This approach hypothesises that after chronic substance use, changes occur in brain systems such as the dopamine reward system and the endogenous opioid system, which maintain substance use and make it difficult to cease use[18].

8.4.2. Behavioural models

Behavioural models of addiction focus on directly observable behaviour. One class of behavioural model concentrates upon the fact that behaviour is maintained (or made more likely) by the consequences (reinforcers) of such behaviour [25]. Drug self-administration is then an example of *instrumental behaviour* because the activities of persons (or animals in an experiment) are instrumental in obtaining the consequences (the substance's effects).

Research with animal subjects has shown that when many psychoactive drugs are available, drug-naïve animals will self-administer them, often to excess[26]. This finding has been replicated with many species of animal, using different drugs and a variety of routes of administration[16 26]. This observation has led to the development of the *operant reinforcement model* of substance use. Substances might be reinforcing in two general ways: through the direct effects of substances upon some sort of reinforcement system in the brain; or through their effects upon other reinforcers (such as social or sexual reinforcers, or through removing aversive stimuli such as distress or dysphoric moods) or behavioural effects (such as increased attention) [16].

Another group of behavioual theories use *classical conditioning* to explain the development and persistence of addictive behaviour [27 28]. According to *cue exposure theory*, cues for substance use are important in the development and maintenance of addictive behaviour [27 29]. A cue that has been present when substances were administered will be more likely to elicit a conditioned response (*cue reactivity*), which is thought to underlie craving. Cue reactivity may explain why someone who was dependent upon a substance but has been abstinent for some time experiences strong cravings when exposed to drug-related cues [27].

There are numerous other theories of the processes involved in the development of dependence[30 31], and it is clear that there is some interaction between the processes identified in the behavioural models and those in the neuroadaptation or neurobiological models of the development of dependence. The operationalisation of the dependence syndrome in the DSM-IV and ICD-10 includes both neuroadaptation and behavioural components. This takes into account that for some drug classes (and for some individuals) either aspect may be more prominent in the development of dependence.

8.5. Complicating Issues

As noted in Chapter 2, pills sold as "ecstasy" may not contain any MDMA at all. This means that persons developing regular or "dependent" use of the drug "ecstasy" may not always be taking MDMA. Although the importance of expectancies in the subjective experience of acute drug effects has been established, the way in which this might facilitate dependent use is as yet unexplored.

Related to this is the possibility that some (or many) pills sold as ecstasy may contain methamphetamine, not MDMA[32] (see Chapter 3). Regular users may therefore be developing dependence upon methamphetamine instead of, or as well as, MDMA. Previous research has attempted to control for the effects of other drug use, including methamphetamine[1 33], but this "other drug use" is what *users believed to be methamphetamine.*

8.6. Animal evidence on the dependence potential of MDMA

The first question that arises about the nature of the MDMA dependence syndrome is the extent to which there is evidence from animal models to support the dependence potential of MDMA. There is evidence that MDMA induces dopaminergic activity in the mesolimbic 'reward' pathway (Robeldo et al, 2004b), but that this is dampened by antagonistic neurotransmitter release in other parts of the reward system due to the drug's activity at serotonergic receptors [34]. Behavioural studies with rodents show that the drug is reinforcing using classical conditioning assessments such as conditioned place preference methods [35] . However, operant conditioning studies where animals need to work progressively harder to receive a dose of the drug show that MDMA is a less potent reinforcer of behaviour than cocaine or methamphetamine [36 37].

Similarly, typical physical or dysphoric signs of a physical dependence syndrome (such as withdrawal) do not develop in animals chronically treated with MDMA [38]; and there are neurobiological reasons why this may be the case. Together, animal studies to date have shown that although MDMA is rewarding, it may be less rewarding than other illicit drugs. As such, it may be the case that MDMA has weaker effects on biological reward systems, and hence the biological neuroadaptive responses to these actions may also be attenuated. This suggests that the course of "dependence" upon ecstasy may differ from other drugs of dependence such as opioids, where the disorder is often chronic, where users are at high risk of developing dependent use, and among whom demand for treatment for such use is high (e.g. [39]).

8.7. Evidence for an "ecstasy dependence" syndrome in humans

For many years, it was thought that it was not possible to become dependent upon ecstasy (MDMA)[40]. This might have been in part because some of the characteristic features of the classic drug dependence syndrome were not common among regular MDMA users. After ecstasy began to be used recreationally, most users used the drug irregularly, in quite specific contexts (e.g. nightclubs), use was time limited (e.g. confined to a weekend evening), and there was little injection of the drug (a route of administration often associated with dependence risk[41]).

As the prevalence of ecstasy use has increased over time in the general population[42] [43], some features of use have been documented that may reflect the development of problematic ecstasy use patterns. Now among regular ecstasy users in Australia, for example, some users report very frequent use[44], significant minorities report experimenting with injection of the drug[45], many users report "bingeing", i.e. using the drug continuously for more than 48 hours[44]. Use is also extending into a wide range of contexts, with the traditional nightclub environment now just one of many common use locations[44]. Users perceive risks[46] and harms[44] [47] associated with their ecstasy use. It is therefore perhaps not surprising that the literature on problematic and putatively dependent ecstasy use has expanded considerably since the mid 1990s.

8.7.1. Current diagnostic classification

In leading psychiatric diagnostic classification systems, there is no ecstasy dependence syndrome included, but it is possible to classify an ecstasy-dependent person as dependent upon hallucinogens and/or amphetamines[12]. This classification has important implications because the dependence syndrome described for each of these drug types differs both nosologically and empirically.

Amphetamine dependence includes a withdrawal syndrome as one of the criteria[12]. Amphetamine withdrawal symptoms include craving the drug, fatigue, psychological distress (irritability, depression, anxiety, disturbed sleep, and problems with concentration) and physical problems that may include sweating, decreased appetite, and body aches[48].

The DSM-IV diagnostic criteria for amphetamine dependence have been shown to be unifactorial[48], as are those for other drugs such as alcohol, opiates and cocaine[49]. There is now

good evidence for an amphetamine dependence syndrome[48 50 51], which typically occurs after a period of sustained regular use. Daily use is particularly risky[52 53], but weekly users are still at risk of developing dependence[54]. Dependence has been associated with mental health, physical, occupational, relationship, financial and legal problems[55-60].

Hallucinogen dependence does not include a withdrawal syndrome as one of the criteria[12]. Considerably less work has investigated the nature and validity of the hallucinogen syndrome. Existing evidence suggests that the syndrome is less severe than for amphetamines, and that hallucinogen dependence is not unifactorial, but conforms to a two-factor structure[61].

8.7.2. Case studies of ecstasy dependence

In 1999, Jansen reported three cases of ecstasy dependence in the literature[62]. Two cases involved persons who had access to large amounts of high purity MDMA, whose use escalated markedly as their tolerance to the effects grew, and for whom the costs of greater use did not present a problem)[62]. The third case involved escalating use by a person suffering from post-traumatic stress disorder (PTSD) who found that MDMA helped him overcome the emotional detachment that had been a core feature of his PTSD. He devoted increasingly large proportions of his income to fund purchase of the drug as his use became more frequent and tolerance increased[62].

Each of these individuals displayed key phenomena of drug dependence. They developed clear tolerance to the effects of the drug; they spent increasing amounts of time using and getting over the effects of using ecstasy; other activities were neglected; they perceived harms related to their use; they had attempted to cease use without success; and they reported mild withdrawal symptoms in the comedown period[62]. All three also had other drug use disorders and one had comorbid mental health problems.

Notably, in two of these cases, there was extremely ready access to the drug. For the other, the symptoms of a pre-existing psychiatric disorder may have played some role in increasing the initial rewarding effects of the drug.

8.7.3. Studies of "ecstasy dependence" among users

There have been a handful of studies examining "dependence" among ecstasy users. All of these have involved the use of interviews designed to measure dependence on different classes of drugs.

An early study[1] found that among a sample of 185 regular ecstasy users (median of 12 days (range 2-100) of use in the past six months), 64% had met criteria for lifetime ecstasy dependence, as assessed by the Composite International Diagnostic Interview (CIDI). Dependent persons typically met criteria for dependence during their heaviest use period. The frequency of such use was not necessarily high: during this heaviest period, 66% were using only one or two days per week, and 25% were using between one to three days per month[1]. Reported "withdrawal" symptoms were highly prevalent, leading the authors to observe the difficulty in distinguishing withdrawal symptoms from the sub-acute 'comedown' effect from dysphoria relating to the absence of the drug which is reversible on reinstatement of use[1].

Nonetheless, those who met criteria for dependence reported greater levels of financial, relationship and social problems; more anxieties about their drug use; higher levels of criminal behaviour; and higher health risk behaviours than those who were not dependent. Multivariate analyses found that these associations were not explained by other drug use[1].

A small US study using the CIDI to assess DSM-IV ecstasy dependence found that among 52 ecstasy users, 43% met criteria for lifetime dependence upon the drug[63]. No information on patterns of use or correlates was provided[63]. Very high self-reported rates of withdrawal symptoms (59%) and "continued use despite knowledge of harm" (63%) were found.

One Washington study of "rave" attendees using the CESAR Arrestee Drug Screener (CADS) found that 17% screened positively for probable ecstasy dependence[64]. Multivariate analyses found that sex, race and other drug use were the strongest predictors of ecstasy dependence[64].

A very small study of US university students who used ecstasy (n = 26) found that around half (n = 14) met criteria for ecstasy abuse or dependence[65]. Those meeting criteria for abuse or dependence reported more lifetime and past year occasions of use, as well as heavier use within each session; but those *without* a use disorder reported more frequent and heavier use in the past month[65].

A novel "ecological momentary assessment" design was used a in a recent study[66]. 22 regular ecstasy-using participants wore wristbands for six weeks and reported on drug use and craving regularly across the period. The researchers found that although craving for ecstasy was low

overall, craving for ecstasy increased over the 24 hours before use, and was higher on Friday nights before the weekends on which ecstasy was used compared to those Fridays when it was not[66].

A study of 200 Taiwanese juvenile justice detainees who used ecstasy (63% had used ecstasy 20 times) measured ecstasy "dependence" using the amphetamine dependence questions from the Kiddie epidemiologic version of the Schedule for Affective Disorders and Schizophrenia (K-SADS-E) [67]. They found that 22% met criteria for "dependence"; 36% reported no dependence symptoms. The most commonly reported dependence symptoms were continued use despite knowledge of problems (37%) and spending considerable time using and recovering from the effects of the drug (30%).

The largest study of dependence among ecstasy users thus far included 1,662 regular Australian users and examined the Severity of Dependence (SDS) [68]. The SDS is a five item self-report scale assessing compulsion to use a drug (the "psychological" component of dependence), with items relating to impaired control over drug taking, preoccupation with a given drug and anxieties about drug taking [53] [69]. Among those who screened positive for dependence upon ecstasy according to the SDS (18% of the sample), 49% used the drug once or twice per week; while 34% used just one to three times per month; only 2% of those who screened positive for ecstasy dependence (n = 7) were using it at least every second day [68]. Nonetheless, the reported financial, legal and work-related harms of ecstasy were more common among this group, as were sexual risk behaviours, overdose, and help seeking behaviours, compared to those who did not screen positively for dependence. Further stratified analyses suggested that, despite high levels of concurrent methamphetamine use, these associations were independent of problematic methamphetamine use.

A German study found that 16% of current ecstasy users met criteria for DSM-IV ecstasy dependence when assessed using a standardised assessment interviews to assess DSM-IV dependence[70]. Finally, a German population-based study of young adults, which assessed drug dependence using the CIDI, which found that small proportions of the young adult population in Germany (0.4%) met criteria for past year ecstasy/hallucinogen/stimulant dependence[71].

8.7.4. The structure of the ecstasy dependence syndrome

Two studies have examined the structure of the ecstasy dependence syndrome, both conducted in Australia. DSM-IV dependence criteria for ecstasy were examined by Topp et al (1997). A bi-

factorial structure was identified, with independent components defined as *'compulsive use'* (use despite problems, giving up important activities because of ecstasy, unsuccessful attempts to stop, withdrawal and excessive time spent obtaining or using) and *'escalating use'* (tolerance, and using more or for longer than intended).

In a 2008 study by Bruno and colleagues, the factor structure of the SDS applied to ecstasy was examined [68]. Multiple studies have shown that the SDS has good test-retest reliability, high internal consistency, and construct validity for opioids, cocaine and amphetamines [69]. The scale is unidimensional for opioids, amphetamine and cocaine and has high diagnostic utility in detecting DSM dependence [50 69 72 73]. In this study [68], dependence upon ecstasy did not have a unifactorial structure, but rather, two related factors provided a good fit to this data, which were defined as 'compulsive use' and 'escalating use'. The same factors were identified ten years earlier by Topp and colleagues using DSM-IV dependence syndrome items.

The two-dimensional structure of the dependence syndrome found in studies of ecstasy users, together with the findings from animal literature, could suggest that the biological basis for a dependence syndrome similar to other drugs, although attenuated, could be present, but that other issues, for example, behavioural reinforcements, may additionally play a strong role in the syndrome [68]. These findings, although limited to the context of users in one country, did comprise a very large (n = 1658) national sample of users; they certainly suggest that the continued classification of ecstasy dependence within the same diagnostic code as amphetamines is not warranted. There is debate as to the categorisation of ecstasy dependence in future revisions of the DSM [74] and evidence certainly suggests that a separate category may be warranted for ecstasy.

These findings carry two important implications. Firstly, the dependence syndrome does not appear to be of the same nature as for drugs such as alcohol, opioids and amphetamine, suggesting a different series of underlying causes, perhaps with a less clear biological basis; this is consistent with the mixed findings from animal research. Secondly, regardless of the nature of any dependence syndrome, some users clearly experience problems related to their use, which cause them distress, and for which they might request help.

8.7.5. The course of ecstasy dependence

Only one study has assessed the prognosis of persons who met diagnostic criteria for ecstasy dependence, using a structured diagnostic interview for DSM-IV[71]. This was a German

population-based study of young adults. The study had a mean follow up period of just over three years and ecstasy use and dependence were assessed each time. The researchers found that those meeting criteria for DSM-IV ecstasy dependence at baseline were highly likely to have remitted three years later – 93% were no longer dependent at follow up[71]. Of this 93%, 50% were no longer using the drug, and of the 43% still using, the majority did not meet criteria for a use disorder. The authors suggested that ecstasy dependence might constitute a "transient phenomenon"[71].

Returning to the criteria for a useful diagnostic entity outlined in Section 8.2, the transience of this syndrome suggests that in contrast to a valid clinical entity, "ecstasy dependence" as assessed in that survey failed to provide useful predictive information about course.

8.7.6. Treatment seeking for ecstasy-related problems

Some users do present for treatment because their ecstasy use has become problematic for them. Routine data collections in Australia[44 75] and the United States[76] have documented persons requesting treatment of their ecstasy use. In Australia, the numbers are very small (less than 1% of all episodes), considering the prevalence of MDMA use in the general population compared to heroin and cocaine use [42]. Ecstasy is more often noted as a secondary drug of concern[44]. This is consistent with surveys of ecstasy users, which consistently find that although some ecstasy users report concerns about their ecstasy use, treatment seeking is very low for this group[44 70].

One study of clients presenting for drug treatment in Texas, United States examined 38,350 treatment episodes between 1988-2003 for persons admitted with problems with so-called "club drugs" (e.g. ecstasy, GHB and ketamine) and compared them with users of alcohol or other drugs[76]. Club drug users were more impaired on five of six Addiction Severity Index (ASI) indices at admission, and they were more likely to have a broader range of heavier, polydrug use patterns. Treatment completion rates were higher for this group than alcohol or other drug clients. At follow-up 90 days after discharge, club drug users continued to report more ASI problems. The authors noted the higher levels of co-occurring mental health and other drug use problems for ecstasy users seeking treatment[76], suggesting that these problems might be more important drivers for presentation to treatment services.

The above data suffer significant limitations, and should not be taken to estimate treatment demand nor treatment need. A reliance on routine data collections to estimate treatment need presupposes that existing drug treatment systems are accessible to, known about, and attractive

to ecstasy users who are in need of help in addressing their drug use or the problems associated with this use. It is quite likely that existing treatment services that are oriented to persons with alcohol, opioid and stimulant drug problems are much less attractive to people with MDMA problems..

These data do suggest, however, that in contrast to alcohol and other drug clients, problematic use of ecstasy alone may be a less significant reason for entering treatment. Problems related to the use of other drugs and mental health may play more of a role in the presentation of MDMA users for treatment. Chapters 9 and 10 examine the evidence on comorbid drug use and mental disorders among ecstasy users.

8.8. Summary and implications

The beginning of this Chapter outlined the core features of a "valid" diagnostic entity, and evidence for those features has been reviewed for ecstasy. The evidence for an ecstasy dependence syndrome is limited in scope and by weak study designs. Animal evidence relevant to the topic suggests that MDMA may be a less potent reinforcer than other drugs but it does nonetheless have dependence potential. This suggests that a) the physiological basis of an ecstasy dependence syndrome might be relatively weaker in comparison to other drugs with very clear and marked dependence potential (e.g. opioids), and b) other factors related to the behavioural and psychological aspects of reward and dependence may make a relatively greater contribution for ecstasy than for other drugs of dependence.

Human evidence suggests that this is the case. Some people do report problems controlling and concern about their use, but the notable lack of case reports of severe tolerance or withdrawal syndromes in the literature suggests that physical features play a more limited role than psychological ones. Although tolerance has been reported, as has withdrawal, the existing literature is based on self-report and there is insufficient data to distinguish between the sub-acute effects of ecstasy intoxication and a "true" withdrawal syndrome. Controlled studies of withdrawal are required to investigate this further.

There is insufficient data to allow a rigorous evaluation of the validity of any "ecstasy dependence syndrome". Prospective studies are required to assess stability of the diagnosis over time, as are multi-method assessments of "dependence" that are not reliant on a single assessment method. Existing studies examining the structure of ecstasy dependence suggest that the nature of dependence upon ecstasy is different to drugs such as alcohol, methamphetamine and opioids. A two factor structure has been identified, as has been the case for hallucinogens, with factors reflecting "compulsive use" and "escalating use" factors.

Regardless of the nature of any MDMA dependence syndrome, there is clear evidence that some ecstasy users become concerned about their use. Although presentation for treatment of ecstasy use appears relatively uncommon compared to the prevalence of its use in the general population, it does occur. Much more study is required but evidence suggests that co-occurring drug use and mental health problems may play a role in presentation for treatment.

8.9. References

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9. Relationships between ecstasy use, the use of other drugs and mental disorders

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9.1. Introduction

This Chapter reviews the relationship or **comorbidity** between ecstasy use and the use of other licit and illicit drugs, and mental disorders. "Comorbidity" has been defined as "any distinct clinical entity that has co-existed or that may occur during the clinical course of a patient who has the index disease under study" (p.456-7)[1]. Within psychiatry, comorbidity is commonly used to refer to the overlap of two or more psychiatric disorders[2]. In this Chapter we will discuss comorbidity between ecstasy and other drug use, and between ecstasy use and mental health problems.

There are good reasons to examine links between ecstasy and other drug use problems or disorders. If they are likely to co-occur, this raises questions about the aetiology of the two types of drug use disorder. Prior to hypothesising about the mechanisms underlying comorbidity, patterns of comorbidity need to be carefully documented.

Ecstasy acutely affects mood as detailed in Chapter Five. One review of the literature has concluded that chronic, heavy use of ecstasy is associated with sleep disorders, depressed mood, persistent elevation of anxiety, impulsiveness and hostility[3]. If such associations exist, does ecstasy use play a causal role in the development of these disorders? Not all studies have found associations between ecstasy use and mental health[4 5] and most studies have been cross sectional.

If there is comorbidity between ecstasy and other drug use problems, and ecstasy use and mental disorders, this may have important implications for assessment and treatment. Persons with comorbid panic disorder and substance use disorders, for example, are more likely to have a chronic disorder, a higher risk of suicidal behaviour, and poorer social functioning[6]. There are also implications for public health policy: if two problems are likely to co-occur this has

implications for the types of service offered. Specifically, it means that drug treatment services for persons with problematic ecstasy use may also need to address comorbid drug use and mental health problems. This is particularly the case if persons with co-occurring drug use disorders have a worse clinical outcome than those with a single disorder.

9.2. Ecstasy use and other drug use

9.2.1. The prevalence of other drug use and related problems

In general, levels of both legal and illegal drug use are higher among people who use ecstasy[7]. This is not an unusual finding – typically, people who use any drug are more likely to also use other types of drugs (e.g.[8]). An association between the use of different kinds of drugs is one of the most consistent findings in epidemiological research on both legal and illegal drugs.

Some types of drug use are more strongly related to ecstasy use than others. One Australian study[7] found that the strength of the relationship between past year ecstasy use and other drug use differed across drug types. In samples of ecstasy users, there are consistently higher rates (compared to peers in the general population) of: cannabis use, other psychostimulant use, use of other "club drugs" such as ketamine and GHB, and heavier alcohol use. In contrast, ecstasy users are less likely than some other types of illicit drug users to report injecting drug use or the use of heroin.

It is important to note that most of the research to date on this issue has examined people who *use* (or have used) ecstasy. To date, there has been little evaluation of other drug use among people who meet criteria for ecstasy use *disorders* or *dependence.* As discussed in Chapter 8, some ecstasy users do report that they are concerned about their use and report problems related to their use. The structure of any ecstasy dependence syndrome, however, seems to be qualitatively different from more "classic" drugs of dependence such as opioids and alcohol. "Problem" users of ecstasy use this drug much less frequently and heavily (even among those who meet "dependence" criteria) than those who develop dependence on drugs such as alcohol and heroin. The disorder may also be more transient. Animal and human evidence suggests that the psychological aspects may feature more prominently for ecstasy (see Chapter 8). This is important when considering the relationship between ecstasy use and other drug use because it suggests a more limited role for biological factors and a greater role for psychological and social aspects that are thought to underlie relationships between other sorts of drug use[9].

9.2.2. Patterns of other drug use

Ecstasy users are typically polydrug users. Use has been associated with the "party" and nightclub scenes, so many other drugs associated with such scenes tend to be commonly used by this group. A study conducted in the US found that among current ecstasy users, 91.3% used at least one additional illicit drug in the past year, while 66.5% used at least two additional drugs and 44.3% used at least three additional drugs. The most commonly used drug was cannabis (97.7%) followed by cocaine (52.6%). In comparison to former ecstasy users and other illicit drug users, current ecstasy users were the group most likely to have used alcohol (98.4%) and to have engaged in binge drinking (62.3%) in the past year. Further, current ecstasy use was associated with alcohol abuse and dependence[10].

In Australia, almost all (94%) of the ecstasy users interviewed in the 2007 national EDRS reported that they "usually" used other drugs with ecstasy (i.e. at least two thirds of the time)[11]. Alcohol and tobacco were the drugs that were most commonly used with ecstasy and heavy alcohol use was common, with 77% of those who reported drinking alcohol when taking ecstasy reportedly drinking more than five standard drinks. Nearly half typically used cannabis (46%) and methamphetamine (44%) with ecstasy. Smaller proportions typically used cocaine (13%), LSD (7%) and nitrous oxide (5%). Fewer than 5% nominated GHB, ketamine, amyl nitrate and MDA as drugs they usually used with ecstasy. The majority of ecstasy users (82%) also reported that they "usually" used other drugs to 'come down' (recovery period) from ecstasy. Cannabis (67%), tobacco (56%) and alcohol (49%) use were the most commonly reported, with nearly three quarters of those who reported alcohol use when coming down, reporting drinking more than five standard drinks[11].

Some researchers have investigated whether there are different classes of ecstasy users, and if ecstasy use is related to increased other drug use within drug use episodes. One US study examined polydrug use among ecstasy users using a latent class analytic approach, which aimed to identify clusters of different patterns or extent of polydrug use[12]**.** A three-class model resulted, and reflected the extent of other drug use rather than particular patterns or types of other drug use among ecstasy users. The authors identified these groups as "Limited range," "Moderate range," and "Wide range" drug use patterns. Predictors of group membership were examined using a multinomial logit model: those who were younger, white and who had more extensive ecstasy use were more likely to be in the "Wide range"[12].

Another study used ecological momentary assessment methods to examine patterns and contexts of ecstasy use with other drug use[13]. The researchers gave wrist actigraph/data recorders to 22

participants to record real-time drug use and ecstasy craving for 6 weeks. Rates of alcohol and other drug use on nights when ecstasy was used were compared with non-use nights; as well as before, during, and after ecstasy use; using generalized estimation equations (GEE). Approximately 70% of ecstasy use episodes occurred on Friday or Saturday nights. No other drug was significantly more likely to be used on ecstasy use nights than comparison nights. On nights when ecstasy was used, other drugs were more likely to be used before or during ecstasy intoxication, but not after ecstasy intoxication[13]. The authors concluded that ecstasy use was not associated with increased other drug use, but formed part of a so-called "natural history" of drug use across an evening that began with alcohol and progressed to a complex pattern of polydrug use[13].

9.2.3. Is ecstasy becoming a "gateway" drug?

There has been considerable debate about the significance of what has often been referred to as the "gateway effect" of cannabis use. This describes a consistently observed temporal ordering of progression to polydrug use observed among young people in many developed societies including Australia, Canada, New Zealand and the USA. Typically, drug use begins with tobacco and alcohol use in early adolescence, with those who begin to use these drugs at an early age and who become regular users being more likely to use cannabis in their mid teens. Those who become regular cannabis users are, in turn, more likely than their peers to use other so-called "harder" illicit drugs such as cocaine and heroin[14-17].

Most discussions of the gateway effect have focused on the explanation of the strong predictive association between cannabis and other illicit drug use. There has been a debate about whether this relationship is causal or whether it reflects the role of other confounding factors (such as a personal or genetic liability to use intoxicating substances)[15 17-22]. The increased availability of ecstasy and related drugs has provided an opportunity to use another class of illicit drugs that has been taken up by more young people than have harder drugs like heroin, including heavier cannabis using young people. It raises the question: does the use of ecstasy and other party drugs increase the likelihood of young people using other illicit drugs, such as the ATS, cocaine, hallucinogens, benzodiazepines and opioids?

Using data from the 2002-2003 US National Survey on Drug Use and Health, Martins and colleagues analysed results for participants aged 12 to 21 years in relation to drug use pathways[23]. The main finding of the study was that the pathways from earlier ecstasy initiation to subsequent cocaine and heroin initiation were stronger than pathways in the opposite direction. In contrast,

the pathway from earlier cannabis initiation to subsequent ecstasy initiation was stronger than the pathway in the opposite direction. Thus, while cannabis may predict subsequent ecstasy use, it is possible that ecstasy use is associated with subsequent illicit drug use[23].

Cross-sectional studies of ecstasy users in most developed countries typically find a pattern of progression from regular ecstasy use to greater levels of use of many of these illicit drugs (with the exception of the opioids)[24]. However, a causal role for ecstasy use is not the only possible explanation of this pattern of drug involvement. It can obviously reflect factors such as drug availability in the dance party setting, less social disapproval of the use of these drugs, and the higher prevalence of their use in the "party drug" using population. Some types of illicit drug use are significantly more common in more recent birth cohorts, reflecting increased drug availability over time and changing social norms surrounding their use in younger populations. It is perhaps not surprising, then, that in recent years with the increased prevalence of ecstasy use, the concept of "gateway drug" has been applied to ecstasy[25].

9.2.4. Possible explanations of associations between ecstasy and other illicit drugs

The challenges in assessing whether MDMA is a gateway drug for other illicit drugs are much the same as those involved in assessing the possible gateway role of cannabis, namely, distinguishing among a number of plausible ways in which ecstasy use and other illicit drug use may be related. These could include the following possibilities: (1) The relationship could be "causal" in the strong pharmacological sense that there is something about the biological effects of MDMA on brain function that makes it much more likely that MDMA users will use other illicit drugs; (2) the relationship could be causal in a weaker, sociological sense that using a drug in social settings where other illicit drugs are more readily available and where social norms are more approving of other illicit drug use, facilitates the use of these other illicit drugs; (3) the relationship may not be causal but may instead arise from shared personal factors that make people more likely to use both MDMA and other illicit drugs[18].

There has been very little prospective research conducted on patterns of involvement with ecstasy and other illicit drug use, but the existing research is briefly summarised below. One study of "recent-onset" ecstasy use in the US National Survey on Drug Use and Health found that recent onset users were more likely to be heavily involved in drug dealing and other drug use. The authors concluded that initiation of ecstasy use might be one indicator of involvement in more deviant behaviour among young people[26]. Another study found that the age of onset of

ecstasy use influenced the initiation of cocaine and methamphetamine use, but not heroin use[25]. Further, one study of ecstasy users found that reductions in ecstasy use were associated with reductions in other drug use[27]. These findings, although based on a very limited number of studies concentrated in North America, suggest that there may be discrete patterns of co-occurring drug use with a stronger tendency for ecstasy to be associated with other stimulant drugs, rather than the opioids. This is consistent with cross-sectional research examining patterns of recent and concomitant drug use among people who use ecstasy (e.g. [28]).

9.3. Does ecstasy use cause depression?

The relationship between ecstasy use and depression is of understandable concern. Persons with co-occurring mood disorders and substance use disorders may have a greater chance of experiencing a recurring mood disorder [29] [30] and attempting suicide[31]. Young people with depressive symptoms may be attracted to using a drug like ecstasy that produces euphoric effects and feelings of improved well-being and closeness to others; those with a predisposition to depression may experience more adverse outcomes from ecstasy use. Many ecstasy users report symptoms of depression in the sub-acute phase of MDMA use. Further, animal studies suggest that MDMA has effects on neurotransmitter systems involved in mood disorders (namely, serotonin and dopamine) (see Chapters 5 and 6).

9.3.1. Biological plausibility

The proposed neurobiological explanation for the association between ecstasy use and depression arises from evidence of post-acute and longer-term decreases in serotonin levels in the central nervous system following use of ecstasy in humans[32]. Persons with mood disorders are likely to have differences in monoamine neurotransmitter function. Reduced serotonin function has been hypothesised to play a significant part in depression, since medications that deplete serotonin may cause depression, and the majority of antidepressant medications appear to work by increasing levels of serotonin in the brain[33-36]. Reduced norepinephrine function has also been hypothesised to be involved in the pathogenesis of depression[33]. Norepinephrine reuptake inhibitors are effective treatments for depression[37]; and depressed persons have reduced norepinephrine function[38]. This is consistent with what is known of the serotonergic and noradrenergic pathways, which are thought to project to systems involved with mood mediation, appetite, sleep and aggression[36] [39].

The interaction between biological factors that may predispose some individuals to depression and external factors, such as drug use, may be understood according to a stress–diathesis model. Parrott (2006) has applied this model as a framework for understanding the association between ecstasy use and neuropsychobiological deficits[40]. Essentially, a multifactorial view is adopted, whereby consumption of ecstasy and other drugs interacts with predisposing variables, such as genetics, personality and neurochemistry, to determine the psychiatric consequence.

9.3.1. Depressive symptoms among ecstasy users

The acute effects of ecstasy (see Chapter 6) include a number of positive effects upon mood, namely, elevated or improved mood, euphoria, a sense of intimacy and closeness to others, shortly after taking the drug[41-48]. These are among the most commonly reported reasons why users take the drug[49].

Controlled experimental studies with humans have found that participants report significantly enhanced mood, a greater sense of well-being and thought disorder during the peak effects of MDMA[50-53] and studies involving standardised assessment of mood and anxiety problems do *not* show elevated symptomatology[54 55] during this period of intoxication.

The sub-acute or "comedown" period has also been studied and users often report low mood and/or poor concentration during this period (see chapter 5) [45 48 50 56]. One study found that older users were more likely to report low mood during this period[45]. Other sub-acute effects commonly experienced by users include energy loss, irritability, muscle aches, loss of appetite and trouble sleeping [45 50 57]. Increased suicidal ideation has also been reported during this sub-acute period. In one small study 8% (n=26) of participants reported suicidal thoughts[57].

A US study found that there was no difference between current ecstasy users and non-illicit drug users in the prevalence of current major depression[10]. However, *former* ecstasy users (no use in past 12 months) were more likely than non-illicit drug users to have a current mood disorder and current major depression. The authors suggested that although current ecstasy users may experience some symptoms of depression, the effects of ecstasy in the development of a clinical depressive disorder may be delayed[10].

Ecstasy use has repeatedly been associated with significant depressive symptoms[5 58-60], however recent meta-analysis of studies investigating depressive symptoms in recreational ecstasy users found a small association, considered clinically irrelevant[61]. Some studies have found no evidence of increased depressive symptomatology among ecstasy users[5 62] or found evidence for anxiety but not depression[63 64]. A recent examination involving Australian regular ecstasy users examined multiple patterns and features of ecstasy use, including frequency of use, amounts used and length of use career. No pattern of ecstasy use was independently associated with depressive symptoms after controlling for known correlates of depression and for other drug use, particularly cannabis[65].

Some[63 66 67] but not all[65] studies have found evidence of a dose-response relationship between ecstasy use and symptoms of depression. However, there are significant issues with the body of work conducted to date, which limit our capacity to draw conclusions about the nature, if any, of this association. The definition of exposure to ecstasy use has often been arbitrary and based upon retrospective reports of total lifetime consumption, with few standard ways of defining the extent of use[68-70], or standardised methods of describing or constructing control groups in ways that mean the groups differ only on ecstasy use behaviours[58 63]. Furthermore, although ecstasy users are typically characterised as polydrug users, many studies have failed to control for other drug use by study participants[61]. Studies that do account for other drug use have often found that the relationship between ecstasy use and psychological distress is attenuated or eliminated entirely after controlling for other drug use, particularly cannabis use [62 65 66 71 72]. Finally, few studies have adequately controlled for known biological and psychosocial risk factors for depression; these predisposing factors may explain the observed association between ecstasy use and depressed mood, and/or may interact with ecstasy and other drug use to predispose some ecstasy users to poorer mental health outcomes[40].

Despite considerable interest in the role of ecstasy in depression, few studies have examined comorbid depression among people with current ecstasy use disorders. One study found that "problematic" ecstasy users (who self-reported that ecstasy use had caused them difficulties) had significantly higher scores on somatisation, depression, and negative psychobiological symptoms as assessed on the BSI[60]. They also had higher levels of self-reported personal and family histories of psychiatric disorders than controls and non-problematic ecstasy users[60].

In summary, the evidence for a causal link between ecstasy use and depression is very mixed. Studies to date have been poorly suited to addressing questions of causality. There is evidence to suggest that persons with pre-existing vulnerabilities, who engage in heavier and riskier drug use in general, are at higher risk of mood problems. Future research needs to carefully evaluate whether ecstasy use per se is related to such mood problems.

9.4. Does ecstasy use cause anxiety?

The term "anxiety disorder" refers to a range of psychological disorders in which the experience of excessive anxiety is a central feature. This excessive anxiety may constitute repeated episodes of intense fear that have a fast onset with a relatively short duration (as in the case of panic disorder), or it may consist of a much more pervasive, persistent and less well-defined state of constant uneasiness, worry and anxiety (such as generalised anxiety disorder). The DSM-IV distinguishes between multiple types of anxiety disorder, such as post-traumatic stress disorder, panic disorder, agoraphobia, social phobia, generalised anxiety disorder (GAD) and specific phobias[73].

9.4.1. Biological plausibility

As reviewed earlier in this monograph, MDMA has effects on multiple neurotransmitters, many of which have been implicated in anxiety and anxiety disorders. There has been considerable discussion of the causal role of alterations in neurotransmitter function among persons with anxiety disorders. It has been argued that serotonergic projections to different areas of the brain are involved in responses to future threats (the dopaminergic structures extending to the frontal cortex and corpus striatum) and to acute events (the brain stem)[35]. Dysfunctions in these two systems have been proposed as explanations for GAD and panic disorder, respectively[35]. These hypotheses are supported by evidence that serotonergic function is altered among persons with GAD[35 74] and evidence that overactivity of the serotonergic system is involved in many anxiety disorders[75 76]. Others have argued that disturbances in dopamine, norepinephrine and GABA function all play a part in anxiety disturbances[76]. Given the wide range of psychiatric problems for which serotonin reuptake inhibitors are effective, Petty and colleagues have argued that serotonin assists in returning the mind to its homeostatic set point[76].

9.4.2. Evidence from animal experimental studies

As discussed in Chapter 5, MDMA has been found in animals to have long term effects upon anxiety-related behaviours[77 78]. MDMA pre-treated rats have been found to have reduced social interaction compared to controls 8–10 weeks after drug administration. MDMA pre-treated rats also take longer to emerge into a novel open field, and show less exploration and rearing in that open field. This provides some evidence for a long-term anxiogenic effect of MDMA, albeit only in some rat strains (see Chapter 5 for more detail).

9.4.3. Anxiety symptoms

As noted in Chapters 5 and 6, symptoms of anxiety[4 59], irritability[47 53 57 79] and fear [46 47 57 42 45 79 80] have been reported as acute effects of ecstasy. Some of the sub-acute effects experienced by users also include irritability [45 50 57].

A few studies have examined the reverse association, namely whether anxiety is related to later ecstasy use. One prospective study found that children who had higher levels of anxiety in childhood were *more* likely to begin ecstasy use in young adulthood[81]. By contrast, an Australia birth cohort study, which controlled for a range of socio-economic and familial risk factors, found no evidence of a link between childhood internalising symptoms (anxiety or depression) and later ecstasy use[82]. Instead, they found a non-specific pathway from early deviant behaviour to later ecstasy use disorders, mediated by experimentation with licit drugs in adolescence. The authors concluded that pathways to ecstasy use in adulthood may differ little from those for other illicit drugs.

Another study examined "problematic" ecstasy users compared with non-problematic ecstasy users, polydrug controls and drug naïve controls on patterns of drug use, psychiatric history and on the Brief Symptom Inventory (BSI)[83]. Problematic users had heavier and earlier onset patterns of ecstasy use, and had significantly elevated anxiety scores compared with non-problematic ecstasy users (who did not differ from polydrug or illegal drug-naïve controls). Problematic ecstasy users were also more likely to have a family psychiatric history than all other groups[83]. The authors concluded that their results suggested that there were distinct groups of ecstasy users, one of whom had little evidence of family or personal history of psychiatric problems, and another group who may have a vulnerability to multiple types of mental health problems[83]. This

pre-existing vulnerability may be compounded by (additive to), or interact with, ecstasy and other drug use to elevate anxiety symptomatology

9.4.4. Anxiety disorders

The previously cited US study[10] also investigated the occurrence of anxiety disorders among current ecstasy users (use in past 12 months), former ecstasy users (use prior to past 12 months), other illicit drug users and non-illicit drug users. Although the authors did not control for other drug use in the ecstasy using groups, they concluded that current ecstasy users were more likely to have a current anxiety disorder, specifically panic disorder and specific phobia, than non-illicit drug users. This finding concurs with case reports of panic disorders following the use of large amounts of ecstasy, which constitute the primary evidence linking ecstasy use with anxiety disorders. There have been similar reports after the use of other stimulant drugs such as cocaine[84]. In total, there are nine case reports of "panic attacks" or "panic disorder" in the literature.

One study reported three cases of apparent ecstasy-precipitated panic disorder[85]. These cases were attributed to ecstasy use because the three patients' panic disorder began during recreational use of ecstasy and continued after cessation of the drug. All three patients responded well to serotonergic antidepressant drugs[85].

McCann and Ricaurte described two patients with prior depressive states who experienced panic attacks after ingestion of high doses of MDMA on a single occasion[86]. Another case series reported the acute experiences of three persons who appeared to have quite marked negative acute anxiety symptoms. The authors described these as "panic attacks" but none persisted beyond the acute period[87].

Another case report concerned a young man who had used large amounts of ecstasy, which had co-occurred with the emergence of psychiatric problems[88]. These problems did not cease following cessation of ecstasy use and "phobic anxiety" remained[88]. The authors attributed this anxiety disorder to the man's ecstasy use[88].

Little research has examined anxiety disorders and their association with ecstasy use among larger samples of ecstasy users. As with other association studies, however, there is limited capacity to draw conclusions about the nature of the mechanism underlying the association. Cross-sectional studies are poorly suited to addressing questions of causality.

Three points seem important here: first, the number of cases in the literature is very small given the large number of people using ecstasy worldwide; second, in the cases noted above,, the effects seemed to either respond extremely well to medication or pass once the period of intoxication passed; and third, in many cases there appeared to be a vulnerability to, or evidence of, prior mental health problems that may have placed these users at increased risk of an anxiety disorder. If ecstasy does produce anxiety disorders these appear to be rare; it seems most likely that if they do occur it is among individuals with pre-existing vulnerability to these disorders.

9.5. Does ecstasy use cause psychotic symptoms?

High doses of potent stimulants such as cocaine and methamphetamine can induce a transient psychotic disorder, the symptoms of which resemble those of psychotic illnesses such as paranoid schizophrenia[89-94]. Symptoms include: mood swings, hallucinations, paranoid delusions, paranoia, panic, impulsivity, and aggression and violence[92-95]. One multi-country study found that among those hospitalised for methamphetamine-induced psychosis, the most common symptoms were auditory hallucinations, strange or unusual beliefs, and "thought reading"[96].

Methamphetamine psychosis often follows a period of recurrent heavy or "binge" use of the drug, which may include escalating doses across use episodes[97]. Psychotic symptoms have been linked to blood levels of the drug[98], with decreasing blood levels typically leading to a reduction in psychotic symptoms[99]; some psychotic symptoms may be experienced by persons vulnerable to psychosis at relatively low blood levels[100-102]. In some countries, the use of crystal methamphetamine, a particularly potent amphetamine, has received attention because of its relationship to methamphetamine-induced psychosis[103-105].

There is extremely limited data on the possibility that chronic use of high doses of ecstasy (MDMA) might induce psychotic symptoms. Two small studies have been published examining this issue, both of which were limited in their capacity to draw conclusions about the nature of any relationship between ecstasy use and psychotic symptoms.

One case report described a man who became aggressive and experienced a "psychotic episode" after consuming ecstasy[106]. One small study followed up 32 patients six months after they were admitted for inpatient treatment after "ecstasy-related hallucinatory-delusive manifestations" and diagnosed as having an "ecstasy-induced psychotic disorder" according to DSM-IV criteria[107]. At

the baseline assessment, severe psychotic symptoms were observed, but these subsided following treatment. The most severe symptoms had remitted by three months after prescription of olanzapine[107].

9.6. Limitations of existing research

9.6.1. Study designs

The research to date has been poorly designed to assess whether ecstasy use co-occurs with other drug use and mental disorders, and how strong any association might be. There has been a reliance on convenience samples of ecstasy users, and upon cross-sectional study designs that do not follow users over time. In order to more confidently draw conclusions about any causal relationship between ecstasy use and mental illness, longitudinal studies will be necessary.

Population-based research on comorbidity is very important because it allows us to distinguish between "artefactual" comorbidity and "true" comorbidity[108]. *Artefactual* comorbidity is comorbidity that arises because of the ways in which samples are selected or the behaviour is conceptualised, measured and classified. *True* comorbidity refers to the actual co-occurrence of two separate conditions at a rate higher than expected by chance.

There are a number of reasons, related to sampling biases, why artefactual comorbidity is more likely in research with clinical populations. The first is Berkson's bias[109], which has been shown to occur in real life settings[110]. This refers to the fact that if a person has two problems at a given point in time, then they are more likely to receive treatment simply because there are two separate disorders for which the person might seek help. The second reason has been called a clinical bias [111]. This refers to the fact that persons who have two disorders may be more likely to seek treatment *because* they have two disorders. Again, this source of bias has been demonstrated empirically[111]. Third, referral biases may exist, whereby some persons will be referred for treatment because of other background factors, such as having a family history of psychopathology. This may make it more likely that persons who are so referred will have a number of different mental health problems[108].

All these biases have probably contributed to variations in the prevalence estimates of comorbid drug use and mental disorders between studies. Hence, while research with clinical populations or convenience samples provides important information about disorder patterns among persons in treatment or who identify as having used ecstasy, they may provide misleading information on how often disorders co-occur in the *general* population of ecstasy users. Such information is

crucial if we are to: assess the treatment needs of the population in general who have problems related to their ecstasy use (whether or not they are currently in contact with treatment services); investigate common factors that may explain the co-occurrence of different mental health problems; and estimate the public health significance of comorbid mental health problems in the general population.

In order to address these issues we need to study patterns of comorbidity in representative samples of the general population. In such samples, the biases that may affect clinical samples do not exist, so observed patterns better reflect general relationships between mental health problems.

9.6.2. Measurement of ecstasy use

Studies examining associations between ecstasy use and mental health have rarely examined in detail the patterns of ecstasy use involved; nor have they typically assessed heavy recent use. Many studies define "ecstasy users" as those having used only a few times during their life. Greater attention needs to be paid to patterns and frequency of ecstasy use in future studies.

9.1.1. Measurement of and control for common factors

Although ecstasy users are typically characterised as polydrug users[7 112 113], most studies of the relationship between ecstasy use and mental disorders have not controlled for the concomitant use of other drugs[61]. Failure to account for use of other drugs makes it difficult to relate findings to one specific drug, particularly given the possible synergistic action of substances like the amphetamines, cocaine and cannabis[113]. Studies that have controlled for other drug use have often found that the relationship between ecstasy use and psychological problems is no longer significant. This has been particularly so after controlling for cannabis use[3 62 66 71 114].

Cannabis often accounts for the associations with anxiety, depression and psychotic symptoms. One longitudinal study found that both cross-sectionally and longitudinally, depression among ecstasy users was primarily associated with their cannabis use[62]. Anxiety, depression and executive dysfunction were examined according to lifetime and past year ecstasy use in a sample of participants with a wide range of ecstasy use[115]; depressive symptoms were found to be related to past year cannabis use[116].

9.7. Summary

An examination of patterns of comorbidity between ecstasy use and mental health is important for a number of reasons. First, it can provide important information about the aetiology of these different disorders. If disorders are likely to co-occur, then it could be the case that there is some causal or other relationship between the two disorders that explains this co-occurrence. Second, it can give important indicators about likely treatment needs of persons with substance use problems. This is important both on a general, service provision level, as well as on an individual, clinical level.

It is biologically plausible that a drug which affects mood and catecholamines might be especially attractive to people with depression, and or that when used chronically, may produce or exacerbate depressive symptoms. The same is true for psychotic symptoms, given the propensity for other drugs in its class to do so. Case studies are suggestive of these outcomes but comprise weak evidence. What is needed are longitudinal studies that measure pre-existing vulnerability to these disorders and that properly control for the effects of other drugs that are used; especially by heavier ecstasy users, viz cannabis, ATS and cocaine.

One of the most important requirements for any study of comorbidity is the need to avoid the significant biases that affect studies of comorbidity in clinical samples. It is important to use general population samples to ensure that these biases are avoided. Only then can questions of aetiology and treatment begin to be answered. To date, the research on the relationship between ecstasy use and mental health has been almost entirely based on convenience samples of ecstasy users. For further advances to be made in this area there needs to be a concerted effort to conduct population-based and longitudinal research into relationships between ecstasy use, mental health and other important variables in order to shed further light on this topic.

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10.The effects of ecstasy use upon cognitive functioning

Edmund Silins

10.1. Introduction

Cognitive deficits have been reported in ecstasy users. These range from deficits in memory to impairments in executive functioning. Poorer memory performance has been associated with heavier patterns of use, with some cognitive deficits enduring after the acute effects of ecstasy have worn off. There have been conflicting findings: some studies have demonstrated subtle cognitive deficits among ecstasy users; others have found deficits on only a few measures of functioning; others still have found deficits only among some groups of users or not found deficits at all.

This issue is a complex one to investigate, given the multitude of factors that should be taken into consideration when assessing 'changes' among those using ecstasy, or when comparing 'relative' cognitive functioning among those who have used the drug and those who have not.

This chapter reviews the different kinds of studies that have attempted to shed light on this question. It also considers the possible mechanisms through which MDMA may affect functioning and summarises some of the key research areas that have been given attention in recent years.

10.2. Associations between ecstasy use and cognitive functioning in humans

10.2.1. Memory and learning deficits

Deficits in memory and learning performance have been demonstrated in numerous cross-sectional studies of ecstasy users[1-14]. Such findings have not been universal: some investigators have reported no differences in memory and learning between ecstasy users and controls[15-18]. Recent studies with larger samples of current and former users[19,20,21], and the first longitudinal studies now being published[22-26] have produced conflicting results. This area of work is considered below.

Verbal memory

In tests of verbal memory, subjects typically have to memorise a section of prose or a multiple series of words in a number of learning trials (i.e. supraspan word lists). Immediate recall is tested after each trial and delayed recall is measured after a set time period (e.g. 20 minutes).

Cross-sectional studies, typically relaying on 'case-control' designs, where ecstasy users are compared to a 'control' group, have found that ecstasy users are significnalty impaired on a range of verbal memory tasks[1,2,20,27-30,8,31,32,33]. Longitudinal investigations have also found an association between ecstasy use and the subtle decline of verbal memory[22,26].
Whilst several other studies have found that ecstasy use had no significant effect on verbal memory[4,10,15,16,34].

There is some evidence that it may be drug use in general, rather than ecstasy use per se, which leads to impairments as a tendency for impaired verbal learning and memory has been found in both current ecstasy users and polydrug controls[21].

In a unique study, Cole et al (2006) tested ecstasy and non-ecstasy using polysubstance users on a variety of cognitive tests after exposure to information about the long-term effects of ecstasy which either stated that ecstasy caused memory loss or that it did not. Ecstasy users who had been primed with information that ecstasy did not cause cognitive deficits performed better than the other groups on a (delayed) verbal memory recall task[35].

Visual memory

Fewer studies of ecstasy users have reported deficits in visual memory; the ability to recall images or objects that they have been shown. Nevertheless, deficits in visual memory have been reported among ecstasy users[1,36,37], and these appear to be associated with the extent of ecstasy use[27]. Other studies, however, have failed to demonstrate an effect of ecstasy on visual memory [7,16,20,36], or were inconclusive[12].

A component of visual memory is spatial memory, which is typically assessed by performance for complex visual arrangements consisting of geometric figures. A single dose of ecstasy was found to impair spatial memory during acute intoxication, but the effects were not detectable 25 hours later[38]. Other findings suggest that the effects of ecstasy on spatial memory may be more enduring[39]. In contrast, spatial memory has also been found to be unaffected by ecstasy exposure[40,41].

Prospective memory

Prospective memory can be characterised as 'remembering to do something at some future point in time'. Numerous cross-sectional studies have demonstrated that ecstasy users are significantly more impaired on prospective memory tasks than non-users[11,42-45]. Longitudinal studies, however, have found that performance in prospective memory tests did not decline with continued use[22].

Executive function

Executive function is thought to be the core process controlling working memory[46]. It is used when planning, organising, strategising and paying attention to details. In some cases, problems with executive function can lead to learning difficulties.

Numerous studies have demonstrated associations between subtle deficits in executive function and ecstasy use[13,16,20,47-53,50,54]. In some investigations, increased ecstasy use correlated with greater impairment[15,41,51]. There is, however, emerging evidence that the deficits associated with ecstasy may also be associated with the concomitant use of other substances, in particular cannabis[37,55,56]. On the other hand, some studies have found no evidence of executive impairment in chronic ecstasy users[5], even when controlling for non-ecstasy drug use[19]. These conflicting findings suggest that longitudinal studies, which adequately control for other drug use, are needed to better assess if chronic ecstasy use leads to long-term impairment in memory and learning.

10.2.2. Other areas of cognitive functioning

Some studies have found that ecstasy users are more impulsive than matched polydrug controls[40,57] but others are contradictory[19,21,58]. It is highly likely (as discussed in Chapter 5) that impulsivity might predict *initiation* of ecstasy use rather than be a *consequence* of its use.

Whilst some studies have found evidence of associated deficits in attention[4,52] and decision making[57] among ecstasy users, other studies have not done so[36,59,60]. Results on self-rated aggression have shown that ecstasy users rate themselves as being more aggressive than controls in the days after ecstasy use[61,62-64]. Delays in reaction time[65] and sleep abnormalities[66] have also been associated with ecstasy use.

10.2.3. Meta-analyses of the association between ecstasy use and cognitive function

A meta-analytic review is one way of synthesising findings from studies that investigate a particular association. Such studies are necessary because the statistical power of small studies may reduce their likelihood of detecting any differences in cognitive functioning between ecstasy users and controls. A primary advantage of meta-analytic techniques is that they combine the results of numerous small studies to estimate a single effect size[67].

A recent meta-analysis by Laws et al (2007) examined the impact of recreational ecstasy use on cognitive function. Ecstasy users showed significantly impaired short-term and long-term memory when compared with non-ecstasy users, either drug-naïve or ecstasy-naïve ones. The visual memory of ecstasy users was relatively normal and appeared to be affected more by concurrent cannabis use. There was no relationship between lifetime consumption of ecstasy tablets and any memory measures[68].

A meta-analysis by, Kalechstien et al (2007) with relatively stringent inclusion/exclusion criteria, revealed that ecstasy users displayed a range of neurocognitive deficits when compared to controls matched in terms of age, education and intellectual functioning. Small to medium effect sizes were observed for the associations between ecstasy exposure and psychomotor speed, attention, verbal learning and memory, nonverbal learning and memory and executive function[67].

These findings must be interpreted with a degree of caution as many of the reviewed studies included subjects with varying amounts of other drug use. This potentially weakens the overall strength of studies, as non-ecstasy drug use may have affected performance on cognitive tests.

10.3. Evidence of ecstasy-related neurotoxicity in humans

Evidence that ecstasy is potentially neurotoxic comes from numerous laboratory studies using neuroimaging to study brain function in exctasy users and controls. Comprehensive reviews of the non-behavioural evidence of MDMA-induced neurotoxicity in humans, and a discussion of the methodological complexities of this area of research, have been published[69-73]. A brief summary is provided here.

10.3.1. Brain imaging studies

Brain imaging studies have provided compelling evidence of MDMA neurotoxicity in humans. Typically, these studies employ Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) or proton magnetic resonance spectroscopy to evaluate the neurotoxic potential of MDMA in living human brain.

The main markers for 5-HT (serotonin) receptor neurotoxicity which have been studied using these techniques are decreases in SERT densities (SERT is a structural element of the pre-synaptic 5-HT neuron that is considered to be a reliable marker of 5-HT neuron integrity[74-77]) and decreases in the neurometabolite NAA (N-acetylaspartate; an amino acid marker for non-specific neuronal loss).

The first report providing direct evidence of MDMA-induced 5-HT neuronal injury in humans was from McCann et al (1998)[78]. In the relatively small (n=28) controlled study, SERT densities were decreased in ecstasy users and the size of the decrease was correlated with the extent of previous ecstasy use. This result was replicated in subsequent studies[41,79-83].

Other studies have reported significantly reduced SERT density in ecstasy users which appear to recover over time with abstinence[28,80-82]. It is also becoming apparent that females may be more susceptible than males to the neurotoxic effects of MDMA, as decreased SERT density is more pronounced in female than in male subjects[81,82].

Studies of NAA (N-acetylaspartate) levels in ecstasy users have produced mixed results. The amino acid NAA is an unspecific marker for neuronal loss. Reneman et al (2002) reported decreased NAA levels in ecstasy users and a significant dose-dependent association was observed[84]. In contrast, other studies have found no difference in NAA levels in ecstasy users[85-87].

PET imaging has also been used to investigate the effects of ecstasy on glucose metabolism in the human brain. Studies have found that glucose uptake in ecstasy users was altered in several brain regions compared to controls[52,88,89]. The reductions were more severe in individuals who started using ecstasy before 18 years of age[88].

The majority of imaging studies mentioned so far have reported markers of neurotoxicity in moderate to heavy current MDMA users and ex-MDMA users with a high lifetime exposure[41,78,80-82]. Few imaging studies have investigated the neurotoxic potential of low dose ecstasy.

In a prospective, controlled study, using magnetic resonance imaging (MRI) no firm evidence was found for any sustained effects of a one-off low dose (mean 2 pills) of ecstasy on human brain function[34]. Similarly, an uncontrolled study of young adults, who had never used ecstasy, but who had a high probability of using in the near future, found no indications for ecstasy-induced structural neuronal damage. However, there was evidence that low doses of ecstasy induced prolonged vasoconstriction in some brain areas. It is not known if this effect is permanent[90]. These findings are relevant to the potential therapeutic use of ecstasy[91].

10.3.2. Cerebrospinal fluid analysis

Several studies of lumbar cerebrospinal fluid (CSF) of ecstasy users have noted decreased concentrations of 5-HTAA[1,52,58,92-94], which is suggestive of neurotoxicity. In some studies, decreased concentrations of 5-HTAA were more prominent among female ecstasy users than males[58], while other studies have reported concentrations of 5-HTAA in CSF at normal levels[95].

10.3.3. Prolactin response to serotonin agonists

Studies have also measured the prolactin response to serotonergic agonists (e.g. L-tryptophan, M-chlorophenylpiperazine, D-fenfluramine). Results indicate that there is a blunted neuroendocrine response to 5-HT among MDMA users. This is suggestive of neurotoxicity[58,96-99].

10.3.4. Electrophysiological measures

Recent studies demonstrate that electrophysiological measures of sensory processing may be used to obtain an indirect indication of central serotonergic neurotransmitter malfunctions[100-102]. One such method involves recording auditory evoked potentials via scalp electrodes and electroencephalogram (EEG) while participants listen to acoustic stimuli. Several studies have identified changes in auditory evoked potentials in ecstasy users compared to controls[103-105]. However, whether the electrophysiological abnormalities observed are actually attributable to ecstasy use is unclear because studies have failed to assess whether auditory evoked potentials change after prolonged ecstasy use over time[103] or after abstinence[104].

10.4. MDMA neurotoxicity in animals

Animal studies have found suggestive evidence of neurotoxicity following MDMA administration. Because MDMA has been shown to have direct and indirect effects on aminergic and serotonergic mechanisms[83,106-110] much of the animal research into its potential neurotoxic effects has focused on these systems.

Animal studies have predominantly used rats[111-120] and non-human primates[94,111,121-126]. All but one of the species tested so far confirms that MDMA causes a selective loss of serotonergic axons; the exception occurs in mice, which have shown neurotoxic alterations in *both* serotonergic and dopaminergic axons[127-129].

10.4.1. Rodent models

Rodent studies have reported dose-dependent and long-term reductions in markers of 5-HT systems after the administration of MDMA[112,115,130-134]. These have included decreased levels of 5-

HT and 5-HIAA (a major metabolite of 5-HT)[112,131,135,136], alteration in 5-HT receptor function/expression[118], decreased number of 5-HT transporters (e.g. SERT; serotonin transporter)[112,117,137,138], and decreased activity of tryptophan hydroxylase[131,134,138,139]. These abnormalities in rats have been shown to last for months or even years after administration of MDMA[111,140-144]. Meyer et al (2002) found that administration of MDMA caused a persistent reduction in SERT (serotonin transporter) in neonatal rats and suggests that early administration of MDMA may permanently damage the developing brain[145]. There is emerging animal evidence that some antidepressant drugs have a protective effect against MDMA-induced neurodegeneration[132,146,147]. However, it remains to be demonstrated if these antidepressant drugs can protect against ecstasy-induced neurotoxicity in humans.

10.4.2. Nonhuman primate models

Studies using nonhuman primates have found similarly long-lasting reductions in markers of 5-HT systems to those reported in rodents[74,94,122,125,148,149]. In comparison to rodents, nonhuman primates have been shown to be more sensitive to the neurotoxic effects of MDMA, resulting in higher rates of 5-HT depletion with smaller doses of MDMA[138,141,150]. In nonhuman primates, dose dependent reductions in 5-HT have been identified in numerous brain regions[125], and in some studies reductions in 5-HT levels were evident up to 7 years after exposure to MDMA[74,141]. Significant MDMA-induced decreases in levels of 5-HIAA have also been reported in the cerebrospinal fluid of nonhuman primates[94,122].

Imaging studies have shown a marked loss of 5-HT terminals in brain tissue from baboons 13 months after MDMA administration[74], and the density of monoamine transporters (which are involved in the re-uptake of neurotransmitters such as 5-HT) was also found to be reduced in these animals[151]. Immunohistochemical studies have revealed marked decreases in brain axon density[125,131,141] and the reorganisation of 5-HT projections in the brains of nonhuman primates treated with MDMA[74,111,141,151].

In 2002, a high profile scientific report received considerable attention because it presented findings in studies of non-human primates that MDMA was far more neurotoxic than first thought[152]. However, the authors later retracted the study because they discovered that they had inadvertently administered methamphetamine rather than MDMA in the earlier experiment[153].

10.4.3. Functional importance of neurotoxicity in animals

Despite the evidence in animals that MDMA is neurotoxic when given in high doses, long-term abnormalities in behaviour are subtle. Indeed, the behaviour of MDMA-treated animals, with clear lesions of the serotonergic system, cannot always be easily distinguished from control animals[154-156]. Nevertheless, studies using rodents and nonhuman primates have reported minor functional changes such as poor memory performance and increased anxiety-related behaviours[114,117,155-165]. Some studies have reported that performance returned to normal within several weeks after MDMA treatment[166-168], while other investigations have yielded conflicting results[163,164,169,170].

10.5. Are animal models applicable to humans?

A much-debated issue in research on the adverse effects of MDMA is how relevant the findings of animal studies are to human users of the drug[106,171-173]. One reason it is difficult to make direct comparisons between the results of animal and human studies is that small mammals tend to eliminate drugs at a faster rate than large mammals, partly because they have proportionally larger livers and kidneys and faster blood circulation times[174,175].

A commonly used technique for estimating equivalent drug doses in different species is allometric interspecies scaling[175,176]. Consistent with its theoretical basis, to achieve a similar effect to that observed in humans, smaller animals, such as rodents, require higher drug doses measured in mg/kg. This consideration underlies the relatively high doses commonly used in rodent toxicity studies. In utilising interspecies scaling techniques, equivalent drug exposures are assumed to produce equivalent drug effects, including neurotoxicity. The validity of interspecies scaling to extrapolate neurotoxic doses of MDMA between animals and humans remains contentious[106,177,178]. This has led to the investigation of 'effect scaling' as an alternate way of equilibrating doses of MDMA in rats and humans. In this approach the lowest dose of drug that produces a specific pharmacological response is determined for rats and humans, and this is then used as a reference to calculate subsequent dosing regimens[106,179].

There are numerous other concerns about current models of animal MDMA-studies and their relevance to humans which contemporary research has begun to address. One concern is that frequency of dosing and dosage exposure in rodent models are not equivalent to human patterns of use. For example, in rodent models, MDMA is typically administered daily, whereas patterns of ecstasy use in humans are not as predictable.

Ecstasy pills have been shown to contain variable amounts of MDMA and other substances[180-183] (see Chapter 2), which is another reason why it is difficult to equate human "ecstasy" consumption with intravenous MDMA administration in animal studies. Such variation leads to uncertainty about the possible effects of other compounds found in ecstasy pills on its apparent neurotoxicity. An additional concern is that many human ecstasy users are polydrug users (see Chapter 9), which is not the case in animal studies.

The route of administration used in most self-administration studies among animals is intravenous (IV), whereas in humans, the conventional route is oral consumption. Parenteral administration (e.g. IV) is thought to increase MDMA toxicity as opposed to oral intake[124]. The IV route has been clearly associated with greater neurotoxicity in monkeys than oral administration[184]. Other concerns include the potential differences between drug tolerance in animal models and humans, and the limited repertoire of behaviours that can be used in animals to assess the negative consequences of MDMA use on brain function.

Animal studies investigating the effects of MDMA do, however, allow researchers to overcome some of the limitations inherent in human studies. To some extent, there appears to be translation between animal and human[172], particularly in regard to the acute effects of MDMA[171,172]. However, animal studies present their own limitations and the translation of data from animal models to human users remains uncertain and contested.

10.6. Mechanisms of MDMA neurotoxicity

Findings from both animal and human laboratory studies have shed some light on the possible mechanisms of neurotoxicity. There is mounting evidence that the formation of MDMA metabolites generates free radicals which in turn induce neurodegeneration[132,139,185-196]. Free radicals are a highly reactive group of atoms that can alter the ability of neural molecules to carry out their normal function. The finding that direct injection of MDMA into specific brain areas of the rat and the mouse does not produce serotonergic or dopaminergic neurotoxicity provides further support to this theory[197,198].

Other studies suggest that MDMA-induced neurotoxicity may be a result of the inhibition of tryptophan hydroxylase (TPH), an enzyme involved in the synthesis of serotonin (5-HT)[139,185]. 5-HTAA receptors have also been implicated in MDMA-induced neurotoxicity[199-201]. 5-HTAA receptors are a type of serotonin receptor which acts in the central nervous system (CNS),

smooth muscle and platelet aggregation. Studies have also demonstrated that endogenous dopamine and the dopaminergic system may also play a role in the mechanisms underlying MDMA-induced serotonin toxicity[202,110,190,199,200,203-206]. Glutamate, an amino acid that is a primary excitatory neurotransmitter in the CNS, has also been implicated[190,207-214]. The role of nitric oxide in MDMA-induced toxicity has been investigated[215] and remains somewhat controversial[216].

More recently, it has been suggested that the acute dose-dependent increase in temperature after MDMA ingestion, reported in rats[217-220] and humans[221,222], may lead to serotonergic neurotoxicity[70]. Further to this, high ambient temperature leads to greater 5-HT terminal axon loss in animals[218]. This has led to the prediction that neurotoxicity in humans may be influenced by environmental conditions. There is also emerging evidence that binge administration of ethanol may enhance the MDMA-induced loss of brain 5-HT terminals[223].

10.7. Are cognitive deficits related to patterns of ecstasy use?

Given the abundance of studies which have demonstrated a wide range of cognitive deficits in ecstasy users, the argument that more intense or enduring patterns of use may increase the likelihood of cognitive problems is compelling. The effect of acute, or 'within session', ecstasy use and 'lifetime' use on cognitive function has therefore been the subject of recent research.

10.7.1. Acute patterns of use

Measures of depression among abstinent regular ecstasy users are positively correlated with the amount of ecstasy consumed during a single (12 hour) occasion of use[224]. Similarly, Verheyden et al (2003) found positive correlations between the amount of ecstasy used on a single occasion, several measures of anxiety and one measure of depression[225]. In keeping with this finding, binge use of ecstasy (that is, using the drug on a continuous basis for more than 48 hours) has been associated with more physical and psychological problems than shorter-duration patterns of use[226]. A study by Thomasius et al (2003), which confirmed drug use by urine and hair analysis, found that psychopathology indices and serotonergic changes were best predicted by the number of ecstasy tablets taken on a typical occasion[30].

Additional evidence of a dose-dependent relationship between ecstasy use and cognitive function comes from investigations of markers of oxidative stress. As mentioned earlier, the formation of

oxygen-based free radicals, which are associated with oxidative stress, are thought to have a role in MDMA-induced neurotoxicity. Studies in humans have shown that markers for increased oxidative stress are correlated with daily MDMA dosage (and also 'lifetime' use)[196].

10.7.2. The importance of cumulative ('lifetime') ecstasy use

Numerous studies have investigated the effect of cumulative dose (i.e. overall amount of ecstasy used during a use career) and frequency of use on cognitive function. Cognitive deficits in heavy ecstasy users have been reported, but typically not on all tasks[16,33,39,57,227,228]. Studies have shown that 'heavy' ecstasy users are more impaired than 'moderate'[27,228] and 'light' users[6,8,12,39,182,228-230] on tests of neurocognitive performance. Fisk et al (2005) found that logical reasoning impairments in ecstasy users correlated with total lifetime ecstasy use[227]. Increased ecstasy use has also been correlated with more pronounced deficits in behavioural aspects of executive function[15,41,51]. Furthermore, psychiatric symptom deficits[231] and self-reported 'psychological problems'[232] have all been found to be associated with lifetime ecstasy use.

A number of studies have shown that 'light' ecstasy users may not show cognitive deficits. Among ecstasy users without a history of other drug use, Halpern et al (2004) found cognitive task performance was unimpaired in those who had used ecstasy on less than 50 occasions, but more experienced users showed significant impairment[233]. Likewise, Back-Madruga et al (2003) observed no visual memory impairment in individuals who had used ecstasy fewer than 50 times, but memory deficits had been reported in those who had used on more than 50 occasions[12]. Another study found that light users (1-99 tablets/lifetime) were not impaired on cognitive tasks, whereas moderate users (100-499 tablets/lifetime) showed some impairment and heavy users (>500 tablets/lifetime) were the most impaired[228]. On many tasks, however, there were no group differences.

One meta-analysis found no support for a relationship between lifetime ecstasy use and cognitive deficits. The authors commented that this finding may be related to: the possible negative effects of one-time MDMA use (such that lifetime use has little further negative effect); premorbid group differences; or the concurrent use of other drugs which may influence cognitive function[29]. Future research might examine these possibilities (see also below) but they suggest a less potent effect of MDMA on cognitive functioning.

Fewer studies have investigated the effect of frequency of ecstasy use on cognitive function. Rendell et al (2007) found that the decrement in prospective memory was associated with the

frequency of ecstasy use: greater deficits were reported among those who used ecstasy at least once every two weeks than among those who had used no more than once a month[42]. Similarly, other work[1] suggests it is the intensity of monthly ecstasy use, rather than lifetime usage, which is the crucial aspect of cumulative use. Another study demonstrated that weekly ecstasy dose was related to subtle deficits in reasoning ability[227]. Others have suggested that it may be 'clinically dysfunctional' use (defined in terms of DSM-IV for lifetime MDMA abuse or dependence), rather than purely 'recreational' use, that is associated with cognitive deficits[13].

Although subtle cognitive deficits have been demonstrated among ecstasy users reporting occasional use or a low cumulative dose, there is a growing body of evidence that chronic, heavy use of ecstasy is associated with cognitive impairment and the severity of that impairment is related to lifetime exposure to ecstasy.

10.8. What is the role of other drug use?

10.8.1. Cannabis

Research consistently shows that extensive polydrug use is the norm among ecstasy users (see Chapter 9). In particular, frequent cannabis use has been widely reported among ecstasy users[18,39,226,234]. As the chronic, heavy use of cannabis has been shown to lead to a subtle decrease in attention and memory function[43,235,236], the cognitive deficits reported in ecstasy users could be due to the effects of cannabis rather than MDMA. Extensive investigations that have attempted to take in to account the confounding role of cannabis have produced conflicting results.

Numerous studies have found that cannabis is associated with the cognitive deficits documented among ecstasy polydrug users[3,18,37,237-239]. For example, one study compared cannabis users, light ecstasy/cannabis users, heavy ecstasy/cannabis users and drug-free controls[18]. It found significant memory impairment in all drug using groups and no difference between those using cannabis and ecstasy and those using ecstasy alone. Whilst many other studies have excluded cannabis as a potential confounder[2,3,5,17,24,39,46,50,60,104,105,240,241], others have found that both ecstasy and cannabis use are associated with cognitive impairment[11,30,36,242].

A recent study by Milani et al (2005) highlighted a potential compensatory effect cannabis use may have on ecstasy-related cognitive problems[243]. In the study, heavy cannabis use was found to exacerbate the psychobiological problems of ecstasy users, whereas light cannabis use was associated with a reduced frequency of problems compared with ecstasy users who did not report cannabis use.

Clearly, there have been divergent findings from studies on this issue and there is ongoing debate about the potential complexities of the psychobiological interactions of cannabis and MDMA[244] A constellation of factors are thought to contribute to the diversity of findings, including: differences in mean lifetime use of cannabis and ecstasy; the sensitivity of particular cognitive tasks to the effects of ecstasy or cannabis; the possibility that the effects of ecstasy and cannabis are in some way interactive; and low statistical power in studies with small samples.

10.8.2. Other psychoactive drugs

Ecstasy users also often consume amphetamines, cocaine, LSD, ketamine and gamma-hydroxybutyrate[19,21,227,245] (see Chapter 9) and use alcohol and tobacco[21,242,245]. Only a handful of studies have investigated the potential confounding effects of some of these drugs. The memory deficits of ecstasy polydrug users were shown to remain significant after statistically controlling for LSD use[9]. Similarly, another study confirmed that neurocognitive deficits among ecstasy users remained significant after controlling for amphetamine, cocaine and LSD use[228].

Impairments in working memory remained significant among current and former ecstasy users after controlling for alcohol, amphetamine and cocaine use[39]. Fisk et al (2005) found reasoning task deficits in ecstasy polydrug users were related to the use of ecstasy, cocaine, alcohol and cannabis but only relationships with ecstasy use remained significant after controlling for the effects of other psychoactive drugs[227].

Schilt et al (2007) examined cognitive performance in a prospective cohort of ecstasy-naïve subjects who reported that they were likely to use ecstasy in the future. Those who started using ecstasy were compared with those who did not after matching on age, sex, intelligence and use of other substances. At 18-month follow-up, verbal memory was significantly poorer among low-dose ecstasy users after controlling for cannabis, cocaine, amphetamines, tobacco and alcohol. However, the cognitive performance of the group who began to use ecstasy was still within the normal range[24].

Verkes et al (2001) assessed ecstasy using males and found that cognitive performance was not related to the cumulative or recent use of any other drugs other than ecstasy[27]. Several studies have assessed ecstasy users who have had very little use of other psychoactive substances[6,196,233]. Cognitive deficits were still noted among these relatively 'pure' ecstasy users[6], and more so among the more experienced ecstasy users[233].

The above studies suggest that significant ecstasy group differences in cognitive performance may not be an artefact of other psychoactive drug use. In contrast, other studies of current ecstasy users which have controlled for other drug use have found overall tendencies for impaired cognition but little evidence of group differences[19,21]. This suggests that it might be polydrug use in general, rather than ecstasy use in particular, that produces cognitive impairment. Further evidence of the complexity of polydrug influences comes from a study that noted impaired task learning was related not only to ecstasy and cannabis use, but also cocaine use over the previous year[30]. There is also emerging evidence of the additive influence of nicotine and ecstasy in relation to self-reported memory deficits[246].

In summary, research has demonstrated subtle cognitive deficits among ecstasy polydrug users. However, few studies have adequately controlled for the influence that substances other than ecstasy may have on cognitive function. It is, therefore, not yet entirely clear whether cognitive deficits among ecstasy users reflect the use of ecstasy, cannabis or other psychoactive drugs. Further investigation of the cognitive effects of individual drugs must be undertaken to more clearly delineate their contribution to cognitive deficits during concomitant use.

10.9. Do sex differences exist?

Males and females differ in their biological response to numerous psychostimulant drugs including amphetamine[247]. Verheyden et al (2002) found that females tended to report mid-week depressed mood following weekend use of ecstasy, whereas males were more likely to experience aggression in the days after ecstasy use[62]. In a controlled study, equal doses of MDMA per kilogram body weight produced stronger subjective effects (i.e. perceptual changes, thought disturbances) in females than males[248] . Furthermore, the experience of a range of acute adverse physical effects after ecstasy use has been more frequently reported by women than men[248,249].

These findings, together with emerging evidence from neuroimaging studies that females are more vulnerable to ecstasy-related serotonin neurotoxicity than males[71], suggest that females could be more prone to ecstasy-related cognitive deficits. Rodgers et al (2003), however, found no effect of gender on memory performance among ecstasy usersr[11]. Likewise, Allott et al (2007) found no clear evidence of gender difference in cognitive function after regular ecstasy use[250].

Overall, relatively few studies have addressed whether gender is a factor influencing ecstasy-related cognitive deficits so this question remains unresolved.

10.10. Are cognitive deficits reversible with abstinence?

Brain imaging studies that have compared recently abstinent current ecstasy users with long-term abstinent users provide suggestive evidence for the reversibility of ecstasy-related deficiencies in serotonin transporter (SERT) densities[28,30,80-82,251]. Whilst the ecstasy-related reduction in SERT densities commonly observed in recent users appears to be reversible, impairments in cognitive function may be more enduring. Deficits in verbal memory have been shown to persist even after long-term abstinence (i.e. 1 year)[23,28,33]. Further evidence that ecstasy-related cognitive deficits may not be fully reversible comes from Wareing et al (2000) who found the executive functioning of former ecstasy users was impaired compared to controls[16]. Similarly, Thomasius et al (2003) found that former users performed worse on measures of verbal memory than a control group[30]. These findings suggest that cognitive performance measures may reveal more subtle and long-lasting deficits than can be detected using brain imaging studies[252]. Another plausible explanation for these findings is that serotonergic neurotoxicity may not necessarily be associated with decrements in cognitive function[177,252].

Other studies are less conclusive, with some finding irreversible and others reversible deficits in memory performance[3,20]. A longitudinal study of 38 ecstasy users reported no decline in memory performance after continued use and no improvement after 18 months of abstinence[25]. In one study of ecstasy using males, ex-users who had been abstinent for over one year performed worse on verbal memory and learning than current users or controls[229]. These findings were thought to reflect pre-morbid differences in serotonin function of abstinent former users or the consequences of ecstasy use that may emerge after abstention.

In summary, the degree to which ecstasy-related cognitive deficits are reversible with abstinence is far from resolved. More research is needed using adequately powered prospective studies of ecstasy users who have had varying baseline levels of ecstasy and other drug use.

10.11. Methodological problems

A number of methodological problems have dogged human research on the effects of ecstasy on cognitive function. First, it is well documented that ecstasy users are often polydrug users[226,245,253-256], and this potentially confounds the role of ecstasy in cognitive impairment. Polydrug use needs to be well assessed and statistically controlled for in studues of the cognitive effects of ecstasy.

Second, the content of ecstasy pills can be highly variable[180-183]. Any deficits observed in ecstasy users may therefore not necessarily be attributable to the effects of MDMA, but to other neurotoxic substances sold as ecstasy.

Third, a substantial proportion of the studies investigating the effects of ecstasy have been retrospective. A known limitation of such studies is that they can not determine if the differences identified between users and controls existed prior to using ecstasy[177,252,257]. For example, certain traits such as antisocial behaviour and sensation seeking/impulsivity are associated with an increased likelihood of experimenting with illicit drugs and developing substance use problems[258-260]. These traits are also associated with poorer cognitive performance[261]. If these traits are more common amongst ecstasy users, in particular heavy users, studies may give the misleading impression that it is ecstasy use which causes cognitive impairment. Further prospective studies are needed to draw more definite conclusions on this issue.

Fourth, the period of abstinence prior to testing is another important factor that needs to be better controlled in studies of cognitive impairment and markers of neurotoxicity. While many studies have employed an ecstasy-free period of one week or more[1,4,7,10,15,22-24,27,52,85,98,104], others have required only 2 or 3 days[9,37,40]. The latter is a short period which means that some observed effects may have been due to subacute intoxication.

Fifth, in many studies, blood/urine screening has been used to confirm abstention[1,10,22-24,27,89,104]. However, there are some problems inherent to using this technique. For example, blood and urine testing can detect cannabis 2-3 weeks after use, but MDMA and other amphetamines can be detected only 24-48 hours after the last dose. Therefore, in the 2-3 weeks before subjects are assessed, it is only possible to objectively confirm abstention from cannabis not MDMA[262]. Hair sample analysis may be a more appropriate way to determine abstention and previous use of drugs, in particular MDMA. Some studies investigating ecstasy-related cognitive impairment have employed this technique[41].

Sixth, numerous studies have relied on self-reported drug use and abstention. Commentators have, at times, called in to question the accuracy of this data as participants may find it difficult to remember how many ecstasy tablets they have taken over months and years.There is evidence that the self-reports of drug users are sufficiently reliable and valid to provide descriptions of the history of their drug use[263,264].

Seventh, a recurring methodological problem is how to define a comparison or 'control' group with which to compare ectasy users. Factors such as age, gender and IQ can be assessed and

matched relatively easily. The latter is particularly important in studies measuring neurocognitive performance. However, determining the most appropriate drug use history is more problematic. In response to this complex issue, researchers are increasingly using multiple control groups, with a range of drug use patterns (e.g. polydrug users without ecstasy use, and light and heavy ecstasy users)[4,9,19,21,23,36,40,240].

10.12. Summary

Subtle impairments of memory and learning performance have been demonstrated in numerous cross-sectional studies of ecstasy users. The most consistent have been subtle deficits in verbal memory, visual memory, prospective memory and executive functioning. Some studies have demonstrated a range of cognitive deficits, others have found that ecstasy users were impaired on only a few measures or were unimpaired.

Recent studies with large samples of current and former ecstasy users, and the first longitudinal studies, have reported conflicting results. In meta-analyses, statistically significant effect sizes have been observed for the associations between ecstasy exposure and a range of learning, memory and executive functioning deficits. The clinical and functional significance of these effect sizes is less clear.

Brain imaging studies have provided convincing evidence of ecstasy-related neurotoxicity in humans, especially among heavier users. However, it is unclear whether the abnormalities observed in markers of neurotoxicity precede or are consequences of ecstasy use.

The available evidence indicates that MDMA-induced neurotoxicity is not caused by the drug itself but by one or more metabolites of MDMA, and that neurotoxicity is likely to be exacerbated by high ambient temperatures. Experiments on rodents and non-human primates continue to demonstrate that MDMA produces long-term degeneration of serotonin nerve endings, but the mechanisms involved are not yet fully understood. Despite animal evidence that MDMA is neurotoxic in high doses, long-term behavioural abnormalities in animals treated with neurotoxic doses have been quite subtle.

A much-debated issue of research on the adverse effects of ecstasy is the relevance of animal studies to humans. Although animal studies allow researchers to overcome some of the limitations inherent in human studies (e.g. uncertainty about dose and premorbid characteristics), they have their own methodological limitations. Estimating equivalent drug doses can be

problematic because of variations in rates of metabolism between species and there are major differences in frequency of dosing and dosage exposure between animals and humans.

The argument that more intense or enduring patterns of ecstasy use may lead to an increased likelihood of cognitive problems is increasingly persuasive. Studies have found a positive correlation between amount of ecstasy used on a single occasion, indices of psychopathology, and serotonergic changes. Although very subtle cognitive deficits have been demonstrated amongst ecstasy users reporting occasional use or a low cumulative dose, there is growing evidence that chronic, heavy use of ecstasy is most strongly associated with these subtle cognitive effects. The severity of impairment is generally correlated with lifetime exposure to ecstasy.

It has been suggested that the cognitive deficits in ecstasy polydrug users may be due to the use of cannabis and other psychoactive substances rather than ecstasy. Investigations that have attempted to take in to account the confounding role of cannabis and other drugs have sometimes but not always found cannabis use to a confounding variable. Studies which have attempted to control for other drug use have produced conflicting results, and it remains unclear whether the cognitive deficits observed in polydrug-using ecstasy users reflect the use of ecstasy, cannabis or recent drug use in general.

Sex is another potential confounding factor. Females report stronger subjective effects of psychostimulant drugs and more frequently report acute adverse physical effects than males. Emerging evidence from neuroimaging studies suggests that females may be more vulnerable to ecstasy-related neurotoxicity than males. Together, this evidence suggests that females may be more prone to ecstasy-related cognitive effects. However, findings from the few studies to date which have directly investigated this hypothesis have not found clear sex differences.

The question of whether ecstasy-related cognitive deficits are reversible with abstinence remains uncertain. Brain-imaging studies suggest that markers of neurotoxicity may be reversible but some studies of cognitive function suggest that impairment of memory in former ecstasy users may persist after long-term abstinence. On the other hand, reversible deficits have been observed, and studies have also found no decline in memory performance after continued use and no improvement after abstinence.

A number of methodological problems have dogged human ecstasy research. Because many ecstasy users are polydrug users the role of ecstasy in cognitive impairment is unclear. The content of ecstasy tablets can also be highly variable so any cognitive deficits may be attributable to substances other than MDMA. A majority of studies investigating the effects of ecstasy have

been retrospective in nature, and therefore it is not possible to determine if any differences observed existed prior to using ecstasy. More prospective studies are needed that are more rigorous in ensuring that residual effects of intoxication do not affect testing.

Self-report of abstention has also been frequently relied on. Whilst there is evidence that self-reports from drug users are sufficiently reliable and valid to provide descriptions of the history of their drug use, some commentators have called this in to question. Other studies have confirmed abstention with blood or urine screening, but these techniques have limitations, particularly in assessing amphetamines. In future studies, hair sample analysis may be a more accurate way to determine abstention and drug use history.

A recurring methodological problem in ecstasy-related research which uses a comparison group is how to define the control condition. Whilst age, gender and IQ can be matched relatively easily, deciding upon the appropriate drug use history for a comparison group is more problematic. Multiple control groups with a range of drug use histories have recently been employed in response to this complex issue.

The findings of the studies presented here raise some additional important questions relating to ecstasy use and cognitive function. Issues that are particularly important to address in future research are: the role of other drugs in cognitive deficits attributed to MDMA; the reversibility of any neurotoxic effects; and the confirmation of gender differences in any neurotoxic effects.

10.13. References

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11. Mortality related to ecstasy (MDMA) use

Edmund Silins

11.1. Introduction

The first reports of deaths in persons who had used 3,4-methylenedioxymethamphetamine (MDMA), commonly known as 'ecstasy', appeared in the scientific literature in the late 1980s[1]. Around this time, the setting in which the drug was used began to change from that of clinical psychotherapy in the 1970s to dance party settings in the 1990s[2,3]. Since then, numerous scientific papers have delineated the potential harms associated with ecstasy use and have identified ecstasy-related fatalities[4-8].

Fatalities have been reported in which MDMA was the only substance identified in toxicology tests[1,9-21]. However, in keeping with patterns of polydrug use among ecstasy users[22,23], and the highly variable content of tablets sold as ecstasy[24-29], a range of other licit and illicit substances have been detected in published cases of ecstasy-related fatalities[1,11,12,14,21,30-40].

11.2. Mechanisms of ecstasy-related mortality

It is not uncommon for several pathophysiological mechanisms to be identified as contributing to ecstasy-related deaths. In many published cases, the cause of ecstasy related deaths is a severe medical complication, such as rhabdomyolysis (the destruction of striated muscle cells), disseminated intravascular coagulation (which results in widespread bleeding and tissue necrosis) and renal failure[8,3,21,41,42]. For example, Walubo and Seger (1999) report on a fatality after a suicidal overdose of MDMA[20]. In this case, 12 hours after ingestion of MDMA, severe hyperthermia developed with evidence of rhabdomyolysis. Subsequently, acute respiratory distress syndrome (ARDS) developed that was accompanied by disseminated intravascular coagulation and renal failure. MDMA was the only drug identified at autopsy and the cause of death was multi-organ failure. In other cases, MDMA has been identified in toxicological tests post-mortem but intoxication has not been determined to play a pathophysiologic role in causing death (e.g. where death has occurred as a result of a stab wound or blunt injury sustained in a car accident)[12,31]. In such cases, it is difficult to determine the extent to which drug-induced behaviour may have contributed to the circumstances of death. The major pathophysiological and non-pathophysiological mechanisms of ecstasy-related mortality are summarised here.

11.2.1. Hyperthermia

Hyperthermia (i.e. body temperature above 38 C) is one of the major symptoms of acute ecstasy-related toxicity that can lead to often fatal conditions such as rhabdomyolysis, disseminated intravascular coagulation, renal failure and liver damage[3,5,12,42-44]. The impairment of temperature regulation among ecstasy users is likely to be a direct effect of MDMA in combination with high ambient temperature, prolonged physical activity and insufficient fluid replacement[3,12].

Gowing et al (2002) identified 69 published cases of acute reactions to ecstasy involving hyperthermia[4]. The outcome in two cases was not reported but the remaining 67 cases, 32 (48%) resulted in death. There was a correlation between body temperature and the risk of mortality. A review of published ecstasy-related fatalities between 1966 and 2000 found that out of a total of 45 deaths, hyperthermia was noted in 13 (29%) cases. In no case, however, was this given as the primary cause of death[41].

An analyses by Williams et al (1998) of 48 consecutive cases of ecstasy intoxication presenting to an emergency department in London, UK, over a 15 month period, found that hyperthermia was

a clinical feature in nine (19%) cases. However, no severe medical complications were reported and there were no fatalities[45].

11.2.2. Disturbances of salt and water balance

Gowing et al (2002) identified 14 cases with a range of symptoms following the use of ecstasy that were reportedly caused by disturbed salt and water balance[4]. These symptoms included: confusion, reduced consciousness, seizures and convulsions. The majority of cases recovered in a matter of days once sodium levels had returned to normal. Three of the 14 cases died as a result of cerebral oedema caused by low sodium levels secondary to over-hydration.

In five of the 14 cases large amounts of water had reportedly been consumed in conjunction with ecstasy use. The administration of MDMA is typically associated with inappropriate release of antidiuretic hormone (a hormone which reduces urine formation)[46-48]. In combination with reduced kidney function associated with hyperthermia, the effect of antidiuretic hormone reduces the body's ability to excrete fluid and may worsen the effects of excessive fluid consumption[4].

11.2.3. Serotonin toxicity

Serotonin toxicity, otherwise known as serotonin syndrome, is a drug-induced toxic state caused by an excess of serotonin within the central nervous system[49,50]. Serotonin is a neurotransmitter (a signalling molecule) thought to have a major influence on mood, sleep, appetite, temperature regulation, pain perception and emesis[51,52]. Depression is frequently associated with low concentrations of serotonin[53] but severe serotonin toxicity can lead to serious medical complications such as hyperthermia, rhabdomyolysis and renal failure.

The acute behavioural and physiological effects experienced by ecstasy users are consistent with the serotonin release that has been induced by MDMA or one of its analogues[54]. MDMA frequently produces a clinical picture resembling mild serotonin toxicity that can produce serious, acute toxicity[18,49,54-57].

There is a lack of case reports of mortality associated with the use of MDMA alone that fit the diagnostic criteria for serotonin syndrome. Mueller and Korey (1998) describe one fatal case of a 20 year old woman who had ingested two ecstasy tablets and developed MDMA-induced toxicity

with features of serotonin syndrome[18]. Toxicology revealed no other illicit drugs were present and she had not previously been treated with any prescription medication.

The potential exists for fatal interactions between MDMA and other serotonergic substances[18,49,54-59], in particular antidepressant drugs such as monoamine oxidase inhibitors (MAOIs). There are documented fatalities arising from the use of ecstasy in combination with MAOIs (e.g. moclobemide)[40]. In four documented cases, death was attributed to serotonin toxicity resulting from the combination of ecstasy with moclobemide. It is not entirely clear why the drugs were taken together as none of the cases had been prescribed moclobemide. The authors speculate that moclobemide was used to enhance the euphoric effect of ecstasy.

11.2.4. Liver damage

Fatal human cases of liver damage, or liver failure, associated with the use of ecstasy are rare[42,60-62]. The precise mechanism of ecstasy-related liver damage is uncertain[5]. Typically, liver damage occurs as part of multi-organ failure attributable to hyperthermia, but this is not so in every case. Gowing et al (2002) identified 39 cases of liver injury apparently unrelated to hyperthermia[4]. Although the majority of cases resolved spontaneously, eleven required transplantation and six were fatal.

11.2.5. Cardiovascular complications

Since the first case of fatal ventricular dysrhythmia following ecstasy use was reported[1], there is mounting evidence in animal and human studies that MDMA may have cardiotoxic properties[11,63-66]. Gowing et al (2002) identified six cases where cardiac function was a primary cause of ecstasy-related deaths[4]. Pre-existing cardiac disease was present in three of these cases, suggesting that underlying disease may be a contributing factor in ecstasy-related cardiovascular fatalities.

11.2.6. Cerebrovascular complications

Several case reports have linked the use of ecstasy with cerebrovascular accidents (e.g. intracerebral and subarachnoid haemorrhage)[67-69]. Gowing et al (2002) found 11 cases of ecstasy-related cerebrovascular injury[4]. A small (n=22) case series of ecstasy-related fatalities in New

York City, examined by Gill et al (2002), identified a single case where subarachnoid haemorrhage was noted as contributing to death[41].

11.2.7. Respiratory complications

Respiratory complications appear to be a factor in some ecstasy-related fatalities. Gowing et al (2002) identified three such cases[4]. MDMA and related derivatives did not appear to have a direct effect on respiratory function: one case had a history of asthma, in another case death was a result of aspiration, and upper airway obstruction was the cause of death in the third case[1,30,70].

11.2.8. Other mechanisms

In some cases, MDMA has been identified in toxicological tests post-mortem but intoxication was not determined to play a pathophysiologic role in causing death. The primary cause of death in such cases is other causes (e.g. mechanical injury). It can only be hypothesized that a drug-induced lack of judgement may have produced the circumstances that resulted in death.

Several studies suggest that ecstasy use may impair driving and therefore be a contributing factor in motor vehicle accidents[71,72]. Gill et al (2002) identified five MDMA related fatalities where death was caused by blunt injury sustained in a car accident[41]. A minority of other fatalities have been reported in which ecstasy was detected post-mortem in deaths attributed to blunt injury following a fall from a window[31] or stab wounds sustained in an assault[31]. Dowling et al (1987) report one case where MDMA was identified in toxicological tests post-mortem and the cause of death was determined to be electrocution resulting from contact with a utility tower[1].

11.3. The epidemiology of ecstasy-related mortality in Australia

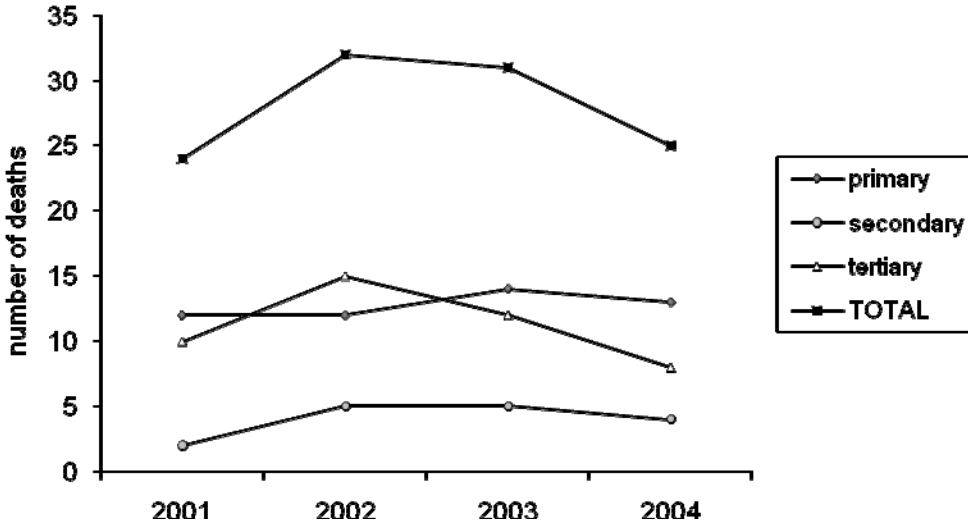
Information regarding illicit drug-related deaths in Australia is provided by the Australian Bureau of Statistics (ABS) Causes of Death (COD) database and the National Coroners Information System (NCIS). The ABS COD database does not identify specific drugs involved, but codes the circumstances of death. This makes it difficult to make an accurate determination of ecstasy-related fatalities in Australia.

Over the four year period 2001-2004, the NCIS identified 112 ecstasy-related deaths in Australia[73]. In 51 (46%) of these cases, ecstasy was determined to be a 'primary' contributing factor, meaning that it produced the physical harm most closely linked to the cause of death. However, only six (5%) of these deaths identified MDMA as the only drug present, suggesting that other substances may have played a part in the majority of ecstasy-related fatalities in Australia during the time period. Since ecstasy was usually one of a range of drugs detected, other drugs were also classified as a primary contributing factor (Figure 12.1).

Over the period 2001-2004, the majority of ecstasy-related deaths were related to road traffic accidents (n=31, 28%) and drug toxicity (n=45; 40%) (Figure2). Among fatalities related to drug toxicity, MDMA was rarely the only drug detected (3 of 45 deaths). Kinner et al (2005) comment that fatalities directly caused by ecstasy appear to be very rare in Australia by comparison with the extent of use. Ecstasy is usually only one of a range of drugs detected at autopsy and a substantial proportion of "ecstasy-related" deaths involve a motor vehicle accident[73].

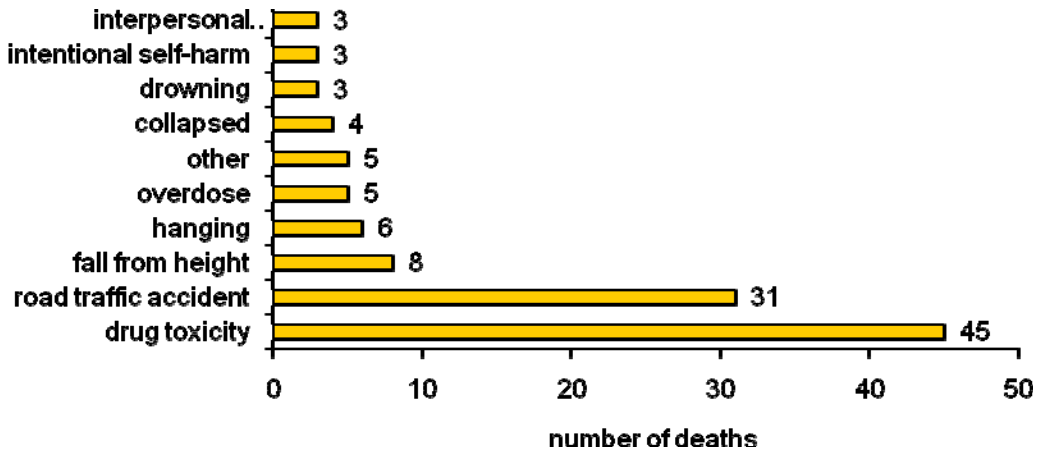
By comparison, in 2004 alone, among those aged 15 to 54 years, there were a total of 374 accidental deaths attributed to opioids in Australia[74]. The rate of accidental deaths due to opioids in Australia was 31.3 per million persons aged 15 to 54 years. This suggests that opioid-related deaths are a far greater public health concern given its much lower prevalence of use than ecstasy.

Figure 11.1: Number of ecstasy-related deaths nationally by level* of contribution to death, 2001 - 2004



*The NCIS defines 'primary contribution' as producing the 'actual physical harm most closely linked to the cause of death' (e.g. drug toxicity); 'secondary contribution' as being 'involved at the start of the injury event' (e.g. road traffic accident); and 'tertiary contribution' as 'other mechanisms involved in injury.

Figure 11.2: Ecstasy-related deaths by cause of death, 2001-4, Australia



11.4. Ecstasy-related mortality in other regions

Several studies provide information on ecstasy-related mortality in other regions. A review of ecstasy-related deaths in England and Wales between 1996-2002 identified 202 cases from a national coroners' database of drug-related deaths[28]. In only 17% of these cases did the coroner's report note that ecstasy was the sole drug detected. The majority of deaths occurred after several substances had been used together with ecstasy.

Results of post-mortem toxicology were available for 183 cases and the presence of one or more enactogenic compounds (e.g. a drug that produces intense feelings of self-awareness) was confirmed in 167 cases. MDMA was found in 143 (86%) cases; MDA in 22 (13%) cases; MDEA in one case and PMA in one case. The study also found a steady increase in ecstasy-related fatalities in England and Wales during the study time frame, from 12 cases in 1996 to 72 in 2002. The increase was attributed to: increased availability of ecstasy in the UK; the availability of more toxic enactogenic compounds (e.g. PMA) which are not immediately distinguishable from ecstasy/MDMA by the drug user; higher rates of reporting from coroners; and a consistent decrease in the cost of ecstasy in the UK. The authors noted a lack of uniformity in the way coroners incorporated toxicological findings into determinations of the cause of death as a limitation of their data.

A subsequent study by Schifano et al (2006) in the UK reported results consistent with the earlier study[75]. It found that the number of ecstasy-related deaths rose from 31 in 1994 to 78 in 2002 but

dropped to 48 in 2003. Over the time period, 394 ecstasy-related deaths were reported, with ecstasy the only drug mentioned in 165 (42%) cases. The study also found that the number of ecstasy-related fatalities was positively correlated with: the prevalence of ecstasy use in the preceding year, the number of persons dealt with for ecstasy-related offences, the number of ecstasy seizures and the number of ecstasy tablets/doses seized. It was negatively correlated with ecstasy price. These findings support the hypothesis that a substantial decrease in ecstasy price facilitated easier access to the drug, increasing consumption, which in turn led to increased ecstasy-related fatalities.

Gore (1999) estimated the ecstasy-related mortality rate in the UK per 10 000 users in the 15-24 year aged group ranged from 0.2 in all users to 5.3 among 'first-time' users[76]. In addition, she highlighted several deficiencies in the data that affected the calculation of drug-specific death rates in this population so these findings must be interpreted with caution.

In the USA, fatality reports were obtained by Patel et al (2004) from participating medical examiners[77]. Thirty-eight (8%) of the medical examiners reported 102 ecstasy-related deaths from 1999 to 2001. In the majority (70%) of cases the primary cause of death was drug toxicity but the role played by drugs other than ecstasy was not known. In the remaining (30%) ecstasy-related fatalities, the primary cause of death was reported to be other causes such as motor car accident.

12.5. Mortality across drug classes

Few longitudinal studies have directly compared mortality rates across different drug classes reflecting the predominance of opiate users in such cohorts[78]. Of those which have made this comparison, higher death rates amongst primary opiate users have consistently been reported, along with elevated death rates for stimulant users[79-83]. For example, Bartu et al (2004) reported that opiate users were 1.4 times more likely to die than amphetamine users, and were 2.4 times more likely to die from overdose[79]. Similarly, Fugelstad et al (1997) reported a substantially higher mortality rate amongst opiate users than amphetamine users[81]. Overall, the findings indicate that opiate use carries the highest risk of death, primarily from overdose.

11.5. Problems with determining ecstasy-related mortality

There are a number of issues which stand in the way of accurately determining the role played by ecstasy in drug-related related fatalities. Numerous studies have found that the content of ecstasy

pills are highly variable[24-29]. For example, an analysis of 5502 ecstasy pills seized by South Australian (SA) Police over a six month period found MDMA was the most common drug detected, present in 89% of pills[25]. Ketamine, detected in 26% of pills, was the second most common drug present. Other substances detected included MDA, PMA (found in 3% of pills), methylamphetamine, paracetamol and caffeine. This suggests that in some ecstasy-related fatalities, the cause of death may be attributable to multiple drug toxicity. The variable content of pills sold as ecstasy underlines the importance of performing toxicology tests post-mortem when investigating ecstasy-related deaths to accurately determine which substances may have played a role. In Australia, this is done routinely for cases which are referred to coronial services.

Polydrug use may also act as a confounding factor. Research consistently shows that extensive polydrug use is the norm among ecstasy users[22,23,84-86]. Consequently, even when MDMA is detected post-mortem, a consideration of other contributing factors is required, especially multiple drug toxicity and pre-existing pathology, before we can conclude that MDMA use was a cause of death. The concomitant use of MDMA and other stimulants may increase the likelihood of serious medical complications[57] while the concurrent use of MDMA with alcohol and cannabis may increase intoxication when driving, with a consequent increased risk of fatality.

Ambulance overdose data and emergency department admissions have also been used to estimate the number of drug-related deaths in Australia. However, differences in the definition of what constitutes a drug-induced death, variations in reporting by individual clinicians and jurisdictional variations in reporting make an accurate determination of drug-related fatalities from this kind of data difficult[87-89]. In addition, hospital data are generally coded according to the International Statistical Classification of Diseases and Related Problems (ICD), produced by the World Health Organization (WHO). This classification was designed to standardise the coding of hospital morbidity and mortality data internationally. The accuracy of the data depends on correct and complete recording by clinicians in medical records. The circumstances of morbidity (e.g. poisoning, behavioural disorders) are the focus when coding rather than the specific drugs involved. In the current version of ICD-10 there is also no distinction made between amphetamines and other illicit drugs such as ecstasy. The misclassification of drug types in this way is likely to result in an under-estimation of ecstasy-related mortality in Australia.

The Australian Bureau of Statistics (ABS) Causes of Death (COD) database may be used to determine the number of drug-related deaths. This database is drawn from state registries of births, deaths, marriages and coronial services and is updated on an annual basis. The ABS COD database utilises ICD coding which, as already mentioned, does not focus on the identity of the specific drugs involved, but rather on the circumstances of death. This factor makes an accurate

determination of ecstasy-related fatalities difficult. Other reported limitations of the ABS COD database are inconsistent terminology in some reporting and delays in the compilation of data[90].

The National Coroners Information System (NCIS) contains jurisdictional data on the results of toxicological analyses, pathology tests and coroners reports from 2001 onwards. Unlike other national databases, NCIS does distinguish between ecstasy and other amphetamine-type stimulants (ATS) in drug-related fatalities. This is a significant strength of the database. Several constraints, however, need to be taken in to account when analysing or interpreting the data: NCIS only captures deaths which are referred to coronial services; in some cases, autopsy and toxicology results are not included on the database; and there may be jurisdictional delays in the inclusion of some data.

The limitations of all these data sources are likely to result in an under-estimate of ecstasy-related deaths. The preferred option would be, of course, to estimate mortality in a prospective cohort study of ecstasy users.

11.6. Summary

Fatalities have been reported where MDMA is the only substance identified by toxicology tests. However, because of patterns of polydrug use among ecstasy users and the highly variable content of pills sold as ecstasy, many ecstasy-related fatalities are attributable to multiple drug toxicity.

The main pathophysiological mechanisms contributing to ecstasy-related deaths are hyperthermia, serotonin toxicity, and disturbances in salt and water balance. In the exceptional cases where ecstasy-related fatalities occur, death is typically a result of several mechanisms acting together to produce severe medical complications or other causes of death such as motor vehicle accident. Nevertheless, although ecstasy-related fatalities are rare, there is emerging evidence that MDMA use may lead to acute biological-metabolic stress in humans[91,92], the long-term effects of which are not yet known.

The ABS COD database and the NCIS can provide information on drug-related deaths in Australia. They are imperfect because of differences in the definition of what constitutes a drug-induced death, variations in reporting by clinicians, jurisdictional variations and the misclassification of drug types probably under-estimate ecstasy-related mortality.

The NCIS identified 112 ecstasy-related deaths over a four year period. By contrast, in one year alone, there were three times more accidental deaths attributed to opioids in Australia. Although ecstasy contributes to a clinically significant number of fatalities, the use of opioids is a far more significant public health concern.

Whilst fatalities related to the use of ecstasy attract the attention of the media and the general public, deaths as a direct result of ecstasy consumption appear to be relatively rare events given the extent of its use. Nevertheless, ecstasy cannot be considered a benign drug as there is evidence that its use can cause fatalities.

There is a need to educate ecstasy users about the potential for fatality particularly when it is used in conjunction with other stimulants, alcohol and some pharmaceutical drugs. Strategies which focus on reducing the likelihood of hyperthermia and education about adequate water consumption are relevant. Because a substantial proportion of ecstasy-related fatalities involved a motor vehicle accident, education about the ability of ecstasy and other drugs to significantly impair driving performance is essential. Peer-led education may play an important role.

If the limitations of routine data sources can be addressed it will be possible to provide a more accurate estimate of the number of ecstasy-related fatalities and to more clearly define the risks associated with ecstasy use . Cohort studies are needed that will allow studies of ecstasy-related fatalities over time, and direct comparisons of mortality rates for different drug classes. Such studies would also provide a better understanding of the interaction between ecstasy use and other mortality risk factors.

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12.The use of MDMA for therapeutic purposes

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12.1. Introduction

There has been a range of indications for which MDMA has been used, advocated or trialled as a therapeutic drug. In this chapter, we consider the history of medical use of the drug and present some of the more recent evidence on its safety and efficacy in the indications for which MDMA has been claimed to be of benefit.

As Chapter 2 discussed, 3, 4- methylenedioxymethamphetamine (MDMA) was first synthesised by Merck in 1912 in an effort to develop new blood clotting agents (haemostatic substances)[1]. In 1952 Merck conducted pharmacological and toxicology tests in its investigation of adrenaline- and ephetonine-like substances[1]; in 1953-4 the University of Michigan conducted toxicity and behavioural pharmacology studies to assess the potential of MDMA as a chemical warfare agent[1].

Chapter 5 has outlined in detail the psychopharmacology of MDMA: some of its effects of have led to the use of MDMA for a range of indications, including a role in the treatment of mental disorders. Its purported uses include treatment of post-traumatic stress disorder and use as an adjunctive medication in psychotherapy and couples therapy. This chapter reviews the existing literature on the use of MDMA for each of these indications.

12.2. The use of MDMA in psychotherapy

MDMA was widely used as a facilitatory drug in psychotherapy in the United States during the 1980s. The introduction of MDMA into therapy can be accredited to Dr Leo Zeff, a psychotherapist who was renowned for his regular use of drug-assisted therapies with his patients, and who was at the forefront of the psychedelic therapy movement in the 1950s and 1960s. Zeff introduced MDMA to hundreds of patients and therapists across the United States and the latter, in turn, began to use MDMA within therapy. It is estimated that between 1977 and 1985, half a million doses were distributed to patients suffering from trauma, depression and other psychological conditions [2].

MDMA was introduced into the therapeutic community because it had several properties that made it apparently well-suited to assist in psychotherapy. Both therapists and clients stated that the 'entactogenic' and 'empathogenic' quality of MDMA, heightened the capacity for introspection and intimacy within therapy. It did this by inhibiting the subjective fear response to emotional threat and temporarily freed the client from feelings of anxiety and depression. Clients reported that the particular state induced by MDMA allowed them to become less defensive and more emotionally open and therefore able to get in touch with thoughts and feelings that were not ordinarily available to them[3].

The safety psychological profile of MDMA was considered superior to that of other psychedelics in several respects. The "MDMA effect" was relatively short-acting and short-lasting, with primary effects lasting approximately 4 hours, followed by a gradual return to baseline over the course of the following 2 or so hours. Participants under the influence of MDMA remained self-aware such that they usually retained the ability to "negotiate" and move toward or away from certain thoughts or emotions [4]. By contrast, LSD had more disruptive effects, which lasted between 8 to 10 hours. By contrast, the effects of MDMA provided a greater sense of self-control, because of the milder altered state of consciousness it produced, compared to other psychedelic substances such as LSD. These beneficial properties made it attractive as an adjunct in psychotherapy.

Advocates argue that the use of MDMA in infrequent and supervised doses, combined with non-drug sessions in a structured and time-limited course of problem-focused psychotherapy, could prove a useful asset to a western health care system that is being overwhelmed with mental health problems [5]. General practitioners are stressed and under resourced, rely heavily on pharmacological treatments to meet increasing demands of patients[6]. While models of

psychotherapy are available that offer brief, time-limited and cost-efficient therapies such as: Cognitive- Behavioural Therapy (CBT) and Interpersonal Therapy (IT), even these streamlined models are time consuming and expensive[3]. Advocates report that the use of psychedelic drug-assisted therapy may be the way to accelerate and deepen the therapeutic process[7]; with the added benefits of cost-efficiency and more effective treatment of chronic mental illness sufferers who have been resistant to other treatment methods and medications[8].

MDMA would be used as a "hybrid" between pharmacotherapy and psychotherapy that incorporated features of both. That is, MDMA would be administered only in conjunction with psychotherapy, not as a sole medication. The most detailed reports on the effects of MDMA used in a therapy setting was published by psychotherapist Dr George Greer, and his wife Requa Tolbert, a psychiatric nurse[9]. Greer administered MDMA as an adjunct to psychotherapy to approximately 80 patients between 1980-1985[9] [10]. Although they did not specify a particular type of psychological issue they were focused on treating, they stated '… that the single best use of MDMA is to facilitate more direct communication between people involved in significant relationships'. They also claimed that 'communication is enhanced during and after the session and that once patients experience the lack of true risk involved in direct communication they will no longer need MDMA to resolve existing conflict issues, nor future issues of conflict' (p. 326)[11].

The practice of the MDMA-assisted therapy by these therapists was client focused, with the client initiating all therapeutic interaction with the therapist after the peak MDMA effects had passed. The therapist remained available and supportive if difficult or painful experiences occurred.

The practice of the MDMA-assisted therapy by Greer and Tolbert involved a questionnaire and interview process. Potential clients had to have been referred by other psychotherapists or by previous MDMA therapy clients. Exclusion criteria were relatively extensive: those with physical medical conditions, psychiatric illness or emotional disturbance were not eligible. Informed consent procedures were also extensive, where possible physical symptoms, side effects of the stimulation of the sympathetic nervous system, post-session symptoms and unwanted or unpleasant psychological effects or emotional material were explained. Data on the potential neurotoxicity of MDMA were unavailable at the time of the therapy, otherwise this issue would also have been discussed [12]. Greer and Tolbert (1990) thought that it was crucial to elicit a positive expectancy about the drug effects if the client was to experience a positive therapeutic outcome. The notion of having a positive expectancy of the MDMA experience prior to ingestion is also reported by recreational users as a vital component in ensuring a positive experience [13].

The drug was ingested after nominating the dosage level of "low, medium or high". The client then either sat quietly waiting to feel the drug's effects or laid down, wearing eyeshades, to remove outside distractions. Often instrumental and classical musical pieces were played. After one-and-a-half to two hours, clients were offered an additional dose of MDMA (usually 50 mg) for the purpose of extending the peak part of the experience by an hour and to make the subsidence of the effects of MDMA more gradual. Couples were encouraged to begin their session separately and come together after they had attended to their individual issues. After clients felt the MDMA state had passed, they usually discussed the experience with the therapist. Usually one to three hours were spent discussing the session to assist the integration of the experience into daily life. The therapist then assisted with the transition back to the usual state of consciousness[12].

Greer detailed the subjective experience of 29 persons who experienced MDMA-assisted therapy. Approximately 90% reported a "personally significant" and generally positive and useful experience in follow-up questionnaires[12 14]. Many reported positive individual effects, improved well-being, and the resolution of relationship problems after therapy. There were no significant physical complications reported from taking the drug, however all 29 volunteers reported some negative drug sequelae described by the authors as 'not-serious'.
Two clients did experience clinical abreactions of increased anxiety, and a significant decreased appetite followed by weight gain in the weeks after MDMA-therapy.

Greer noted that the limitation of his study was the absence of a standardised clinical measure to assess changes pre- and post- MDMA use in therapy[12 14]. The majority of positive evidence was provided anecdotally. He also acknowledged the need for double-blind randomized controlled trials of MDMA use, within therapy, to allow for more definitive data on its effects on well being. It is also not known whether clients met criteria for any mental disorders; no studies have been conducted using MDMA since the drug was scheduled in the USA.

12.3. MDMA for the treatment of post-traumatic stress disorder (PTSD)

Posttraumatic Stress Disorder (PTSD) is an anxiety disorder that may present when a person experiences or witnesses a stressful event that involves death, the threat of death or serious bodily injury to the self or another (DSM-IV)[15]. This intense experience causes reactions characterized by intense fear and feelings of helplessness or terror. The core features of PTSD as defined by DSM-IV are detailed in Table 13.1. It is estimated PTSD affects between 1.3-9% of the adult population[16].

1. Person has been **exposed to a traumatic event** in which both of the following were present: Experienced, witnessed or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others; The person's response involved intense fear, helplessness or horror.
2. The traumatic event is **persistently re-experienced** in one or more of the following ways: Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions; Recurrent distressing dreams of the event; Acting or feeling as if the traumatic event were recurring; Intense psychological distress at exposure to internal or external cues that symbolise or resemble an aspect of the traumatic event; Physiological reactivity on exposure to internal or external cues that symbolise or resemble an aspect of the traumatic event.
3. **Persistent avoidance of stimuli associated with the** trauma and numbing of general responsiveness (not present before the trauma) as indicated by three or more of the following: Efforts to avoid thoughts, feelings or conversations associated with the trauma; Efforts to avoid activities, places or people that arouse recollections of the trauma; Inability to recall an important aspect of the trauma; Markedly diminished interest or participation in significant activities; Feeling of detachment or estrangement from others; Restricted range of affect (e.g. loving feelings); Sense of foreshortened future.
4. **Persistent symptoms of increased arousal** (not present before the trauma) as indicated by two or more of the following: Difficulty falling or staying asleep; Irritability or outbursts of anger; Difficulty concentrating; Hypervigilance; Exaggerated startle response.
5. Duration of the disturbance is more than one month.
6. The disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning.

The unique properties of MDMA make it a potentially useful treatment of PTSD. It enhances feelings of openness, comfort, communication, trust and introspection and lowers anxiety and

fear, thereby allowing a client to have a controlled re-experience of the event without eliciting the strong negative emotion usually associated with it. This controlled re-experience of the traumatic event may have the long term benefit of reducing the most incapacitating symptoms of PTSD such as avoidance (MDMA may help in reducing phobic behaviour), hyperactivation (MDMA may help in reducing anxiety associated with thoughts of the event) and emotional numbing.

Rick Doblin, an advocate for the use of MDMA in therapy has suggested that 'MDMA-assisted therapy should be explored in patients who need some assistance in processing difficult emotions that have a deep seated component of fear and/or anxiety. The main categories of patients that fit this description are people suffering from Posttraumatic Stress Disorder (PTSD) and people facing terminal illness'[4]. Dobin's Multidisciplinary Association for Psychedelic Studies (MAPS) is campaigning to have MDMA registered as a prescription medication. It currently has three studies underway that involve MDMA-assisted therapy in the treatment of PTSD[4].

Several MDMA-assisted therapy double-blind randomised controlled trials are currently in progress and at the stage of phase II trials [17]. In the United States, patients that have previously been resistant to treatment are being treated; in Israel, patients with war- and terrorism- related PTSD are being treated and in Switzerland, patients with chronic PTSD are undergoing treatment. (www.maps.org/research/). Although the preliminary results from the pilot studies appeared to show some positive effects of the use of MDMA-assisted therapy, in Spain in 2002, the pilot PTSD study for treatment resistant victims of sexual assault had a crucial organisation withdraw support, and the study was cancelled[18].

12.4. Limitations and issues

There are a number of important problems with MDMA as a potential therapeutic drug, which have been summarised in a recent review by Parrott[19]. First, there has been no neurochemical rationale or explanatory model for MDMA and its purported clinical gains[19]. Indeed, the proponents of therapeutic use of MDMA specifically state that MDMA would not act as a pharmacotherapeutic agent[4], but rather, as an aid to psychotherapy[20],

Second, not all of the acute effects of MDMA are positive ones. As reviewed in Chapters 5 and 6, it is not uncommon for some ecstasy/MDMA users to report having experienced unpleasant mood states as well as cognitions. Further, from the existing evidence available on the acute effects of MDMA, it does not appear to be simple to assess who will have a positive reaction and who a negative reaction, prior to consumption of the drug. Finally, if such reactions do occur, there is no drug that may be administered to reverse the unpleasant effects. All of these problems raise some challenges for testing and use of a drug as an aid for both mood and cognitions during psychotherapy[19].

Third, as reviewed in Chapter 6, setting and expectancies seem to be particularly important determinants for the eventual experience that a user will have after consuming MDMA. Importantly, both of these preconditions may not be positively geared among persons in treatment for psychiatric problems (indeed, it might be expected that the opposite would be the case) [19].

Fourth, even if the acute experience of MDMA is a completely positive one, very well-controlled research has *also* documented a clear "come down" recovery period (Chapter 6), whereby even people without pre-existing psychiatric problems will report lowered mood, energy and sometimes irritability. This may therefore comprise a particular risk for clients who have pre-existing lowered mood states, who may be at risk of worsened mood and perhaps increased suicide risk[19]. Indeed, even the proponents of MDMA-assisted psychotherapy advised against the use of MDMA among persons with psychiatric problems because of the risk of later adverse outcomes[11].

12.5. Summary

There may be a case to be made for re-assessing the therapeutic value of psychedelic substances such as MDMA, as an adjunct to therapy for the treatment of anxiety and depressive symptoms in cases where other treatments have not been effective. One organisation has begun to conduct randomised-controlled trials of the efficacy of MDMA-assisted therapy treatment of PTSD. The proposal continues to be met with political and scientific controversy and criticism, no doubt because of the legal classification of the drug.

Further research into possible therapeutic effects of MDMA, and evaluation of possible adverse and long term reaction effects, continues to be needed. The likelihood of some adverse effects of the drug's use in the therapeutic setting will likely hamper research into this potential use of the drug.

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13.Summary and implications

Wayne Hall and Louisa Degenhardt

13.1. Acute Health Effects

In general, it is easier to assess the acute adverse health effects of a drug like MDMA than the effects of its chronic use [1]. This is for several reasons. First, it is usually clearer in the case of acute effects that they follow drug use because the two occur closely together in time and we know which came first. Second, if the effects of the drug are not dangerous, they can be reproduced in humans by giving the drug under controlled conditions. Third, if the effect is dangerous, it can often be reliably produced in a suitable animal model.

We can accordingly be confident that MDMA produces the positive psychoactive effects often reported by users, namely, euphoria, relaxation, sociability, closeness to others [2 3]. These effects have been reliably reported by the majority of users in both experimental studies of MDMA effects and in observational studies of recreational users [4]. The same is true of some of the more commonly reported adverse acute effects, such as, nausea, teeth-grinding, anxiety, difficulty sleeping, and depressive symptoms the day after use [4].

It has been more difficult to assess the causal contribution that MDMA use has made to rarer and more serious adverse effects that include hyperthermia (dangerously elevated body temperature), hyponatraemia (an imbalance in the body's sodium levels), heart attacks and liver failure. There are case reports of all of these outcomes among MDMA users, including users who have died as a consequence [5-7]. When these effects were first reported in the mid 1990s it was difficult to assess whether they were: rare events that were coincidental with MDMA use; attributable to the effects of other drugs (especially the stimulants) which were often taken together with MDMA; very rare consequences of MDMA use that only occurred at doses that were much higher than are generally used recreationally; rare effects that were due to unusual forms of personal vulnerability; the results of interactions between the MDMA and other

recreational or prescribed drugs; or the effects of contaminants produced in the process of illicit manufacture of MDMA [5 6 8].

Evidence from animal studies, and an accumulation of human cases series in the medical literature accompanied by good clinical and toxicological evaluations has clarified the causal role of MDMA in some of these adverse events [5]. The evidence for a causal role of MDMA is arguably clearest in the cases of hyperthermia and hyponatraemia. These effects have been produced in animals when MDMA administered under conditions of increased temperature like that of human users [5]. An accumulation of fatalities in MDMA has also demonstrated that these deaths can occur in persons whom toxicological evidence indicates have only used MDMA [5]. What is less certain is how often these events occur and what characteristics of users, or the circumstances of MDMA use, increase the risk of their occurrence.

The causal role of MDMA in liver disease and adverse cardiovascular events is less clear for a number of reasons, namely, there have been far fewer such deaths among MDMA users and so less opportunity to study the contribution that MDMA and other drugs have made to these deaths [5]; animal studies do not report these outcomes as common ones; and cardiovascular and cerebrovascular deaths are more often reported after the use of amphetamines and cocaine [9] that have often been used by MDMA users who develop these complications.

13.2. Chronic Health Effects

Animal evidence that MDMA has neurotoxic effects on serotonergic neurons has raised concerns about the possible effects of chronic MDMA use on the emotional and cognitive functioning of human users. These effects of MDMA have been more difficult to evaluate than the acute adverse effects because of the time lag between MDMA use and the occurrence of these adverse effects, with the longer the time interval raising more numerous alternative explanations of the association that need to be excluded [1].

Suggestive evidence of neurotoxicity in human MDMA users has emerged over the last decade from neuroimaging and neuropsychological studies of regular MDMA users [5 8 10]. Some brain imaging studies [11 12] have reported reduced density of serotonin binding in several brain regions of MDMA users that correspond to areas showing post mortem changes in baboons following neurotoxic doses of MDMA[13 14]. Modest behavioural and cognitive deficits have been observed in laboratory animals given neurotoxic doses of MDMA [15]. There have been case reports of neuropsychiatric sequelae after MDMA use [16 17], and there are controlled studies reporting cognitive and emotional problems in MDMA users [8 10 18].

Adverse effects of MDMA on mood are biologically plausible. Persons who are depressed and who have committed suicide show abnormal serotonin function [19] and many users report transient depression in the days following MDMA use that takes up to a week to resolve [20 21]. This pattern of mood change is consistent with MDMA's short-term effects on the levels of brain serotonin [21]. There are also a high prevalence of depressive symptoms reported by Australian MDMA users [22] that were related to their frequency of MDMA use, the usual reported dose of MDMA, binge use of MDMA, and the number of other drugs that were used to manage the after-effects of MDMA use. [22]

It is also biologically plausible that serotonergic damage may adversely affect memory and higher cognitive function because the hippocampus (which is intimately involved in memory function) is densely innervated by serotonergic neurons that appear to be most susceptible to MDMA's neurotoxic effects. [23] There is some animal evidence that high doses of MDMA produces deficits in working memory in rats. [24] Human studies also suggest that MDMA disrupts short-term memory (e.g. [20 25]) and longer term memory and cognition (e.g. [20 25-28]). Some studies have show greater memory deficits in MDMA users than in a control group of polydrug users who have not used MDMA. [28]

A common interpretative problem with these findings is that regular MDMA use is correlated with other types of illicit drug use that may also adversely affect mood, memory and cognitive performance. Generally, the heavier the MDMA use, the more likely that the person also uses psychoactive drugs [22 29 30] that may explain associations between MDMA use and poor memory performance and impaired mood. The use of other drugs such as cannabis, ATS and cocaine, is a special challenge, for example, in interpreting the causal role of MDMA use in producing symptoms of depression.

When studies fail to find any adverse effects of chronic MDMA use on memory or cognitive performance interpretation may be is unclear for different reasons. Is this because MDMA has few, if any such effects in humans? Is it because most human subjects have not had enough exposure to MDMA to produce such effects? Is it because the studies have not had the sensitivity to detect any such effects? Answers to these questions depend upon the likely magnitude of any adverse effects, their relationship to MDMA dose, frequency and duration of use, and the ability of studies with the small sample sizes of users to detect them [31]. The issue of statistical power and expected effect size requires more attention in the design and reporting of studies of human users.

13.3. Implications for Research

We can in principle specify the type of evidence that would enable confident inferences to be made about the adverse health effects of MDMA use in humans. This would be evidence from prospective studies in which a large representative sample of MDMA-naïve subjects were comprehensively assessed psychologically and then randomly assigned to receive either MDMA or placebo. Their mood, memory and cognitive abilities would then be assessed over a period of years, if not decades, to see what if any effects MDMA use had on these outcomes. For obvious ethical reasons no such study will ever be done. In its absence, we have to rely upon the consillience of evidence from a variety of different types of observational and experimental human studies, supported by tests of biological plausibility in suitable animal models.

One obvious priority is the conduct of large observational studies of the effects of MDMA on psychological outcomes in young adults. These studies will need to include large and representative samples of young people. This will ensure that a broader pattern of MDMA use is sampled and the relationship assessed between varying doses and durations of MDMA use and mood, memory, cognitive performance and psychosocial outcomes. These studies can be most economically conducted by ensuring that existing cohort studies of young adults inquire about the use of illicit drugs like MDMA. A growing body of similar research on the effects of cannabis use provides a useful model of the study designs and methods of analysis that can be used in such studies [32-34]. This is the type of study that will also be required to produce credible estimates of the relative and attributable risks of the various adverse outcomes that have been attributed to MDMA use.

A second priority will be more detailed and better controlled studies of the adverse effects of regular MDMA. This requires larger, better controlled clinical, neuropsychological and neuroimaging studies of psychological functioning in regular MDMA users. These studies need to use more appropriately matched and larger control groups than has been done to date. Traditionally these samples have been opportunistically recruited by advertisement and snowball sampling. In future such samples could be obtained from the more regular MDMA users identified in cohort studies. Polydrug users who have not used MDMA in these cohort studies would be a suitable comparison group, in addition to young people who have not used any illicit drug. The polydrug using control group controls for some of the pre-existing psychological differences (e.g. impulsivity, rebelliousness) that predispose some young people to be more likely to use MDMA and for the effects of other illicit drug use.

There is also a place for a research strategy that is intermediate between epidemiological and clinical approaches, namely, intensive studies of large samples of young adults who have been selected as being at high and low risk of illicit drug initiation, as defined by social and family characteristics and personal history (e.g. poor school performance in secondary school). These samples would be comprehensively assessed before the age of initiation of MDMA and other illicit drugs using neuropsychological, neuroimaging and psychosocial measures. The samples would then be prospectively followed and regularly assessed using the same neuropsychological and neuroimaging methods to assess any effects that MDMA use has on cognitive performance. Statistical methods would be used to separate out the effects of any pre-existing differences between the two groups in characteristics [35].

Finally, MDMA users who show signs of impaired memory and mood disorders should also be followed over time to determine whether their problems resolve with abstinence, or indeed, increase with continued use and age. PET and other imaging studies could be combined with neuropsychological assessments of large samples to assess any relationships between decreases in serotonin uptake in specific brain regions and memory loss, mood disorders and cognitive performance. This would parallel similar studies of the cognitive effects of chronic cannabis use [36].

13.4. References

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