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The development of materials on ecstasy and related drugs (ERDs) for health care practitioners

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THE DEVELOPMENT OF MATERIALS ON ECSTASY AND RELATED DRUGS (ERDS) FOR HEALTH CARE PRACTITIONERS

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ABBREVIATIONS

5-HTP	5-hydroxytryptophan
ACT	Australian Capital Territory
ADHD	Attention deficit hyperactivity disorder
ADRAC	Adverse Drug Reactions Advisory Committee
BDI	Beck Depression Inventory
BZP	Benzylpiperazine
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPDP	Continuing Professional Development Program
DMT	Dimethyltryptamine
DXM	Dextromethorphan
ERDs	Ecstasy and related drug(s)
FRACGP	Fellowship of the Royal Australian College of General Practitioners
GHB	Gamma-hydroxybutyrate
GP	General practitioner
HATS	Hunter Area Toxicology Service
IT	Information technology
LSD	*d*-lysergic acid
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MDA	3,4-methylenedioxyamphetamine
MDMA	3,4-methylenedioxymethamphetamine
NARI	Noradrenaline reuptake inhibitor
NASSA	Noradrenaline and specific serotonin antagonist
NCIS	National Coroners Information System
NMS	Neuroleptic malignant syndrome
NSW	New South Wales
NT	Northern Territory
PCP	Phencyclidine
PMA	Paramethoxyamphetamine
QLD	Queensland
REU	Regular ecstasy user(s)
RIMA	Reversible inhibitor of monoamine oxidase
SA	South Australia
SDS	Severity of Dependence Score
SNRI	Serotonin-noradrenaline reuptake inhibitors
SPSS	Statistical Package for the Social Sciences
SSRI	Selective serotonin reuptake inhibitor
TAS	Tasmania
TCA	Tricyclic antidepressants
VIC	Victoria
WA	Western Australia

EXECUTIVE SUMMARY

The amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) or 'ecstasy' is a widely used illicit drug. Research consistently shows that extensive polydrug use is the norm among ecstasy and related drug (ERDs) users and that a range of pharmaceuticals (e.g. benzodiazepines, sidenafil) and supplements (e.g. 5-hydroxytryptophan (5-HTP), St. John's wort) are deliberately combined with ecstasy, often for contradictory purposes. This practice is of concern as the popularity of ecstasy is continuing to increase in Australia and a number of ecstasy-pharmaceutical combinations can have serious health consequences. One of the emerging harms associated with ecstasy use is serotonin toxicity, commonly referred to as serotonin syndrome.

Generaly, doctors are well positioned to respond to patients with drug-related issues because of their accessibility, credibility and likely frequent exposure to patients with substance use problems. Evidence also suggests that people prefer a response to substance use problems to come from their general practitioner (GP). Unfortunately, there is evidence that the involvement of GPs in screening for illicit drug use is limited, and consequently many problems may remain undetected or be misdiagnosed. Little is known about the extent of screening for ERDs use when young people are prescribed pharmaceutical drugs by their GP. Furthermore, among Australian healthcare professionals in general practice and hospital settings, there is a lack of research exploring the awareness of ERDs and the potential harms of concomitant use of pharmaceutical drugs. The present study grew from these concerns, and aimed to:

- Identify gaps in knowledge among GPs about the effects and harms of ERDs use and the management of young people who are prescribed pharmaceutical drugs.
- Identify gaps in knowledge among frontline (e.g. Emergency Department) healthcare professionals about the effects and harms of ERDs use.
- Identify the patterns of use related to the practice of combining ecstasy with pharmaceutical drugs, in particular antidepressants, and to explore the experiences of ERDs users when visiting a GP.
- Inform the development of resource materials on ERDs for healthcare practitioners.

Serotonin toxicity

The view that serotonin toxicity is a drug-induced toxic state caused by an excess of serotonin within the central nervous system has been well supported over several decades. A comprehensive review of the literature reveals that numerous substances have been implicated in serotonin toxicity including a range of illicit drugs (e.g. ecstasy, methamphetamine, cocaine, *d*-lysergic acid (LSD)), antidepressants (e.g. *Nardil, Prozac, Aurorix, Efexor*), opiate analgesics (e.g. tramadol), migraine medications (e.g. dihydroergotamine) and supplements (e.g. St. John's wort, 5-HTP). When these substances are used with ecstasy, there is a demonstrated potential for increased toxicity.

Survey of general practitioners

A random sample of 2000 GPs stratified to include metropolitan and non-metropolitan areas across Australia were surveyed. Questionnaires were returned by 199 GPs. The mean age of GPs was 54 years and the majority were male.

This study identified numerous deficits in relation to GP's knowledge of ERDs and associated problems. Among GPs there was a self-reported lack of knowledge about ecstasy and ecstasy-related problems, and subsequently, a majority reported they did not feel well prepared to discuss the health risks associated with ecstasy use. Only half of GPs reported having a clear idea of their responsibilities in helping patients who were using ecstasy. A relatively small minority of GPs agreed they had a working knowledge of other drugs such as methamphetamine and gamma-hydroxybutyrate (GHB). There was a strong demand for ERDs-related resource materials among GPs.

ERDs-related presentations were commonly reported by GPs. Approximately half of the GPs surveyed mentioned that they saw such presentations on a yearly or more frequent basis. GPs were more likely to see methamphetamine-related presentations than ecstasy-related presentations. Presentations related to GHB were very rarely seen by GPs in their practice.

Among GPs overall, there was limited evidence of screening for ecstasy use when prescribing antidepressants or sidenafil (e.g. *Viagra*) to young patients (i.e. aged less than 30 years). Only a small minority routinely (e.g. always) screened for ecstasy use when prescribing antidepressants. Younger GPs, and those who saw ecstasy-related presentations more frequently, were more likely to screen for ecstasy use when prescribing antidepressants to young patients. Of further concern is that on those occasions when GPs prescribed antidepressants, few routinely discussed the complication of serotonin toxicity with their patients. Acute presentations of serotonin toxicity were seen very infrequently by GPs.

Survey of frontline healthcare professionals

An additional arm of this project included the delivery of a presentation on current trends in ERDs and associated problems to interested frontline healthcare professionals at 12 hospitals in major centres across Australia. Attending healthcare professionals completed a survey which aimed to identify gaps in knowledge about the effects and harms of ERDs use, the incidence of ERDs-related presentations and resource development.

In contrast to the findings from GPs, a substantial majority of frontline healthcare professionals agreed they had a working knowledge of ecstasy, methamphetamine, GHB, cocaine and ketamine (in the context of illicit use). Subsequently, a large majority felt prepared to discuss the health risks associated with the use of these drugs. There was a strong demand for ERDs-related resource materials among frontline healthcare professionals, particularly in relation to the clinical management of ERDs users.

ERDs-related presentations were seen with greater frequency in the hospital setting than in general practice. Among frontline healthcare professionals, acute presentations related to methamphetamine were most commonly reported, this was followed by ecstasy- and GHB-related presentations. Contrary to reports in the popular media, only a relatively small proportion of frontline healthcare professionals saw ERDs-related presentations on a daily basis. As would be expected, acute presentations of serotonin toxicity were more

commonly reported by frontline healthcare professionals at major hospitals than by GPs in their practice.

Interviews with ERDs users

Evidence that healthcare professionals in general practice and the hospital setting regularly manage patients with ERDs-related problems suggested a need to explore, in more depth, the experiences of ERDs users when they use serotonergic drugs and substances. In-depth interviews were conducted with 30 ERDs users who had recently combined ecstasy and antidepressant drugs.

The mean age of participants was 34 years and the majority were male. Participants reported the recent use of ecstasy and a wide range of other licit and illicit drugs, several of which have been implicated in serotonin toxicity. The majority of participants had recently used the powdered ('speed') or crystalline ('ice') form of methamphetamine and all reported an extensive history of cannabis use. Consistent with selection criteria, a large proportion of participants were regularly taking antidepressant drugs for a current health condition. Participants, on average, reported low levels of depressive symptoms.

There was generally a high incidence of the use of prescription pharmaceuticals with ecstasy among participants. This included the use of antidepressant drugs for non-medical purposes to counteract the negative after-effects of ecstasy, and to a much lesser extent, the use of antidepressants putatively to intensify and lengthen the ecstasy 'high'. Benzodiazepines (e.g. *Valium*) or sleeping tablets were typically used with ecstasy to assist with sleep during the 'comedown' period. Sidenafil and other similar drugs were frequently used with ecstasy to counteract the erectile dysfunction secondary to ecstasy use. This practice is of some concern as the use of sidenafil and other similar drugs in this way may lead to an increased likelihood of sexual risk-taking while intoxicated. Other substances taken before, during or after ecstasy use included methylphenidate (e.g. *Ritalin*), 5-HTP, St. John's wort and multivitamins.

It was not uncommon for pharmaceutical drugs to be attained without prescription, and friends were the main source of prescription drugs attained in this way. The second most common source of pharmaceutical drugs was from drug dealers. Benzodiazepines, sidenafil and antidepressants were the drugs most commonly acquired from these sources.

The majority of participants had told their GP about their use of ecstasy and the GP's response in most cases was reported to be professional and non-judgemental. For many, the nature of the therapeutic relationship was such that they would feel comfortable raising questions about ecstasy and other drugs with the GP they saw regularly.

During consultations where participants were prescribed pharmaceutical drugs such as antidepressants, sidenafil, benzodiazepines and sleeping tablets, few mentioned that the GP asked them about their use of ecstasy, however, in many cases, the GP already knew of their ecstasy use. Based on participants' experiences when they visit a GP, prior to being prescribed benzodiazepines, sleeping tablets or antidepressants, most were assessed for symptoms of anxiety, sleeplessness or depression respectively. When prescribed sidenafil and other similar drugs, however, only a small minority reported being screened for erectile dysfunction. In cases where GPs prescribed benzodiazepines and sleeping tablets, it was encouraging to find that they frequently discussed with patients possible alternatives to taking the pharmaceuticals prescribed.

Recommendations

This study highlights that a wide range of drugs and supplements have serotonergic properties and have been implicated in serotonin toxicity. When used with ecstasy, many of these substances have a demonstrated potential for increased toxicity, this is particularly the case with some antidepressants. As perhaps would be expected, ERDs-related presentations were found to be more common in the acute hospital setting than in general practice. Nevertheless, in both settings there was a strong demand for ERDs-related resource materials. There is convincing evidence that, among GPs, screening patients for ecstasy use is rarely carried out. In-depth interviews with ERDs users revealed a group of polydrug users potentially at risk of serious health consequences. In regard to the findings presented here, a number of recommendations are enunciated below:

General practitioners

It is important that GPs are well informed of the effects of ERDs and the harms associated with their use. A strong demand for such information has been demonstrated and resources which focus on the following are likely to be of benefit to GPs:

- Management of ERDs users in general practice
- Referral of ERDs users
- Effects and harms of ERDs
- Effects and harms of ERDs and the concomitant use of pharmaceutical drugs
- Harm minimisation strategies for ERDs users
- Specific information on ecstasy, methamphetamine, GHB and ketamine
- Screening of patients who present to GPs with symptoms related to ERDs use

Methods of resource delivery which are likely to be effective in the general practice setting may include:

- Pamphlets and booklets
- Fact-sheets and bulletins
- Continuing Professional Development Programs (CPDP)
- Internet-based resources (e.g. *Medical Director*)
- Seminars/workshops

Collaboration with organisations such as the Fellowship of the Royal Australian College of General Practitioners (FRACGP) or the Australian Medical Association (AMA) would help facilitate the development and implementation of a series of ERDs-related seminars or workshops specifically tailored to the needs of GPs.

In addition, information may be disseminated through existing publications for medical practitioners (e.g. *Medical Observer, Australian Medicine*). This could be in the form of a series of ERDs-related articles appearing over several weeks or months. Consideration should also be given to purchasing space within these publications where bulletins or fact-sheets pertaining to ERDs can be published.

GPs are ideally placed to respond to people who present with drug-related problems. There is evidence that screening for ecstasy use was limited among GPs. This strongly suggests a need to increase awareness among GPs of the importance of screening for ERDs use, especially among younger patients, and to develop a screening tool that will improve the screening of patients who present to GPs with ERDs-related symptoms.

There is also scope for developing an ERDs-related training module suitable for graduate medical programs. Collaboration with tertiary institutions may help to facilitate this.

Frontline healthcare professionals

Frontline healthcare professionals have a set of needs in relation to resources on ERDs which vary somewhat from those of GPs. For this group, resources which focus on the following are likely to be of benefit:

- Clinical management of ERDs users in the acute care setting
- Referral of ERDs users
- Effects and harms of ERDs
- Effects and harms of ERDs and the concomitant use of pharmaceutical drugs

An internet or web-based resource would be easily accessible to frontline healthcare professionals who frequently work in a busy clinical environment. A resource with a focus on the clinical management of ERDs users in the hospital setting would be particularly well received. Attention should be paid to providing information on methamphetamine and GHB, as acute presentations to hospitals are frequently associated with these drugs.

The development of a brief intervention, with proven efficacy, which can be administered by frontline healthcare professionals prior to the discharge of a patient who has presented with ERDs-related problems is essential. Such a brief intervention may also help to increase the referral of people with ERDs-related problems to drug and alcohol treatment services. Developing a brief intervention for people who have presented to hospital after GHB overdose is a priority.

Given the success of the ERDs presentations delivered to frontline healthcare professionals as part of this study, consideration should be given to the development of a formal series of ERDs-related presentations that could be delivered to healthcare professionals in the hospital setting.

Potential also exists to adapt the Ecstasy and Related Drug Trends Bulletin, published quarterly by NDARC as part of the Ecstasy and Related Drug Reporting System (EDRS), for GPs and frontline healthcare professionals and distribute it to interested clinicians.

Ecstasy and related drug users

The use of a wide range of licit and illicit substances by ERDs users is of concern. There is a need to more clearly delineate strategies which will inform users of the potential harms of this practice. It is crucial that resources targeting ERDs users, and young people who may be more likely to experiment with ERDs, be developed which focus on the following:

- Strategies to prevent ERDs use

- Harms associated with ERDs use
- Potential harms of combining ERDs with pharmaceutical drugs
- Strategies to minimise the harms associated with ERDs use
- Accessing drug and alcohol treatment services

The following approaches are likely to be effective in accessing ERDs users:

- Pamphlets and booklets
- Internet and web-based sites aimed at young people
- Internet and web-based sites aimed at ERDs users
- Fact-sheets (linked to internet and web-based sites)

Forming partnerships with organisations that maintain existing, popular, youth-oriented internet sites (e.g. *Enlighten*) may be a way to further disseminate relevant health information to ERDs users.

Peer-led education interventions play an important role in propagating health messages to young people about the harms associated with ERDs use. Collaboration with established peer-led education organisations (e.g. *KIS*, Manly Drug Education and Counselling Centre, NSW; *Save-a-mate*, Red Cross, Australia) is vital.

There is scope to develop ERDs-related learning modules specifically for peer-led organisations. These modules could then be offered to peer-led education organisations and subsequently integrated into the training these organisations provide for their peer educators on ERDs.

In addition, collaboration with relevant government departments (e.g. Department of Education, Science and Training; DEST) will aid the development and implementation of best practice policies in education and training related to ERDs. For example, findings from this study could be used to enhance school-based resources such as the Resilience Education and Drug Information (REDI) resources, part of the National School Drug Education Strategy (NSDES), which focuses on preventing and reducing drug related harm in young people.

Further ERDs-related research

As large gaps still remain in knowledge about the effects of ERDs and their potential to interact with pharmaceuticals, supplements and each other further research into this area is essential. There is a pressing need to explore the long-term effects of ERDs use and a prospective study, preferably utilising a large cohort of ERDs users, would be valuable and contribute greatly to current knowledge.

1 INTRODUCTION

The amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) or 'ecstasy' is a widely used illicit drug (United Nations Office on Drugs and Crime, 2005). Since 2001, the use of ecstasy in Australia has increased and it has now become the second-most popular illicit substance after cannabis (Australian Institute of Health and Welfare, 2005). Whereas most other illicit drugs show patterns of stable or decreasing use in recent surveys, the proportion of Australians aged 14 years and over reporting use of ecstasy significantly increased between 2001 and 2004. According to the 2004 National Drug Strategy Household Survey, 3.4% of Australians had used ecstasy during the last 12 months and 7.5% had used ecstasy in their lifetime (Australian Institute of Health and Welfare, 2005).

Recent research among ecstasy and related drug (ERDs) users shows that a range of pharmaceuticals and supplements are deliberately used in a variety of combinations and often for contradictory purposes (Copeland et al., 2006). This practice is of concern as the popularity of ecstasy is continuing to increase in Australia and a number of ecstasy-pharmaceutical combinations can have serious health consequences (Australian Institute of Health and Welfare, 2005; Copeland et al., 2006). In particular, one of the emerging harms associated with ecstasy use is serotonin toxicity, commonly referred to as serotonin syndrome.

1.1 Patterns of drug use among ecstasy users

Research consistently shows that extensive polydrug use is the norm among ecstasy users (Australian Institute of Health and Welfare, 2002; Cottler & Womack, 2001; Degenhardt et al., 2005; Dunn et al., 2007; Topp et al., 1999). A 2006 study of a sentinel population of regular ecstasy users (REU) across Australia found, on average, REU had used seven drugs in the preceding six months. The main illicit drugs REU had recently used were cannabis (83%), methamphetamine powder ('speed', 64%), crystalline methamphetamine ('ice', 49%), cocaine (37%), methamphetamine base (34%), LSD (29%), ketamine (14%) and GHB (8%) (Dunn et al., 2007). Hence the term ERDs will be used in this report to describe the wide variety of drugs which may be used by ecstasy users in a particular setting.

A proportion of REU in that study also reported using a range of pharmaceuticals. It is worthwhile noting that among some ecstasy users, the use of pharmaceutical drugs may be related to various aspects of their ecstasy use. Recent use of antidepressants among REU ranged from 6% in QLD up to 20% in NSW. Recent use of benzodiazepines (e.g. *Valium, Serapax, Mogadon*) among REU was lowest in ACT (20%) and highest in QLD (37%). Recent use of pharmaceutical stimulants (e.g. *Ritalin*) among REU ranged from 7% in NSW to a high of 60% in WA, almost three times the national average (21%)(Dunn et al., 2007). This suggests that a substantial proportion of pharmaceutical stimulant use is likely to be for non-medical purposes.

Typically, REU have used other illicit drugs on the same occasion they used ecstasy. Cannabis was used by nearly half (45%) of REU in conjunction with ecstasy. More than one-quarter (27%) of those that reported use of other drugs with ecstasy used methamphetamine powder ('speed'); other drugs reported included crystal

methamphetamine (17%), methamphetamine base (9%), cocaine (5%) and LSD (5%)(Dunn et al., 2007).This pattern of polydrug use has potentially serious health consequences as several of the drugs REU have reported using show serotonergic potency (e.g. amphetamine, cocaine, LSD), even more so if used with ecstasy, and have been implicated in severe serotonin toxicity (Boyer & Shannon, 2005; Hall & Buckley, 2003; Sampson, 1999).

A recent cross sectional survey of 216 adults, who had used ecstasy at least once in the previous six months, highlighted an emerging trend in polydrug use which is of particular concern (Copeland et al., 2006). That study found about a quarter of participants had deliberately used pharmaceuticals in conjunction with ERDs in order to achieve a specific effect. Most pharmaceuticals were combined with ecstasy, however, participants also reported combining pharmaceuticals with amphetamines, ketamine, crystal methamphetamine and GHB in an attempt to negate certain side-effects. The pharmaceuticals most likely to be used in conjunction with ERDs were sidenafil (e.g. *Viagra*) and benzodiazepines. Sidenafil was most likely to be used to gain or maintain an erection, although some people combined the pharmaceutical with ecstasy for its perceived aphrodisiac qualities. Benzodiazepines were typically used to assist with the comedown period after ecstasy use. A number of participants also reported deliberately taking antidepressants together with ERDs. In the context of ecstasy use, this was regarded by participants as a way to enhance the effects of ecstasy, or to ease the recovery period following acute ecstasy intoxication. This practice was associated with a number of negative health consequences. The study found that people who deliberately used antidepressants together with ecstasy were more likely to report potentially serious serotonergic effects such as muscle rigidity, nystagmus (involuntary eye movement), dizziness, headache and profuse sweating, than those who only used ecstasy (Copeland et al., 2006).

Copeland et al. (2006) found a difference between the proportion of ERDs users who had ever used pharmaceuticals and the proportion who had ever been prescribed these drugs. For example, 22% had used pharmaceutical stimulants while only a relatively small fraction (4%) of these people had ever been prescribed them; and 37% had used antidepressants while only 25% had ever been prescribed this drug class. This discrepancy suggests that ERDs users obtain pharmaceutical drugs from sources other than general practitioners (GP). In keeping with this, friends were found to be the most common source of pharmaceutical drugs among ERDs users.

Further exploration of the accessibility of prescription pharmaceutical drugs to ERDs users and the potential harms of combining ecstasy with other serotonergic drugs and substances is essential.

1.2 Screening and intervention for illicit drug use

Among one group of regular ecstasy users, Copeland et al. (2006) found that doctors were mainly used for information relating to the side effects of ERDs, including information on the potential harms of combining ERDs with pharmaceutical drugs. Generaly, doctors are well positioned to respond to patients with drug-related issues because of their accessibility, credibility and likely frequent exposure to patients with substance use problems (Deehan et al., 1998; Roche, 1993; Sanson-Fisher et al., 1986).

Evidence also suggests that people prefer a response to substance use problems to come from their general practitioner (Hindler et al., 1995; Roche et al., 1996; Roche et al., 2002; Wallace & Jarman, 1994). The research into relatively brief interventions by general practitioners has been encouraging and shows that these strategies can be effective ways to reduce or eliminate smoking and the misuse of alcohol (Cormack et al., 1989; Fiore et al., 1990; Israel et al., 1996; Kaner et al., 2007; McIntosh et al., 1997; Ockene et al., 1999; Richmond & Anderson, 1994). Furthermore, brief interventions for excessive drinking have been shown to still have a significant effect over 12 months later (Fleming et al., 1997). Whether similar strategies can also be effective in reducing the misuse of ecstasy and other illicit drugs remains to be demonstrated.

Unfortunately, there is evidence that the involvement of general practitioners in screening for illicit drug use is limited (Blum et al., 1996; Friedman et al., 2001; Kamerow et al., 1986; Maheux et al., 1999), and consequently many problems may remain undetected or be misdiagnosed. Little is known about the extent of screening for ERDs use when young people are prescribed pharmaceutical drugs by their GP. Furthermore, among Australian healthcare professionals in general practice and hospital settings, there is a lack of research exploring the awareness of ERDs and the potential harms of concomitant use of pharmaceutical drugs.

1.3 Serotonin toxicity

As mentioned earlier, one of the potential harms associated with the use of ecstasy and other serotonergic substances is serotonin toxicity. A comprehensive search was conducted to identify all relevant studies, regardless of publication status, up to and including 2006. On-line databases searched included Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline and PubMed. Search terms included, but were not limited to: ecstasy (MDMA) and other widely used illicit drugs; serotonin syndrome/toxicity; monoamine oxidase inhibitors (MAOIs); selective serotonin reuptake inhibitors (SSRIs); tricyclic antidepressants (TCAs); reversible inhibitors of monoamine oxidase (RIMAs); serotonin-noradrenaline reuptake inhibitors (SNRIs); and other known serotonergic pharmaceuticals and supplements. A minority of search terms were sourced from websites related to ecstasy use. In addition, where appropriate, national medical and pharmacological experts were consulted.

Serotonin toxicity, otherwise known as serotonin syndrome, is a drug-induced toxic state caused by an excess of serotonin within the central nervous system. (Gillman, 2004, 2006b). Serotonin is a neurotransmitter, a signalling molecule, thought to have a major influence on mood, sleep, appetite, temperature regulation, pain perception and emesis (Boyer & Shannon, 2005; Sporer, 1995). Depression is frequently associated with low concentrations of serotonin (Hall & Buckley, 2003). Serotonin also regulates intestinal action, blood vessel constriction, uterine contraction, blood clotting and bronchoconstriction (Ener et al., 2003). The quantity and action of serotonin is closely regulated by a combination of reuptake mechanisms, feedback loops and metabolising enzymes. The molecular mechanism of serotonin action is complex (Boyer & Shannon, 2005; Hall & Buckley, 2003). In simple terms, serotonin is produced in nerve cells where it is stored until it is needed for neurotransmission. After nerve stimulation, serotonin is released into the space between nerve cells and binds to receptors to effect neurotransmission. A feedback loop stops the production of serotonin and a reuptake mechanism returns serotonin back to nerve cells where it is later broken down.

1.3.1 Implicated substances

A striking number of substances have been associated with serotonin toxicity including a range of illicit drugs, antidepressants, opiate analgesics, migraine medication and herbal products (Boyer & Shannon, 2005; Ener et al., 2003; Gillman, 2006a; Hall & Buckley, 2003; Sampson, 1999). These substances are listed in Table 1.

The increased use of agents which effect serotonergic pathways, especially antidepressants, has resulted in serotonin toxicity being recognised more frequently over the last decade (Adverse Drug Reactions Advisory Committee, 2004; Mackay et al., 1999a; McManus et al., 2000; Sporer, 1995). It is difficult to associate an overall rate of morbidity or mortality with serotonin toxicity as the extent of toxicity depends on the type and quantity of substance ingested (Gillman, 2006b). Generally drugs with two different mechanisms of action on serotonin must be combined before elevations of central nervous system serotonin reach potentially fatal levels. Nearly all reported cases of serotonin toxicity have occurred in people taking a combination of antidepressants and other psychotropic agents (Birmes et al., 2003; Boyer & Shannon, 2005; Hall & Buckley, 2003; Sampson, 1999). These potentially fatal interactions have serious ramifications for people using antidepressants therapeutically who may incidentally use, deliberately or not, other serotonergic agents including ecstasy.

Patterns of antidepressant drug use

It is particularly relevant to examine patterns of antidepressant drug use as a substantial proportion of these drugs have been implicated in serotonin syndrome. In most developed countries the antidepressant market has expanded greatly. The situation in Australia has followed the international trend, with utilisation rates rising dramatically over the last decade. Between 1990 and 1998 the use of antidepressants in Australia increased almost three-fold (Mant et al., 2004; McManus et al., 2000). The classification and brand names of antidepressants prescribed in Australia are listed in Table 2.

In Australia, a new market opened in 1990 with the introduction of fluoxetine. Moclobemide followed in 1992 along with sertraline and paroxetine in 1994. Venlafaxine entered the market in 1996 (Hegarty, 2005; McManus et al., 2000). In 2002, SSRIs dominated the antidepressant market in Australia and represented the majority (65%) of antidepressant sales. The percentage of total antidepressant sales represented by other antidepressants or classes of antidepressant was as follows: the SNRI venlafaxine, 14%; TCAs, 9%; the RIMA moclobemide, 5%; all other antidepressants, including MAOIs, 5% (Mant et al., 2004).

A greater awareness of new medical therapies, better tolerability of newer antidepressants, and subsidised access to new pharmacological agents is likely to have driven the rapid uptake of antidepressants (Mackay et al., 1999b; Mant et al., 2004; McManus et al., 2003). Since the late 1990s the growth in antidepressant prescribing has begun to plateau (Mant et al., 2004). In keeping with the global increase in the use of antidepressants, reports of serotonin toxicity have become more frequent (Mackay et al., 1999a; Sporer, 1995).

Table 1: Substances implicated in serotonin toxicity and effect on serotonin

Inhibit serotonin reuptake	Inhibit serotonin metabolism	Release serotonin
SSRIs	St John's wort^	amphetamine
paroxetine		methamphetamine
sertraline	**MAOIs**	MDMA^
fluoxetine	tranylcypromine	cocaine^
fluvoxamine	phenelzine	
citralopram	nialamide	**Serotonin precursors**
	isoniazid	
SNRIs	iproniazid	
venlafaxine	isocarboxazide	5-hydroxytryptophan
sibutramine	pargyline	L-tryptphan
milnacipranº	selegiline	
duloxetineº	clorgyline	**Partial serotonin agonists** **
	furazolidone	
TCAs	procarbazine	
clomipramine	linezolid	LSD
imipramine		dihydroergotamine
	RIMA	bromocriptine
Opioid analgesics	moclobemide	buspirone
tramadol		lithium*
meperidine		
fentanyl		
methadone		
dextromethorphan		
dextropropoxyphene		
pentazocine		
Antihistamines		
chlorpheniramine		
brompheniramine		

ºNot yet available in Australia
^Also inhibits serotonin reuptake
*Mechanism of action not entirely known
**Partial serotonin agonists can act as agonists which stimulate a receptor and/or antagonists which block a receptor

Table 2: Antidepressant drug classification and brand name

Type of antidepressant	Drug name	Brand name
Tricyclic antidepressants (TCAs)	clomipramine*	Anafranil, Placil
	imipramine*	Melipramine, Tofranil
	nortriptyline	Allegron
	amitriptyline	Endep, Tryptanol
	dothiepin	Dothep, Prothiaden
	trimipramine	Surmontil
	doxepin	Deptran, Sinequan
Monoamine oxidase inhibitors (MAOIs) (irreversible)	phenelezine*	Nardil
	tranylcypromine*	Parnate
Selective serotonin reuptake inhibitors (SSRIs)	citalopram*	Celapram, Cipramil, Talam, Talohexal
	fluoxetine*	Auscap, Fluohexal, Lovan, Prozac, Zactin
	escitalopram	Lexapro
	sertraline*	Zoloft
	fluvoxamine*	Faverin, Luvox, Movox
	paroxetine*	Aropax, Oxetine, Paxtine
Reversible inhibitors of monoamine oxidase A (RIMAs)	moclobemide*	Arima, Aurorix, Clobemix, Maosig, Mohexal
Serotonin/noradrenaline reuptake inhibitors (SNRIs)	venlafaxine*	Efexor, Efexor-XR
	milnacipran*º	Ixel, Midalcipran
	duloxetine*º	Cymbalta, Xeristar
Other antidepressants	mirtazapine (NASSA†)	Avanza, Axit 30, Mirtazon, Remeron
	mianserin	Lumin, Tolvon
	robexetine (NARI‡)	Edronax

*Antidepressants with clinically relevant serotonergic potency (Dunkley et al., 2003; Gillman, 2005)
ºNot yet available in Australia
†NASSA=Noradrenaline and specific serotonin antagonist
‡NARI=Noradrenaline reuptake inhibitor

1.3.2 Diagnosis and management

As early as 1960 there were case reports of serotonin excess or toxicity (Oates & Sjoerdsma, 1960). Three decades later Sternbach derived diagnostic criteria for what was termed the serotonin syndrome (Table 3) (Sternbach, 1991). A number of difficulties with the diagnosis of serotonin syndrome more recently have been identified, particularly with the use of Sternbach's criteria. A significant problem is the inclusion of four criteria that relate to mental status. As only three are required to occur for the diagnosis of

serotonin syndrome, this weights the definition towards patients with an abnormal mental state. For example, someone with delirium (e.g. anticholinergic delirium) would meet the clinical criteria (confusion, hypomania, agitation, inco-ordination) (Dunkley et al., 2003). In addition, the severity of the symptoms of serotonin syndrome were not taken in to account by Sternbach (Hegerl et al., 1998). Subsequently, numerous commentators have revised the original criteria proposed by Sternbach (Dunkley et al., 2003; Gillman, 2006a; Hegerl et al., 1998; Radomski et al., 2000).

Table 3: Sternbach's diagnostic criteria for serotonin syndrome

1. Recent addition or increase in a known serotonergic agent
2. Absence of other possible causes (e.g. infection, substance abuse etc.)
3. No recent addition or increase of a neuroleptic agent*
4. At least three of the following symptoms:
mental status changes (confusion, hypomania), agitation, myoclonus, fever, hyper-reflexia, diaphoresis, shivering, tremor, diarrhoea, inco-ordination

* Used in the treatment of schizophrenia or other psychoses

As a modification of Sternbach's diagnostic criteria, Hegerl et al. (1998) developed and validated a scale to assist assessment of the presence and severity of the symptoms of serotonin toxicity in some patients. Their scale consisted of specific symptoms of serotonin toxicity which were graded in severity from zero (not present) to three (severe) (Hegerl et al., 1998). Radomski et al. (2000) analysed the clinical profile of all published cases (n=62) of serotonin syndrome up to 1995. The findings suggested amendments to the Sternbach diagnostic criteria and a classification of serotonin syndrome in to three groupings on the basis of the severity of clinical presentation (i.e. mild serotonin-related symptoms, full-blown serotonin syndrome and toxic states). The analysis of a prospective clinical database of more than 2220 cases of serotonin toxicity, maintained by Whyte et al. since 1987, has enabled a list of drugs with clinically relevant serotonergic potency to be compiled (Dunkley et al., 2003; Gillman, 2005, 2006a). The research team also developed the concept of serotonin toxicity as a spectrum of serotonin-related side effects progressing to toxicity (Dunkley et al., 2003; Gillman, 2006a). A brief review of serotonin toxicity by Ener et al. (2003) also alludes to this concept. Serotonin toxicity can be considered as a triad of clinical features consisting of autonomic signs, neuromuscular changes and altered mental status (Table 4) (Dunkley et al., 2003; Gillman, 2006a). Omitting any of these parts during assessment of the patient could lead to an inaccurate diagnosis.

Table 4: Triad of the clinical features of serotonin toxicity

Neuromuscular hyperactivity:
Tremor, clonus, myoclonus, hyperreflexia, pyramidal rigidity*
Autonomic hyperactivity:
Diaphoresis, fever, tachycardia, tachypnea, mydriasis
Altered mental status:
Agitation, excitement, confusion*

*Advanced stage only

The most likely clinical presentation of serotonin toxicity is one of rapid onset, usually within 24 hours of the introduction of a serotonergic agent (Birmes et al., 2003). The serotonin toxic person is most likely hyper-vigilant (very alert) or agitated, with tremor and hyper-reflexia (exaggerated reflexes). Clonus (repeated, rhythmic muscle spasms) and myoclonus (jerky muscle spasms) start in the lower limbs and become generalised as toxicity increases. Then fever, sweating, mydriasis (dilated pupils), tachycardia (rapid heart rate) and tachypnoea (rapid breathing) become more evident. These features are not usually severe. Other symptoms may include shaking, shivering and trismus (clenched jaw). Pyramidal rigidity (fixed rigidity) develops later in severe cases. This can impair breathing if it affects truncal muscles and can lead to raised levels of carbon dioxide in the blood. Rigidity and fever of greater than 38.5°C indicates life-threatening toxicity (Dunkley et al., 2003; Gillman, 2005, 2006b). People with serotonin toxicity resulting from illicit drug use such as ecstasy usually present to emergency departments with more advanced symptoms. This is because the early, mild signs of serotonin toxicity are generally perceived by ERDs users as within the normal range of drug reactions (Parrott, 2002).

Neuroleptic malignant syndrome (NMS), a life-threatening neurological disorder caused by an adverse reaction to antipsychotic drugs, is commonly thought of as the principal differential diagnosis. The features that distinguish serotonin toxicity from NMS are myoclonus, clonus and hyperreflexia (Dunkley et al., 2003; Ener et al., 2003; Gillman, 2005; Sampson, 1999). In addition, the signs and symptoms of NMS typically evolve over several days, whereas in serotonin toxicity symptoms usually develop more rapidly (Birmes et al., 2003; Boyer & Shannon, 2005). Other major differential diagnoses include infectious causes, herpetic encephalopathy, heat stroke, myocardial necrosis, delirium tremens, and intoxication by adrenergic or anticholinergic agents (Birmes et al., 2003).

Mild to moderate serotonin toxicity usually resolves completely within 24 to 72 hours after the serotonergic agent is withdrawn (Sampson, 1999). Symptoms, however, may become severe before the effects of the ingested drugs wear off. In these cases, appropriate intervention must be promptly initiated (Gillman, 2005). Early transfer to an intensive care unit and consultation with a toxicologist is recommended (Gillman, 2005). The management of serotonin toxicity is mainly supportive and can include hydration, antihypertensive drugs and anticonvulsants. Severe late stage serotonin toxicity may require intubation combined with cooling and neuromuscular relaxants to reduce muscle necrosis and minimise the likelihood of rhabdomyolosis and renal failure (Baker et al., 2004; Sampson, 1999).

Serotonin (5-HT2A) antagonists may be used to block the stimulation of serotonin receptors and help ameliorate serotonergic symptoms. (An antagonist is a molecule which blocks the stimulation of a receptor, whereas an agonist is a molecule which stimulates a receptor). A range of 5-HT2A antagonists have been demonstrated to reduce the hyperpyrexia (fever) associated with serotonin toxicity (Gillman, 2006b). Rapid reduction of temperature is an important response to hyperthermia related to ecstasy use as research suggests a strong correlation between body temperature and the risk of mortality (Gowing et al., 2002). In life-threatening cases of toxicity, chlorpromazine has been used with good effect and no fatalities. There is some evidence that benzodiazepines may be an appropriate adjunct to treatment with 5-HT2A agonists (Gillman, 2004).

1.3.4 Ecstasy use and serotonin toxicity

The acute behavioural and physiological effects experienced by ecstasy users are consistent with the serotonin release induced by 3,4-methylenedioxymethamphetamine (MDMA) or one of its analogues. To a lesser extent, MDMA also inhibits the reuptake of serotonin and other neurotransmitters such as dopamine (Parrott, 2002).

MDMA is rapidly absorbed following oral administration, it is detectable in the blood within 30 minutes and has a half-life of about 6-8 hours (Green et al., 2003). At doses of 1.0 mg/kg and above, MDMA exhibits all its characteristic features (Dumont & Verkes, 2006), which is in line with the desirable doses reported by ecstasy users. A large dose of MDMA will rapidly deplete about 80% of the serotonin stored in presynaptic nerves (Green et al., 2003). Ecstasy tablets have been reported to generally contain between 80 and 150 mg of MDMA (Henry, 1992; Schifano, 1991). Over two-thirds of REU in a national survey reported typically taking more than one ecstasy tablet on any occasion. In all States and Territories the median number of ecstasy tablets taken in a typical use episode was two tablets (Dunn et al., 2007).

MDMA will frequently produce in users a clinical picture resembling mild serotonin toxicity and has demonstrated potential for serious, acute toxicity (Gillman, 2006b; Mueller & Korey, 1998; Oesterheld et al., 2004; Parrott, 2002; Ricaurte & McCann, 2005). Relatively small increases in the amount of MDMA used have been shown to produce large rises in MDMA concentrations in the blood which may help to explain why some people are prone to serious adverse health consequences, including acute serotonin toxicity (de la Torre et al., 2000).

Ecstasy-related morbidity and mortality

A recent review of papers published between 1995-2000 identified 158 cases of acute adverse effects, primarily hyperthermia and hyponatraemia, associated with the use of MDMA. One quarter of these cases were fatalities. MDMA was the only drug detected, by blood or urine analysis, in a substantial proportion of the total cases identified, suggesting that MDMA alone can produce adverse effects serious enough to result in death (Gowing et al., 2002). Although a number of the acute adverse effects identified by the authors of the review may be associated with serotonin toxicity (i.e. hyperthermia and seizures) the presence of serotonin syndrome, as such, in these cases was not assessed. There are only a few case reports of mortality associated with the use of MDMA alone

that fit the diagnostic criteria for serotonin syndrome (Mueller & Korey, 1998; Vuori et al., 2003).

Nevertheless, it remains that the incidence of ecstasy-related fatalities is relatively low in comparison to the likely frequency of its use (Gowing et al., 2002; White et al., 1997). Over the four year period 2001-2004, the National Coroners Information System (NCIS) identified 112 ecstasy-related deaths in Australia, however, drug toxicity was identified as a cause in less than half (40%) of these cases (Kinner et al., 2005). To what extent other drugs played a part in these ecstasy-related fatalities is uncertain.

To accurately determine the morbidity associated with ecstasy use is difficult as ERDs users do not typically come into contact with health professionals (Dunn et al., 2007). In addition, ERDs users who are experiencing distress usually access a range of medical and health services in a variety of settings (Stafford et al., 2005). A number of methodological problems also contribute to making it difficult to interpret the role played by ecstasy in any health complications associated with use of the drug. As has been mentioned, ecstasy users tend to use a range of licit and illicit drugs on a single occasion. In addition, the content of ecstasy pills has been found to be highly variable (Baggott et al., 2000; Camilleri & Caldicott, 2005; King, 2000; Ramsey et al., 2001; Schifano et al., 1998; Schifano et al., 2003).

Given the potent serotonergic properties of MDMA, reports that a substantial proportion of REU have deliberately combined pharmaceutical substances, in particular antidepressants, with ecstasy suggests a need for further exploration of the risks associated with this practice (Copeland et al., 2006).

1.3.5 Ecstasy and the concomitant use of serotonergic substances

1.3.5.1 Serotonin releasers

Amphetamine

The stimulant compound amphetamine, and its derivatives such as methamphetamine, is a relatively potent serotonin releaser with some inhibitory effects on serotonin reuptake (Feinberg, 2004; Hall & Buckley, 2003). There is a risk of precipitating serotonin toxicity from the use of amphetamine or its derivatives (Ener et al., 2003), mainly if combined with MAOIs, but also other serotonergic drugs (Gillman, 2005, 2006b; Prior et al., 2002). The degree to which the toxicity with MAOIs is serotonergic, however, is uncertain as amphetamine does not always produce typical serotonergic side effects (Gillman, 2006b).

In Australia from 1984 to 2000, there was a 26% increase each year in the total rate of use, for medical purposes, of the pharmaceutical stimulants dexamphetamine and methylphenidate (e.g. *Ritalin*) (Berbatis et al., 2000). These pharmaceutical drugs are widely used in the treatment of attention deficit hyperactivity disorder (ADHD). Cautious monitoring is advised in people taking dexamphetamine and either the SNRI venlafaxine or SSRIs, as life-threatening serotonin toxicity has been associated with this drug combination (Prior et al., 2002).

Around half a million Australian adults are current users of methamphetamine (McKetin et al., 2005). Two-thirds of REU recently used methamphetamine powder ('speed'), and more than one-quarter (27%) reported that they usually used this drug in conjunction

with ecstasy. Other forms of methamphetamine were less likely to be used together with ecstasy. Crystal methamphetamine was usually used in combination with ecstasy by 17% of REU (Dunn et al., 2007). The serotonergic properties of pharmaceutical stimulants and methamphetamine suggests there is a need for information on the potentially serious health consequences of using these drugs in combination, or using them together with ecstasy.

As mentioned, tablets sold as ecstasy frequently contain varying amounts of MDMA and other substances. Methamphetamine is a common substitute for MDMA in ecstasy tablets (Australian Crime Commission, 2006). Up to 55% of ecstasy tablets sold in Australia during 2001-2002 contained methamphetamine (Australian Bureau of Criminal Intelligence, 2002). This suggests that a substantial proportion of ecstasy users are unknowingly using methamphetamine or inadvertently using methamphetamine in combination with MDMA. In a unique animal study, the use of MDMA and methamphetamine in combination was associated with greater adverse acute effects and long-term effects than equivalent doses of either drug alone. The study found that methamphetamine exacerbated the acute hyperthermic effect of MDMA and the authors suggest that humans using these drugs together may be particularly susceptible to adverse hyperthermic reactions at high ambient temperatures. In addition, results demonstrated that the combination of these drugs was associated with serotonin-related neurotoxicity in rodents (Clemens et al., 2004).

Cocaine

In addition to enhancing levels of the neurotransmitters dopamine and noradrenaline, cocaine (benzoylmethylecgonine) is a releaser of serotonin (Aronson et al., 1995; Ener et al., 2003; Li et al., 1996; Mason et al., 2000). The discernible serotonergic effects of cocaine suggest that it may strongly influence the course of serotonin toxicity (Birmes et al., 2003; Ener et al., 2003; National Prescribing Service Limited, 2005a). The use of cocaine with other agents that have serotonergic properties may, therefore, have potentially serious health consequences, including severe serotonin toxicity. Slightly more than one-third of REU in Australia had recently used cocaine, and 5% reported that they usually used cocaine in conjunction with ecstasy (Dunn et al., 2007).

1.3.5.2 Inhibitors of serotonin metabolism

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) may be prescribed for depression, as already mentioned, but are also used to treat anxiety, Parkinson's disease, tuberculosis, leukaemia and non-Hodgkin's lymphoma. Several MAOIs have antibiotic properties and are used in the treatment of bacterial infections.

MAOIs reduce or prevent the enzyme monoamine oxidase (MAO) from breaking down various neurotransmitters including serotonin. There are two types of MAO enzymes, MAO-A and MAO-B. Some MAOIs inhibit only one MAO enzyme (selective MAOIs), whereas others inhibit both enzymes (non-selective MAOIs). MAOIs can be either irreversible (MAOI) or reversible (RIMA). Older generation antidepressants (e.g. phenelezine, tranylcypromine) are examples of irreversible MAOIs and prevent serotonin breakdown for longer than RIMAs (e.g. moclobemide). The effects of MAOIs last longer than previously thought (Gillman, 2006b). Some MAOIs can have enduring effects for

up to 40 days (Arnett et al., 1987; Fowler et al., 1994). It typically takes about two weeks to regenerate 50% of MAO activity after MAOI use (Ener et al., 2003). People who have stopped using an MAOI may, therefore, still be prone to interactions with other agents long after they have forgotten they were ever using it (Gillman, 2005). The use of irreversible MAOIs in Australia has fallen substantially since 1990 following the introduction of SSRIs and the RIMA moclobemide (Mant et al., 2004).

Cases of serotonin toxicity have been reported from ecstasy interactions with the MAOI phenelzine as early as 1987 (Kaskey, 1992; Smilkstein et al., 1987). The use of ecstasy in combination with MAOIs can give rise to fatalities and these have been documented (Vuori et al., 2003). In these four cases, death was attributable 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. However, the authors speculate that moclobemide was used to enhance the euphoric effect of ecstasy, with fatal consequences. Further evidence that this drug combination increases the likelihood of severe serotonin toxicity comes from animal studies. In rodents, ecstasy has been shown to produce a significantly greater increase in serotonin concentration when administered with moclobemide (Freezer et al., 2005).

Research shows that a proportion of ERDs users combine ecstasy with moclobemide and are therefore placing themselves at risk of serious health consequences. In a recent Australian study, among ERDs users who had combined illicit drugs with pharmaceuticals, 4% reported deliberately using ecstasy and moclobemide to achieve a specific effect (Copeland et al., 2006). A number of user websites also warn of the potentially fatal interaction between ecstasy and MAOIs (Blue Light, 2006; Enlighten, 2006).

St. John's wort

The herbal extract St John's wort (*Hypericum perforatum L.*) is available in supermarkets and health food stores and is typically used for depression (Ang-Lee et al., 2001; Ernst, 2002). A recent randomised controlled trial found St. John's wort was as effective as the SSRI antidepressant paroxetine in the treatment of moderate to severe depression (Szegedi et al., 2005). St. John's wort may also be used in the treatment of anxiety and as a wound-healing agent (Bressler, 2005).

St. John's wort has serotonergic properties and has been implicated in serotonin toxicity (Ener et al., 2003; Fugh-Berman, 2000; National Prescribing Service Limited, 2005a). The mechanisms of action of St. John's wort have not yet been clearly delineated (Hall & Buckley, 2003; Singh, 2005). In laboratory studies, St. John's wort inhibits the reuptake of serotonin, noradrenaline and dopamine with potency comparable to that of some pharmaceutical antidepressants (Butterweck, 2003; Chatterjee et al., 1998; Muller et al., 1998). St John's wort is also thought to inhibit the metabolism of serotonin and therefore has some MAOI properties (Ener et al., 2003). The various mechanisms of action create a potential for interaction between St. John's wort and numerous other serotonergic agents (Singh, 2005). The serotonin reuptake inhibiting properties of St. John's wort suggest that in combination with MAOIs the development of severe serotonin toxicity is more likely. Whereas the MAOI properties of St. John's wort imply that in combination with SSRIs, or serotonin releasers such as ecstasy, there is an increased likelihood of serotonin toxicity. User websites also advise against combining St. John's Wort with ecstasy (Enlighten, 2006). There is generally a lack of data on the clinically significant adverse effects of combining St. John's wort with serotonergic substances.

1.3.5.3 Inhibitors of serotonin reuptake

Substances which are known to inhibit the reuptake of serotonin include SSRI and SNRI antidepressants, a range of opioid analgesics, and some TCAs and anthistamines (Gillman, 2005). These substances increase serotonin levels, primarily by blocking the transporter molecule responsible for its uptake.

The most likely therapeutic drug combinations implicated in life-threatening or fatal cases of serotonin toxicity is the combination of MAOIs with substances which inhibit the reuptake of serotonin (Gillman, 2005). In these cases, rapid deterioration and deaths have been documented (Gillman, 1998; Otte et al., 2003; Power et al., 1995). Findings from the Hunter Area Toxicology Service (HATS) database demonstrate that in about 50% of the cases where the reversible MAOI moclobemide and substances which inhibited the reuptake of serotonin were used together, moderately severe serotonin toxicity developed (Gillman, 2005).

Selective serotonin reuptake inhibitors

SSRIs directly act on the neurotransmitter serotonin, inhibiting the molecular pump responsible for serotonin uptake and stimulating serotonin release to a certain degree. A long lasting increase in the availability of serotonin, such as that which is caused by regular use of SSRIs, results in a reduction in the number of serotonin receptors, a process known as 'down regulation' (Trevor, 1999).

Findings from the HATS database suggest that the combination of MAOIs with SSRIs was one of the strongest predictors of serotonin toxicity severe enough to cause fatalities (Gillman, 2006a). Approximately 15% of overdoses of an SSRI alone exhibited moderate serotonin toxicity, but in these cases toxicity was not life-threatening (Gillman, 2006a).

Early work by McCann and Ricaurte (1993) suggested that the SSRI fluoxetine had little impact on the psychological or subjective effects of ecstasy. Few conclusions, however, could be drawn from those findings given the uncontrolled nature and small sample size of the study. A more rigorous controlled study found the physiological and subjective effects of ecstasy were reduced in participants who were administered citalopram, the later by about 60%. This study also found that in addition to attenuating the acute psychological effects of ecstasy, at the same time citalopram prolonged them by up to two hours compared to ecstasy alone (Liechti et al., 2000).

Copeland et al. (2006) found that among ERDs users who had combined antidepressants with ecstasy, more than one-third had done so for the putative purpose of increasing the strength of the ecstasy 'high' and that 13% had done so to extend the length of ecstasy intoxication. This is of some concern as it has been demonstrated that higher than usual levels of MDMA in the blood for greater periods of time could increase the risk of acute toxicity and long-term harm (Hegadoren et al., 1999).

In animal experiments SSRIs, such as fluoxetine and citalopram, have been shown to block the MDMA-induced release of serotonin (Gudelsky & Nash, 1996; Hekmatpanah & Peroutka, 1990; Mechan et al., 2002; Schmidt, 1987). User internet websites and associated 'chat rooms' provide conflicting information and commentary on the various ways SSRIs effect users of ecstasy (Blue Light, 2006; Enlighten, 2006).

Protective effects of serotonin reuptake inhibitors

Experiments on animals continue to demonstrate that MDMA produces long-term degeneration of serotonin nerve endings, however, the mechanisms involved are not yet fully understood (Bull et al., 2006; Farfel & Seiden, 1995; Lyles & Cadet, 2003; Montoya et al., 2002; Sanchez et al., 2001; Shankaran & Gudelskey, 1998; Wallace et al., 2001). The available evidence indicates that MDMA-induced neurotoxicity is not caused by the drug itself but by one or more metabolites of MDMA (Easton & Marsden, 2006; Hayat et al., 2006), and is exacerbated by high ambient temperatures (Sanchez et al., 2004). Evidence suggests good translation between rat and human in relation to the acute effects of MDMA, but it is less certain whether this is the case with regard to the chronic degenerative effects (Boot et al., 2000; Easton & Marsden, 2006; Green et al., 2003). Subsequently, debate continues over the possible long-term neurotoxic effects of ecstasy use (Bolla et al., 1998; Boot et al., 2000; Cole & Sumnall, 2003; Green et al., 2003; Parrott et al., 2000; Reneman et al., 2001).

There is mounting evidence, however, that ecstasy does have neurotoxic effects on the human brain, especially in heavy users (Bolla et al., 1998; Boot et al., 2000; Cole & Sumnall, 2003; Daumann et al., 2006; Green et al., 2003; Parrott et al., 2000; Reneman et al., 2001), and that the level of neurotoxicity is likely to be dose dependant (Reneman et al., 2006). Emerging evidence from neuroimaging studies suggests that females may be more vulnerable than males to serotonin neurotoxicity related to MDMA use (Reneman et al., 2006).

The findings from animal studies that some antidepressants have a protective effect against MDMA-induced neurodegeneration are, therefore, of particular interest. The SSRI fluoxetine has been shown to prevent the long-lasting neurotoxic effects of MDMA (Malberg et al., 1996; Sanchez et al., 2001; Schmidt, 1987). When administered concurrently with MDMA, or given two and four days earlier, fluoxetine provided complete protection, and significant protection when given seven days earlier, from MDMA-induced degeneration of serotonin nerve endings (Sanchez et al., 2001). Co-administration of fluoxetine completely blocked the reduction in serotonin concentrations one week after MDMA. When fluoxetine was administered after MDMA, however, the depletion of serotonin was only partially blocked for up to six hours (Schmidt, 1987). Fluoxetine may also play a role in reversing the MDMA-induced exacerbation of dopamine toxicity (Goni-Allo et al., 2006). The MAO-B inhibitor deprenyl, administered before MDMA, has also been shown to have neuroprotective effects against MDMA toxicity (Sprague & Nichols, 1995).

It has not yet been demonstrated if antidepressants can protect against MDMA-induced neurotoxicity in humans. A proportion of ERDs users, however, report this as one reason they deliberately combine antidepressants and ecstasy (Copeland et al., 2006; Oesterheld et al., 2004). Copeland et al. (2006) found that among ERDs users who had taken antidepressants and ecstasy, one in five did so for the putative effect of preventing neurotoxicity. Commentators from John Hopkins University, USA, warn that research in to the neuroprotectice effects of SSRIs is inconclusive and that using SSRIs with ecstasy may simply redirect harm to other parts of the brain (Sabo, 2000).

Tricyclic antidepressant drugs

The TCAs have varying potencies for serotonin reuptake inhibition and several have been implicated in serotonin toxicity (Gillman, 2006b). With the introduction of SSRIs and the RIMA moclobemide over the last decade, TCAs currently represent a relatively

small proportion of the antidepressants used in Australia. The proportion of antidepressant use represented by TCAs dropped from 90% in 1990 to 13% in 2002 (Mant et al., 2004).

Fatalities from serotonin toxicity have been reported from the combination of MAOIs with the TCAs clomipramine and imipramine. Serotonin toxicity has also been reported in a small number of cases where these TCAs were taken in overdose (Gillman, 2006a). Findings from the Hunter Area Toxicology Service (HATS) database indicate that the combination of the TCA clomipramine with MAOIs was as strong a predictor of serotonin toxicity severe enough to cause fatalities as the combination of SSRIs with MAOIs (Gillman, 2006a). Due to competition at the serotonin transporter site, TCAs are likely to diminish the effects of ecstasy if used concurrently (McGregor, 2006).

Opioid analgesics

Although the analgesic effects of opioids are mediated by opioid receptors, a number of opioid analgesics affect serotonin and other neurotransmitters such as noradrenaline and dopamine (Codd et al., 1995; Steinmiller et al., 2003). Meperidine (pethidine), tramadol, methadone, fentanyl, dextromethorphan and dextropropoxyphene are all weak serotonin reuptake inhibitors and have been implicated in serotonin toxicity (Gillman, 2005, 2006b). Opioid analgesics with anomalous properties such as tramadol and pethidine may also work as serotonin releasers (Gillman, 2005).

Approximately 40 cases of serotonin toxicity involving opioid analgesics have been reported (Gillman, 2005), and details of these cases can be found in an updated review by (Gillman, 2006b). Fatalities due to serotonin toxicity have been reported with tramadol, meperidine (pethidine), fentanyl and dextromethorphan. Other opioid analgesics associated with less severe (non-fatal) serotonin toxicity are dextropropoxyphene and methadone (Gillman, 2006b).

Gillman (2005) highlights a lack of clinical and pharmacological data on the serotonergic potency of these drugs, and cites this as one reason it is difficult to estimate with precision the risks associated with their use. From the available HATS data, Gillman (2005) concludes that pethidine, tramadol, dextromethorphan and methadone may infrequently precipitate serotonin toxicity when administered in conjunction with MAOIs, but only in large doses or susceptible individuals. Fentanyl has a very low potency for serotonin reuptake inhibition compared to other opioid analgesics and the extent to which it interacts with MAOIs and other serotonergic substances is not entirely clear (Gillman, 2005). Gillman (2005) suggests it is probable fentanyl and MAOIs have been used in combination many times and cases have not been reported because the drugs have been used with impunity.

Since the marketing of tramadol (e.g. *Tramal*) in Australia in late 1998, the Adverse Drug Reactions Advisory Committee (ADRAC) has received 171 reports of suspected adverse reactions. Six of these reports describe the serotonin syndrome. ADRAC advises that caution be used with tramadol in people taking other medications known to increase serotonin levels (Adverse Drug Reactions Advisory Committee, 2001).

Dextromethorphan (e.g. *Robitussin*) is a cough suppressant widely available in pharmacies. The use of dextromethorphan, at recommended doses, carries with it an increased risk of serotonin toxicity if combined with antidepressants of any class (National Prescribing Service Limited, 2004). A recent case report describes serotonin syndrome in a person regularly taking the SSRI Citalopram and concomitant use of dextromethorphan capsules (Cameron, 2006).

Anecdotal evidence suggests that dextromethorphan is being used for non-medical purposes by a proportion of regular ecstasy users (Blue Light, 2006; Degenhardt et al., 2005). It has been reported that dextromethorphan, at very large doses, produces disassociative effects similar to those of LSD and ketamine (Publishers Group LLC, 2006). A popular user website strongly warns against combining dextromethorphan with antidepressants (Blue Light, 2006).

Limited clinical and experimental data shows that morphine and its analogues such as codeine, oxycodone and buprenorphine are not serotonin reuptake inhibitors. A review by Gillman (2006b) found no reliable reports of serotonin toxicity associated with these drugs.

Antihistamines

Chlorpheniramine and brompheniramine are widely available, older generation antihistamines with some sedative effects. They are used extensively with oral decongestants in cold and flu remedies (Walls et al., 2005). These antihistamines inhibit the reuptake of serotonin and have been shown to have serotonergic potency (Gillman, 2006a).

An updated review by Gillman (2006b) highlights a handful of cases of serotonin toxicity where chlorpheniramine may have played a part. The intravenous form of chlorpheniramine, which is not available in Australia (National Prescribing Service Limited, 2005a), has been implicated in serotonin toxicity (Gillman, 2006b). The use of chlorpheniramine is contra-indicated in people taking MAOIs (Therapeutic Goods Administration, 2005).

1.3.5.4 Serotonin precursors

Serotonin precursors give rise to serotonin after a metabolic process. 5-Hydroxytryptophan (5-HTP) and L-tryptophan are serotonin precursers with demonstrated serotonergic potency (Gillman, 2006a).

5-hydroxytryptophan

5-HTP is an amino acid the body converts to serotonin. It is also available as a dietary supplement extracted from the plant *Griffonia Simplicifolia* (Jorm et al., 2004). It is used as an adjunct in the treatment of depression, fibromyalgia, obesity, insomnia and chronic headache. Although there is relatively little information about the effectiveness of 5-HTP, there is some evidence that it may help ameliorate these conditions (Das et al., 2004). 5-HTP is not widely available in Australia but can be imported with certain restrictions.

As 5-HTP has demonstrated serotonergic potency (Ener et al., 2003; Gillman, 2006a), its use with other serotonergic agents, particularly SSRI and MOAI antidepressants, is in theory more likely to precipitate serotonin toxicity (Das et al., 2004; Ener et al., 2003). A review by (Juhl, 1998), however, found no reported cases of serotonin toxicity induced by 5-HTP up to the time of publication. In the course of this review, no cases appear to have been reported to date. Fatalities from serotonin toxicity associated with 5-HTP

overdose have occurred in dogs (Gwaltney-Brant et al., 2000), but not in humans (Gillman, 2006b).

Copeland et al. (2006) found that a proportion of REU combined their use of ecstasy with 5-HTP in the belief that it would decrease the negative after-effects of ecstasy or prevent neurotoxicity. Scores of anecdotal reports from ecstasy users of the effects of combining 5-HTP with ecstasy suggest this practice is not uncommon among ERDs users (Blue Light, 2006). In animal studies, 5-HTP was shown to attenuate MDMA induced serotonergic neurotoxicity (Sprague et al., 1994).

A variety of sources refer to 'pre-loading' or 'post-loading' (Enlighten, 2006; Maxwell, 2005; Oesterheld et al., 2004). These are 'street' terms for the deliberate use of dietary supplements, including 5-HTP, and pharmaceuticals before or after ecstasy. Given the demonstrated serotonergic potency of 5-HTP, there is a theoretical risk of serotonin toxicity if 5-HTP is used with MDMA, however, there are no published cases to date. Some user websites caution against taking 5-HTP prior to ecstasy (Enlighten, 2006).

L-tryptophan

The serotonin precursor L-tryptophan has demonstrated serotonergic potency and was once widely used in the treatment of depression and sleep disorders (Ener et al., 2003; Gillman, 2006a; National Prescribing Service Limited, 2005a; Sampson, 1999). Nowadays, L-tryptophan is a drug which is prescribed little by most practitioners (Gillman, 2006b).The serotonergic side-effects produced by L-tryptophan are dose related (Gillman, 2006a). When combined with MAOIs, L-tryptophan provides improved antidepressant efficacy, and in animals, greater increases in serotonin than MAOIs alone. No cases of severe serotonin toxicity or fatalities have been reported with MAOIs and L-tryptophan, however, they would be expected in cases of overdose (Gillman, 2006b). In animal studies, L-tryptophan was shown to attenuate MDMA induced serotonergic neurotoxicity (Sprague et al., 1994).

1.3.5.5 Partial serotonin agonists

LSD

d-lysergic acid (LSD) is structurally similar to serotonin and this characteristic contributes to its serotonergic potency (Silbergeld & Hruska, 1979; Trulson et al., 1976). The precise mechanism of action of LSD is uncertain, however, it is thought to have agonistic and antagonistic effects on serotonin depending on which receptor it affects. LSD stimulates 5-HT2 serotonin receptors producing hallucinogenic effects. 5-HT1A receptors also contribute to the effects of LSD, however their specific role is less clear (Krebs & Geyer, 1994; Penington & Fox, 1994).

LSD has been implicated in serotonin syndrome in humans but whether it can precipitate symptoms severe enough to be life-threatening is yet to be established (Boyer & Shannon, 2005; Hall & Buckley, 2003; Rossi, 2005). There is preliminary evidence suggesting serotonin reuptake inhibitors, such as fluoxetine and sertraline, may interact acutely with LSD. In a small number of cases, the use of these antidepressants exacerbated the LSD flashback syndrome in LSD users (Markel et al., 1994). The full extent of interaction of LSD with serotonergic agents, including other illicit drugs, is largely unknown. In Australia among REU, just less than one-third had recently used

LSD, and 5% reported that they usually used LSD together with ecstasy (Dunn et al., 2007).

Migraine medication

Anti-migraine drugs such as dihydroergotamine (e.g. *Dihydergot*) and bromocriptine (e.g. *Kripton*) are partial serotonin agonists and stimulate serotonin receptors (Gillman, 2006a; National Prescribing Service Limited, 2005a). These drugs, however, have not demonstrated any clinically relevant serotonergic potency (Gillman, 2005), and the risk of severe serotonin toxicity precipitating from their use is presented as more of a theoretical concern (Buckley, 2003). The National Prescribing Service cautions against using these drugs either in combination or with other serotonin agonists (National Prescribing Service Limited, 2005b).

Benylpiperazine

Benylpiperazine (BZP) substances are derived from pepper plants and can also be synthetically produced. Preparations containing BZP are marketed as dietary supplements and promoted by manufacturers as 'herbal ecstasy', a legal alternative to the use of amphetamines. Currently these products are not for sale in Australia, but are available over the counter in New Zealand and other countries. BZP substances are particularly popular with young people and are reported to have stimulant and hallucinogenic effects (Austin & Monasterio, 2004).

BZP has been shown to mirror the effects of MDMA and has serotonergic potency (Baumann et al., 2005). BZP is believed to inhibit the reuptake of serotonin and act as a serotonin agonsist (Maurer et al., 2004). However, relatively little is known about the way BZP interacts with other serotonergic pharmaceuticals and substances. Case reports describe adverse reactions in BZP users which ranged from mild to life-threatening (Austin & Monasterio, 2004; Gee et al., 2005; Yates et al., 2000). However, serotonin toxicity was not implicated in these cases. As BZP has substantial serotonergic potency, concomitant use with MDMA or amphetamine is cautioned against (Gee et al., 2005).

Serotonin toxicity is one of the potential harms associated with the use of a wide range of serotonergic substances, in particular ecstasy. Further exploration of the potential harms of combining ecstasy with other serotonergic drugs and substances is essential. In addition, there is a need to explore the accessibility of prescription pharmaceutical drugs to ERDs users. Little is known about the extent of screening for ERDs use when young people are prescribed pharmaceutical drugs by their GP. Furthermore, among Australian healthcare professionals in general practice and hospital settings, there is a lack of research exploring the awareness of ERDs and the potential harms of concomitant use of pharmaceutical drugs.

1.4 Aims

The aims of the study were:

1. To identify gaps in knowledge among general practitioners about the effects and harms of ERDs use and the management of young people who are prescribed pharmaceutical drugs.
2. To identify gaps in knowledge among frontline (e.g. Emergency Department) healthcare professionals about the effects and harms of ERDs use.
3. To identify the patterns of use related to the practice of combining ecstasy with pharmaceutical drugs, in particular antidepressants, and to explore the experiences of ERDs users when visiting a general practitioner.
4. To inform the development of resource materials on ERDs for healthcare practitioners.

1.5 Data analysis

Means were reported for continuous, normally distributed variables. Where continuous variables were skewed, medians were reported. Categorical variables were analysed using McNemar's test for correlated proportions. Logistic regression, using the backward stepwise method, was utilised with categorical and continuous variables. Descriptive analyses were also employed. Thematic analyses of qualitative data were conducted. Statistical Package for the Social Sciences (SPSS) for Windows, Version 14.0 (SPSS Inc, 2006), was used for all analyses.

1.6 Ethical approval

The study was approved by the University of New South Wales Human Research Ethics Committee.

2 SURVEY OF GENERAL PRACTITIONERS

2.1 Recruitment and procedure

In July 2006, questionnaires were distributed to a random sample of 2000 GPs stratified to include metropolitan and non-metropolitan areas across Australia (Table 5). Participants were selected at random, by a third independent party, from a nationwide database of GPs. The number of GPs selected in each jurisdiction was proportional to the population of each State and Territory. Where possible, the sample in each jurisdiction was equally divided between metropolitan and non-metropolitan GPs.

Table 5: Stratification of GP sample

State/Territory	Metropolitan	Non-metropolitan*	Total
NSW	338	338	676
VIC	266	232†	498
QLD	184	183	367
WA	128	59†	187
SA	155	18†	173
TAS	28	28	56
ACT	34	-	34
NT	7†	2†	9
	1140	**860**	**2000**

*Includes areas classified as regional, rural and remote
†All GPs listed on database in these regions

The cover letter and questionnaire were mailed out to GPs in July 2006. The voluntary nature of participation was emphasised and participants received no remuneration. A reply-paid envelope was included for the return of the completed questionnaire. Return of the questionnaire was accepted as consent to participate. The questionnaire was anonymous and all information collected was treated confidentially. There was no follow-up of non-respondents.

2.2 Measures

The forty-six item questionnaire consisted of domains related to knowledge of a range of ERDs, frequency of acute and chronic drug-related presentations, perceived health risks of ecstasy and the concomitant use of pharmaceutical drugs, screening practices when prescribing sidenafil, screening practices when prescribing antidepressant drugs and resource development.

Eight questions asked GPs to rank on a six-point Likert scale their level of disagreement/agreement with a range of statements relating to their knowledge of ecstasy, methamphetamine, cocaine, GHB and ketamine.

Prior to analysis, response categories for these items were dichotomised into 'overall disagreement' (somewhat disagree, disagree, strongly disagree) and 'overall agreement' (somewhat agree, agree, strongly agree).

Ten items related to the frequency with which GPs saw acute and chronic drug-related presentations for ecstasy, methamphetamine, cocaine, GHB and ketamine. Respondents marked one of the following categories: never or almost never, yearly, every few months, monthly, every few weeks, weekly, every few days, daily. Prior to analysis, categories were combined in those cases where individual cell sizes were small.

Five items related to the perceived health risks of ecstasy and the concomitant use of benzodiazepines and sleeping tablets, sidenafil and a range of antidepressants. Respondents were asked to report the perceived risk to health of using these substances in this way as no risk, slight risk, moderate risk, significant risk, serious risk or hazardous risk.

Three items each related to sidenafil and antidepressant drugs and the frequency with which GPs prescribe these drugs to patients less than 30 years, how often they screen for ecstasy use when they prescribe them and how often they suspect any non-disclosure. One item related to the frequency with which GPs discussed the complication of serotonin toxicity when they prescribed antidepressants. Five items related to antidepressant seeking behaviour, and included the frequency with which GPs suspected patients may be seeking antidepressant drugs for non-medical purposes which could be associated with ecstasy use and what characteristics, if any, were most common to this group.

Three items related to resource development. These included a range of questions on how useful a resource on ERDs would be and how such a resource could be most effectively delivered.

The remaining eight items related to gender, age, in what year GPs commenced unsupervised practice, membership to the Fellowship of the Royal Australian College of General Practitioners (FRACGP), specialist qualifications and the location and nature of their practice.

The questionnaire was designed such that it could be completed within approximately 20 minutes.

2.3 Results

Questionnaires were returned from GPs located in the majority of States and Territories across Australia and the results are summarised below.

Response rate

Questionnaires were mailed out to 2000 GPs and a total of 299 were returned. Of these, 39 were completed by non-GPs and 61 were returned uncompleted (e.g. 'no longer at this address' or 'deceased') and, therefore, these were not included in the analysis. Based on the return of 199 valid questionnaires, the response rate was calculated to be 10%.

2.3.1 Sample description

The characteristics of respondents are presented in Table 6. The mean age of GPs was 54 years (SD 8.7; range 34-81) and 40% were aged 55 years or older. The majority (72%) of GPs were male. Compared to population data on Australian GPs, the sample in this study contained a slightly larger proportion of females (25% vs 28%) and almost twice the proportion of GPs aged 55 years or older (22% vs 40%) (Britt et al., 2004). The median year GPs reported commencing unsupervised general practice was 1981 (range 1953-2003). Less than half (42%) of GPs were a member of the Fellowship of the Royal Australian College of general Practitioners (FRACGP). One-third (31%) reported that they held qualifications in a specialty area which included women's health, medicine/surgery, aviation medicine, paediatrics, alternative therapies, public health, family medicine and anaesthetics. The majority (94%) of respondents described the practice they mostly work in as a 'general practice', as opposed to 6% who described it as a 'specialty or other practice'. Questionnaires were returned from GPs in all States and Territories except for NT, with a majority being returned from GPs in NSW (31%) and VIC (30%). Most GPs reported that that the location of their practice was suburban (41%), and the remainder described the location as regional (24%), rural or remote (22%) or urban/inner city (13%). The majority (39%) of respondents reported that they were from practices where four or more GPs usually worked. Just less than one-third (31%) were from practices where two or three GPs worked and an equal (31%) proportion reported that they were the only GP at the practice.

2.3.2 Knowledge of ERDs and associated problems

GPs were asked a range of questions about their working knowledge of ERDs and ERDs-related problems (Table 7).

Ecstasy

A majority (70%) of GPs disagreed overall that they had a working knowledge of ecstasy and ecstasy-related problems. In keeping with this, a similar (71%) majority disagreed overall that they felt well prepared to discuss the health risks associated with ecstasy use. Half (50%) of GPs agreed overall that they had a clear idea of their responsibilities in helping patients who are using ecstasy. Reassuringly, about two-thirds (63%) of GPs agreed overall that they could, if needed, easily find someone who would be able to help them determine the best approach to manage a patient who was regularly using ecstasy.

Other illicit drugs

Forty percent of GPs agreed overall that they had a working knowledge of methamphetamine and methamphetamine-related problems. A slightly smaller (34%) proportion agreed overall that they had a working knowledge of cocaine and cocaine-related problems. Seventeen percent agreed overall that they had a working knowledge of GHB and GHB-related problems, and an almost equally small (15%) proportion agreed overall that they had a working knowledge of ketamine and ketamine-related problems (in the context of illicit use).

Table 6: Characteristics of GPs

	N (%)
Mean age in years (SD; range)	54 (8.7; 34-81)
Male	143 (72)
Median year commenced unsupervised practice (range)	1981 (1953-2003)
Member of FRACGP*	84 (42)
Completed specialist qualification:†	60 (30)
Women's health	37 (19)
Medicine/surgery	8 (4)
Aviation medicine	6 (3)
Paediatrics	5 (3)
Alternative therapies	4 (2)
Public health	4 (2)
Anaesthetics	3 (2)
Other speciality‡	9 (5)
Type of practice:	
General practice	187 (94)
Specialist or other practice	12 (6)
State/Territory of practice:^	
NSW	62 (31)
VIC	59 (30)
QLD	36 (18)
SA	18 (9)
WA	14 (7)
TAS	7 (4)
ACT	3 (2)
Location of practice:	
Suburban	82 (41)
Regional	47 (24)
Rural or remote	44 (22)
Urban/inner city	26 (13)

*Fellowship of the Royal Australian College of General Practitioners
†Several GPs had completed more than one specialist qualification
‡Including occupational health, family planning, mental health, dermatology, opioid replacement therapy, nutrition, venereology
^No questionnaires were returned from GPs in NT

Table 7: Knowledge of ERDs and associated problems among GPs

Questionnaire item	Overall agreement* N (%)
I feel I have a working knowledge of ecstasy and ecstasy-related problems.	59 (30)
I feel well prepared to discuss the health risks associated with ecstasy.	57 (29)
I feel I have a clear idea of my responsibilities in helping patients who are using ecstasy.	99 (50)
If I felt the need, I could easily find someone who would be able to help me determine the best approach to manage a patient who was regularly using ecstasy.	124 (63)
I feel I have a working knowledge of methamphetamine and methamphetamine-related problems.	79 (40)
I feel I have a working knowledge of cocaine and cocaine-related problems.	68 (34)
I feel I have a working knowledge of GHB and GHB-related problems.	34 (17)
I feel I have a working knowledge of ketamine and ketamine-related problems (in the context of illicit use).	29 (15)

*6-point Likert scale responses were dichotomised into overall disagreement (somewhat disagree, disagree, strongly disagree) and overall agreement (somewhat agree, agree, strongly agree)

2.3.3 Frequency of ERDs-related presentations

GPs were asked how frequently they saw drug-related presentations, both acute and chronic, in their practice (Table 8). Slightly less than half (49%) of GPs reported that that they never or almost never saw drug-related presentations related to any of the illicit drugs asked about in the questionnaire. The remainder saw either acute or chronic presentations related to at least one of the drugs asked about in the questionnaire yearly or more frequently.

Acute presentations

The proportion of GPs that saw acute methamphetamine-related presentations was double the proportion that saw acute ecstasy-related presentations every few months or more frequently (14% vs 7%). This difference was significant at the 0.05-level (OR=2.2, 95% CI 1.11-4.29), suggesting GPs were about twice as likely to see an acute methamphetamine-related presentation than an acute ecstasy-related presentation every few months or more frequently in their practice.

Acute cocaine-related presentations were seen by 3% of GPs every few months or more frequently. An almost equal minority saw acute GHB-related presentations (3%) or acute ketamine-related (2%) presentations every few months or more frequently.

Chronic presentations

The proportion of GPs that saw chronic methamphetamine-related presentations was more than double the proportion that saw chronic ecstasy-related presentations every few months or more frequently (29% vs 13%). This difference was significant at the 0.05-level (OR=2.9, 95% CI 1.72-4.85), suggesting GPs were about three times as likely to see a chronic methamphetamine-related presentation than a chronic ecstasy-related presentation every few months or more frequently in their practice. Chronic cocaine-related presentations were seen by 7% of GPs every few months or more frequently. A relative minority saw chronic GHB-related presentations (4%) or chronic ketamine-related (2%) presentations every few months or more frequently.

Table 8: Frequency of drug-related presentations as reported by GPs

Questionnaire item	Never or almost never N (%)	Yearly N (%)	Every few months or more frequently* N (%)
I see acute ecstasy-related presentations…	171 (86)	14 (7)	14 (7)
I see chronic ecstasy-related presentations…	155 (78)	19 (10)	25 (13)
I see acute methamphetamine-related presentations…	151 (76)	19 (10)	28 (14)
I see chronic methamphetamine-related presentations…	114 (58)	26 (13)	58 (29)
I see acute cocaine-related presentations…	186 (94)	7 (4)	6 (3)
I see chronic cocaine-related presentations…	170 (85)	15 (8)	14 (7)
I see acute GHB-related presentations…	188 (95)	6 (3)	5 (3)
I see chronic GHB-related presentations…	188 (95)	4 (2)	7 (4)
I see acute ketamine-related presentations…	194 (98)	2 (1)	3 (2)
I see chronic ketamine-related presentations…	193 (97)	2 (1)	4 (2)

*As relatively few GPs saw drug-related presentations more frequently than every few months, responses were collapsed into the following categories: 'never or almost never', 'yearly' and 'every few months or more frequently' (every few months, monthly, every few weeks, weekly, every few days, daily)

2.3.4 Health risks of ecstasy and the concomitant use of pharmaceutical drugs

The majority (72%) of GPs disagreed overall with the statement, 'In general, I feel well prepared to discuss the health risks associated with ecstasy and the concomitant use of pharmaceutical drugs'.

GPs were asked to score the perceived risk to health of using ecstasy with benzodiazepines and sleeping tablets; sidenafil; TCA/SSRI/SNRI antidepressants; and, MAOI/RIMA antidepressants. Possible scores ranged from one (no risk to health) to six (hazardous risk to health), therefore, the higher the score the greater the perceived risk to health (Table 9).

The perceived risk to health was highest for ecstasy and the concomitant use of MAOI/RIMA antidepressants (mean score 4.9). This was followed by TCA/SSRI/SNRI antidepressants (mean score 4.4) and benzodiazepines and sleeping tablets (mean score 4.3). The perceived risk to health was lowest for ecstasy and the concomitant use of sidenafil (mean score 3.9).

Just over one-quarter (26%) of GPs scored the perceived risk to health of using ecstasy with MAOI/RIMA antidepressants as *greater* than the perceived risk to health of using ecstasy with TCA/SSRI/SNRI antidepressants. Of some concern is that a majority (60%) of GPs scored the perceived risk to health of using ecstasy with MAOI/RIMA antidepressants as the *same* as that for using ecstasy with TCA/SSRI/SNRI antidepressants; and that 4% scored the perceived risk to health of using ecstasy with MAOI/RIMA antidepressants as *less* than that for using ecstasy with TCA/SSRI/SNRI antidepressants.

Table 9: Perceived risk to health from ecstasy and the concomitant use of pharmaceutical drugs as reported by GPs

Perceived risk to health for ecstasy and the concomitant use of…	Mean score*
MAOI/RIMA antidepressants	4.9
TCA/SSRI/SNRI antidepressants	4.4
Benzodiazepines and sleeping tablets	4.3
Sidenafil	3.9

* Possible scores ranged from one (no risk to health) to six (hazardous risk to health)

2.3.5 Sidenafil and screening for ecstasy use

The majority (69%) of GPs reported that they had never prescribed sidenafil to patients aged less than 30 years (Table 10). Of those that had prescribed this drug to patients aged less than 30 years, approximately half (53%) mentioned that they never screened for ecstasy use. Seventeen percent reported that they screened frequently or very frequently and a minority (8%) reported that they always screened for ecstasy use when they prescribed sidenafil to patients aged less than 30 years.

Amongst the GPs who prescribed sidenafil to patients aged less than 30 years and screened for ecstasy use, a minority (12%) reported that they never suspected any non-disclosure. Twenty-one percent reported they very rarely or rarely suspected any non-disclosure and an equal proportion (21%) suspected non-disclosure occasionally. A majority (45%) reported that they frequently or very frequently suspected non-disclosure of ecstasy use.

Table 10: Sidenafil and screening for ecstasy use among GPs

Questionnaire item	N (%)
How often do you prescribe sidenafil to patients aged less than 30 years? (n=199)	
Never	138 (69)
Very rarely or rarely	47 (24)
Occasionally	12 (6)
Frequently or very frequently	2 (1)
When you prescribe sidenafil to patients aged less than 30 years, how often do you screen for ecstasy use? (n=60)	
Never	32 (53)
Very rarely or rarely	9 (15)
Occasionally	4 (7)
Frequently or very frequently	8 (17)
Always	5 (8)
When you prescribe sidenafil to patients aged less than 30 years and screen for ecstasy use, how often do you suspect any non-disclosure? (n=33)	
Never	4 (12)
Very rarely or rarely	7 (21)
Occasionally	7 (21)
Frequently or very frequently	15 (45)

2.3.6 Antidepressant drugs and screening for ecstasy use

One potential negative effect of the use of serotonergic substances, such as antidepressant drugs, is serotonin toxicity. The majority (65%) of GPs reported that they never or almost never saw acute presentations of serotonin toxicity of any aetiology in their practice (Table 11). Just over one-quarter (26%) reported that they saw this health condition yearly, 8% had seen this health condition in their practice every few months and one GP saw serotonin toxicity in their practice on a monthly basis.

When GPs prescribed antidepressant drugs to patients, the minority (6%) reported that they never discussed the complication of serotonin toxicity. Slightly less than one-quarter (23%) rarely or very rarely discussed this health condition with patients, 26% discussed the health condition occasionally, one-third (33%) discussed it frequently or very frequently and 13% had always discussed the complication of serotonin toxicity when they prescribed antidepressants.

Table 11: Frequency of presentations and discussion of the complication of serotonin toxicity among GPs

Questionnaire item	N (%)
I see acute presentations of serotonin toxicity of any aetiology I my practice… (n=197)	
Never or almost never	127 (65)
Yearly	52 (26)
Every few months	17 (8)
Monthly	1 (1)
When you prescribe antidepressant drugs to patients how often do you discuss the complication of serotonin toxicity? (n=196)	
Never	12(6)
Very rarely or rarely	45 (23)
Occasionally	50 (26)
Frequently or very frequently	64 (33)
Always	25 (13)

The minority (5%) of GPs reported that they had never prescribed antidepressant drugs to patients aged less than 30 years (Table 12). Of the majority who had, just less than half (47%) mentioned that they never screened for ecstasy use, 26% very rarely or rarely screened, 6% screened occasionally and 13% screened frequently or very frequently. A minority (8%) reported that they always screened for ecstasy use when they prescribed antidepressant drugs to patients aged less than 30 years.

Amongst the GPs who prescribed antidepressant drugs to patients aged less than 30 years and screened for ecstasy use, a minority (8%) reported that they never suspected any non-disclosure (of ecstasy use). Thirty-four percent reported they very rarely or rarely suspected any non-disclosure and an almost equal proportion (37%) suspected non-disclosure occasionally. Nineteen percent reported that they frequently or very frequently suspected non-disclosure of ecstasy use and the remainder (2%) always suspected non-disclosure.

Predictors of screening for ecstasy use when prescribing antidepressant drugs

Using the backward stepwise method, a logistic regression was conducted to determine the predictors, if any, of very frequently/always screening for ecstasy use when

prescribing antidepressant drugs. Six predictor variables, highly correlated with the outcome variable, were selected. These were the location of practice (e.g. urban/inner city, suburban, regional, rural/remote), age, gender, frequency of acute presentations of serotonin toxicity, frequency of acute ecstasy-related presentations and frequency of acute methamphetamine-related presentations.

Table 12: Antidepressant drugs and screening for ecstasy use among GPs

Questionnaire item	N (%)
How often do you prescribe antidepressant drugs to patients aged less than 30 years? (n=198)	
Never	10 (5)
Very rarely or rarely	63 (32)
Occasionally	87 (44)
Frequently or very frequently	38 (19)
When you prescribe antidepressant drugs to patients aged less than 30 years, how often do you screen for ecstasy use? (n=184)	
Never	87(47)
Very rarely or rarely	48 (26)
Occasionally	11 (6)
Frequently or very frequently*	24 (13)
Always	14 (8)
When you prescribe antidepressant drugs to patients aged less than 30 years and screen for ecstasy use, how often do you suspect any non-disclosure? (n=102)	
Never	8 (8)
Very rarely or rarely	35 (34)
Occasionally	38 (37)
Frequently or very frequently	19 (19)
Always	2 (2)
Among patients aged less than 30 years, how often do you suspect they may be seeking antidepressant drugs for non-medical purposes which could be related to ecstasy use? (n=103)	
Never	50 (49)
Very rarely or rarely	39 (38)
Occasionally	9 (9)
Frequently or very frequently	5 (5)

*In this combined category, the number of GPs who reported 'very frequently' was 7 (4%)

Both the age of GP and the frequency with which a GP saw ecstasy-related presentations in their practice were significant predictors of very frequently/always screening for ecstasy use when prescribing antidepressant drugs. For every year age decreased, the likelihood a GP would screen very frequently/always for ecstasy use when prescribing antidepressant drugs increased by 6% ($P<0.05$). A GP who saw ecstasy-related presentations monthly or more frequently was eight times more likely to screen for ecstasy use when prescribing antidepressant drugs than a GP who saw ecstasy-related presentations in their practice less frequently than monthly ($P<0.05$).

Antidepressant-seeking behaviour

GPs were asked, among patients aged less than 30 years, how often they suspected antidepressant-seeking behaviour which could be related to ecstasy use. A majority (49%) reported that they never suspected this behaviour, 38% very rarely or rarely suspected it, and a minority suspected antidepressant-seeking behaviour which could be related to ecstasy use occasionally (9%) or frequently or very frequently (5%) (Table 12).

The GPs who suspected patients of seeking antidepressant drugs for non-medical purposes which could be related to ecstasy use were asked which antidepressants were requested most often and what were the reasons given for requesting them. This question was answered by 20 GPs out of the 53 that were eligible to answer and several listed more than one antidepressant drug.

The majority (n=16) of GPs who responded to this item reported that SSRIs (e.g. *Prozac*) were the most frequently reported antidepressant requested, one GP reported 'TCAs generally' were the most frequently requested and one other GP mentioned that SNRIs (e.g. *Efexor*) were the most requested. One GP mentioned nefazodone *(e.g. Serzone)*, no longer available in Australia, as the antidepressant most requested. Typical reasons given for requesting these antidepressants included depression, lack of energy/motivation, relationship problems, agitation, anxiety and that a repeat prescription was required.

GPs who suspected patients of seeking antidepressant drugs for non-medical purposes which could be related to ecstasy use, were asked at which times through the week was this behaviour most prevalent. Just less than two-thirds (63%) mentioned that they did not recognise any pattern. This behaviour was reported as most prevalent on the weekend by 15% of GPs, most prevalent early in the week (e.g. Monday or Tuesday) by 10% of GPs and most prevalent late in the week (e.g. Thursday of Friday) by 7% of GPs. One GP mentioned this behaviour was most prevalent mid-week (e.g. Wednesday) and one other reported an 'other' pattern, and specified that this was during 'lunch hour'.

GPs were asked what characteristics, if any, were most common to those patients they suspected of seeking antidepressant drugs for non-medical purposes which could be related to ecstasy use. This item contained five separate open-ended questions, and a minority of GPs responded to all parts. Of those that did respond, the majority (n=6) reported these patients were typically aged 18 to 28 years, four GPs reported these patients were typically aged 20 to 30 years, three reported that the typical age of these patients was between 14 to 30 years, two reported 'under 30' years and two reported 'under 25' years. The majority (78%, n=18) of GPs had noted that typically these patients were male.

The clinical symptoms most frequently reported by GPs as being associated with these patients were depression (reported by n=7 GPs), anxiety (n=6), poor sleeping patterns (n=5) and agitation (n=2). A minority of GPs reported other symptoms such as chronic fatigue, confusion, diarrhoea, mood swings and thought disorder.

A wide range of complex histories were listed as characteristic of this group of patients, and included acopia, chronic depression, bipolar disorder, 'party drug' use, polydrug use, drug dependence, denial of illicit drug use and a tendency 'not to hold down a job'.

2.3.7 Resource development

In relation to the statement, 'I would find a resource for general practitioners on ecstasy and related drugs such as methamphetamine, cocaine, GHB and ketamine very beneficial', the vast majority (96%) agreed overall and half (48%) strongly agreed with the statement.

GPs were asked to select from a range of options, what particular information they would find most useful in a resource on ERDs. Generally, GPs selected more than one option. Most (91%) GPs reported they would find information on the 'effects and harms of ecstasy and the concomitant use of pharmaceutical drugs' most useful, followed by information on the 'effects and harms of ecstasy and related drug use' (89%) and 'management of ecstasy and related drug users in general practice' (82%). Other information GPs would find useful in a resource is presented in Table 13.

Table 13: Information most useful in a resource on ERDs as reported by GPs

What information would you find most useful in a resource on ecstasy and related drugs?*	**N (%)**
Effects and harms of ecstasy and the concomitant use of pharmaceutical drugs	181 (91)
Effects and harms of ecstasy and related drug use	177 (89)
Management of ecstasy and related drug users in general practice	163 (82)
Harm minimisation	159 (80)
What is ecstasy, methamphetamine, cocaine, GHB and ketamine	151 (76)
Referral of ecstasy and related drug users	132 (66)
Trends in ecstasy and related drug use	129 (65)
Prevalence of ecstasy and related drug use	120 (60)

*More than one response was permitted

In relation to how such a resource would be most effectively delivered, from the options available, a majority (46%) reported 'publication or fact sheet', one-third (34%) reported 'Continuing Professional Development Program (CPDP)' and one-fifth (22%) reported 'seminar' (Table 14). Other suggestions made by a minority of GPs included a DVD, filmed case scenarios, adding information to existing medical software (e.g. *Medical Director*) or a specialist presentation at a local clinical meeting. A relatively small proportion of GPs selected more than one option. One GP commented, 'keep it under four pages or no-one will read it', one other mentioned, 'preferably not a publication, case-study based please'.

Table 14: Most effective method of resource delivery as reported by GPs

How would a resource be most effectively delivered?*	N (%)
Publication or fact sheet	91 (46)
CPDP	67 (34)
Seminar	43 (22)
CD-ROM	37 (19)
Internet or web-based	37 (19)
CPDP (online)	16 (8)

*More than one response was permitted

2.4 Discussion

Knowledge of ERDs and associated problems

This study identified numerous deficits in relation to GPs' knowledge of ERDs and the associated problems which need addressing. Among GPs there was a self-reported lack of knowledge about ecstasy and ecstasy-related problems, and subsequently, a majority reported they did not feel well prepared to discuss the health risks associated with ecstasy use. Only half of GPs reported having a clear idea of their responsibilities in helping patients who were using ecstasy. A relatively small minority of GPs agreed they had a working knowledge of other drugs such as methamphetamine and GHB. As GPs are well positioned to respond to patients with drug-related problems and evidence suggests people prefer a response to substance use problems to come from their GP (Hindler et al., 1995; Roche et al., 1996; Roche et al., 2002; Wallace & Jarman, 1994), these important issues require attention.

It is also somewhat troubling that a majority of GPs reported the perceived risk to health of using ecstasy with MAOI/RIMA antidepressants as the same, or less, than that of using ecstasy with TCA/SSRI/SNRI antidepressants, when the risk is likely to be greater (Silins et al., 2007). In keeping with this, most GPs did not feel well prepared to discuss the health risks associated with ecstasy and the concomitant use of pharmaceutical drugs. This strongly suggests a need to inform GPs of the potential negative health consequences which can arise from the use of ecstasy and pharmaceutical drugs, in particular antidepressants.

Frequency of ERDs-related presentations

Of some concern is that whilst GPs generally reported a shortfall of knowledge about ERDs and associated problems, ERDs-related presentations were commonly reported by GPs. Approximately half of the GPs surveyed mentioned that they saw such presentations on a yearly or more frequent basis. It is not surprising that GPs were more likely to see methamphetamine-related presentations than ecstasy-related presentations as it is generally accepted there are more harms associated with the use of methamphetamine than with the use of ecstasy. Presentations related to GHB were very rarely seen by GPs in their practices. This was not an unexpected finding given that people experiencing GHB-related problems would be more likely to present to hospital

with acute signs of overdose. Interestingly, despite acute serotonin toxicity being recognised more frequently in recent years(Adverse Drug Reactions Advisory Committee, 2004; Mackay et al., 1999a; McManus et al., 2000; Sporer, 1995), the majority of GPs reported hardly ever seeing such presentations and none reported seeing them more frequently than monthly.

Prescription drugs and screening for ecstasy use

Among GPs overall, there was limited evidence of screening for ecstasy use when prescribing antidepressants or sidenafil to patients aged less than 30 years. Approximately 50% of GPs who prescribed antidepressants or sidenafil to these patients reported never screening for ecstasy use, and only a small minority routinely (e.g. always) screened. Generally, our findings are consistent with other evidence that the involvement of GPs in screening for illicit drug use is limited (Blum et al., 1996; Friedman et al., 2001; Kamerow et al., 1986; Maheux et al., 1999). Of further concern is that on those occasions when GPs prescribed antidepressants, few routinely discussed the complication of serotonin toxicity with their patients.

The predictors of screening for ecstasy use when prescribing antidepressants were found to be age of the GP and the frequency with which GPs saw ecstasy-related presentations in their practice. Younger GPs and those who saw ecstasy-related presentations more frequently were more likely to screen for ecstasy use when prescribing antidepressants to young patients. Results suggest there may be scope to improve screening rates among older GPs and those who practice in locations where fewer ecstasy-related presentations are seen, such as non-metropolitan areas.

Reassuringly, antidepressant-seeking behaviour related to ecstasy use was not commonly reported. The majority of GPs rarely suspected such a behaviour among young patients. The characteristics identified by GPs as most common to these patients, when this behaviour was noted, was that they were typically male, aged 18 to 28 years and presented with clinical symptoms of depression or anxiety.

Resource development

In keeping with the self-reported lack of knowledge among GPs on ERDs and associated problems, there was, reassuringly, a strong demand for relevant resource material. GPs primarily wanted more information on the effects and harms of ecstasy and the concomitant use of pharmaceutical drugs. Other information GPs requested be included in a resource were details on the effects and harms of ERDs use, and management of ERDs users in general practice. The minority of GPs wanted more information on the prevalence of ERDs use. A publication or fact-sheet was by far the preferred method of delivery. Frontline healthcare professionals, such as those working in Emergency Departments at major hospitals, also manage a proportion of patients who present with substance use problems, in particular, acute drug-related presentations. It was hypothesised that the needs of frontline healthcare professionals in relation to a resource on ERDs may be different from the needs of GPs, and this aspect was addressed by a separate component of the study.

Limitations

The relatively low response rate among GPs suggests that the sample may not be representative of GPs in general. However, the response rate was similar to rates

reported from other surveys of medical practitioners where there was no intensive follow-up (Braithwaite et al., 2003; Lensing et al., 2000). GPs that were more interested, confident or knowledgeable in addiction medicine may have been more likely to return the questionnaire and this may have affected findings.

3 SURVEY OF FRONTLINE HEALTHCARE PROFESSIONALS

An additional arm of this project included the delivery of a presentation on current trends in ERDs and associated problems to interested frontline healthcare professionals at major hospitals across Australia. The target audience was primarily medical, nursing and other healthcare professionals who saw ERDs-related presentations frequently. Typically, the presentation was scheduled during the hospital's regular 'in-house' training session within the Emergency Department and lasted for about one hour.

Attending healthcare professionals completed a survey which aimed to identify gaps in knowledge about the effects and harms of ERDs use, the incidence of ERDs-related presentations and resource development.

3.1 Recruitment and procedure

During February 2007, key emergency department personnel at major hospitals in each Australian capital city were contacted via email and telephone, provided with details of the ERDs presentation and invited to incorporate the presentation into the department's regular 'in-house' teaching session. Presentations were delivered to frontline healthcare professionals at 12 hospitals in eight major centres around Australia between March 2007 and May 2007 (Table 15). Attending healthcare professionals were asked to complete an anonymous questionnaire. Where possible, the survey was completed prior to the delivery of the presentation. Participation was voluntary.

Table 15: Location of ERDs presentations

	Recruited hospitals
ACT	Canberra Hospital, Canberra
NSW	Royal North Shore Hospital, Sydney
	Royal Prince Alfred Hospital, Sydney
	St Vincent's Hospital, Sydney
NT	Royal Darwin Hospital, Darwin
QLD	Princess Alexandra Hospital, Brisbane
	Prince Charles Hospital, Brisbane
	Gold Coast Hospital, Southport
	Royal Brisbane Hospital, Brisbane
SA	Flinders Medical Centre, Adelaide
VIC	St Vincent's Hospital, Melbourne
WA	Sir Charles Gairdner Hospital, Perth

3.2 Measures

The 33 item questionnaire was based closely on the instrument used to survey GPs. For ecstasy, methamphetamine, cocaine, GHB and ketamine, four items related to frontline healthcare professionals' knowledge of these drugs and related problems, how well prepared they felt to discuss the associated risks, how supported they felt when dealing with drug-related presentations and how frequently they saw acute presentations related to these drugs.

One item related to the frequency with which frontline healthcare professionals saw acute ecstasy-related presentations of serotonin toxicity and one other related to the frequency of acute presentations of serotonin toxicity of any aetiology.

Four items related to resource development and asked how beneficial a resource on ERDs would be, which drugs frontline healthcare professionals wanted to know more about, what information they specifically wanted to know and how a resource on these drugs could be most effectively delivered.

Demographic items related to the healthcare professional's main role (e.g. medical practitioner, nurse) and the department where they mostly worked (e.g. Emergency). Four items related to how relevant, interesting and informative the presentation on current trends in ERDs and associated problems was for attending frontline healthcare professionals.

To allow comparability, the response categories used in the frontline healthcare professionals questionnaire were the same as those used in the GP questionnaire. The questionnaire was designed such that it could be completed within approximately five minutes.

3.3 Results

The major hospitals where presentations to frontline healthcare professionals were delivered were located in Sydney (n=3), Brisbane (n=3), Gold Coast (n=1), Melbourne (n=1), Adelaide (n=1), Darwin (n=1), Perth (n=1) and Canberra (n=1). Questionnaires were completed by 192 frontline healthcare professionals.

3.3.1 Sample description

A majority of frontline health care professionals who completed the questionnaire were from NSW (31%), QLD (27%) and VIC (15%). Just less than three-quarters (70%) of respondents were medical practitioners and a substantial proportion (90%) reported working in the emergency department (Table 16).

Table 16: Characteristics of frontline healthcare professionals

	N (%)
Jurisdiction:	
NSW	59 (31)
QLD	51 (27)
VIC	29 (15)
ACT	15 (8)
SA	13 (7)
NT	13 (7)
WA	12 (6)
Main role:	
Medical practitioner	135 (70)
Nursing practitioner	42 (22)
Other*	14 (7)
Department:	
Emergency	172 (90)
Toxicology	4 (2)
Addiction medicine	3 (2)

*Included medical students, social professionals, occupational therapists

3.3.2 Knowledge of ERDs and associated problems

Generally, a majority of frontline healthcare professionals agreed that they had a working knowledge of ERDs and associated problems (Table 17). The proportion who agreed overall was highest for methamphetamine and methamphetamine-related problems (86%) and lowest for GHB and GHB-related problems (75%).

3.3.3 Preparedness to discuss health risks associated with ERDs use

A majority of frontline healthcare professionals agreed overall that they felt well prepared to discuss the health risks associated with the use of ecstasy, methamphetamine, cocaine, GHB and ketamine (Table 18). The proportion who agreed overall was highest for methamphetamine (80%) and lowest for GHB (71%).

Table 17: Working knowledge of ERDs and associated problems as reported by frontline healthcare professionals

I feel I have a working knowledge of…	Overall agreement* N (%)
Ecstasy and ecstasy-related problems	157 (82)
Methamphetamine and methamphetamine-related problems	166 (86)
Cocaine and cocaine-related problems	146 (76)
GHB and GHB-related problems	143 (75)
Ketamine and ketamine-related problems	156 (81)

*6-point Likert scale responses were dichotomised into overall disagreement (somewhat disagree, disagree, strongly disagree) and overall agreement (somewhat agree, agree, strongly agree)

Table 18: Preparedness to discuss health risks associated with ERDs use as reported by frontline healthcare professionals

I feel well prepared to discuss the health risks associated with…	Overall agreement* N (%)
Ecstasy	143 (75)
Methamphetamine	154 (80)
Cocaine	141 (74)
GHB	136 (71)
Ketamine	143 (75)

*6-point Likert scale responses were dichotomised into overall disagreement (somewhat disagree, disagree, strongly disagree) and overall agreement (somewhat agree, agree, strongly agree)

3.3.4 Perceived level of support available for managing ERDs patients

If frontline healthcare professionals felt the need, a substantial majority agreed overall that they could easily find someone who would be able to help them formulate the best approach to manage a patient who presented with ERDs-related problems (Table 19).

Table 19: Perceived level of support available for managing ERDs patients as reported by frontline healthcare professionals

If I felt the need, I could easily find someone who would be able to help me formulate the best approach to manage a patient who presented with…	**Overall agreement* N (%)**
Ecstasy-related problems	177 (92)
Methamphetamine-related problems	174 (91)
Cocaine-related problems	171 (89)
GHB-related problems	167 (87)
Ketamine-related problems	167 (87)

*6-point Likert scale responses were dichotomised into overall disagreement (somewhat disagree, disagree, strongly disagree) and overall agreement (somewhat agree, agree, strongly agree)

3.3.5 Frequency of ERDs-related presentations

The frequency with which frontline healthcare professionals saw ERDs-related presentations varied considerably depending on the particular drug asked about (Table 20, Table 21). A substantial majority of frontline healthcare professionals reported that they never or almost never saw acute ketamine-related presentations (59%) or acute cocaine-related presentations (47%). In keeping with this, a relatively small proportion reported that they saw acute presentations related to these drugs on a weekly or more frequent basis (weekly/every few days/daily) (cocaine 2%; ketamine 2%). On the other hand, the proportion of frontline healthcare professionals that reported that they saw acute presentations related to methamphetamine, ecstasy and GHB weekly or more frequently was considerably larger (36%, 26%, 14% respectively). Eight percent (n=15) of frontline healthcare professionals saw acute methamphetamine-related presentations on a daily basis and these frequent presentations were reported in NSW, QLD and WA.

Table 20: Frequency of acute ecstasy, methamphetamine and cocaine-related presentations as reported by frontline healthcare professionals

Questionnaire item	N (%)
I see acute ecstasy-related presentations…	
Never or almost never	28 (15)
Yearly	18 (9)
Every few months	35 (18)
Monthly	18 (9)
Every few weeks	41 (21)
Weekly	34 (18)
Every few days	16 (8)
I see acute methamphetamine-related presentations…	
Never or almost never	25 (13)
Yearly	11 (6)
Every few months	28 (15)
Monthly	20 (10)
Every few weeks	38 (20)
Weekly	31 (16)
Every few days	22 (12)
Daily	15 (8)
I see acute cocaine-related presentations…	
Never or almost never	90 (47)
Yearly	30 (16)
Every few months	42 (22)
Monthly	11 (6)
Every few weeks	11 (6)
Weekly	3 (2)

Table 21: Frequency of acute GHB and ketamine-related presentations as reported by frontline healthcare professionals

Questionnaire item	N (%)
I see acute GHB-related presentations…	
Never or almost never	62 (32)
Yearly	26 (14)
Every few months	33 (17)
Monthly	20 (10)
Every few weeks	21 (11)
Weekly	16 (8)
Every few days	9 (5)
Daily	1 (1)
I see acute ketamine-related presentations…	
Never or almost never	114 (59)
Yearly	32 (17)
Every few months	26 (14)
Monthly	3 (2)
Every few weeks	9 (5)
Weekly	1 (1)
Every few days	1 (1)

3.3.6 Frequency of acute presentations of serotonin toxicity

Slightly less than one-third (32%) of frontline healthcare professionals never or almost never saw acute presentations of serotonin toxicity of any aetiology (Table 22). Acute presentations of serotonin toxicity of any aetiology were seen every few months or more frequently by about half (54%) of frontline healthcare professionals.

When asked how frequently frontline healthcare professionals saw presentations of serotonin toxicity specifically related to ecstasy use, 40% reported never or almost never. However, acute ecstasy-related presentations of serotonin toxicity were seen every few months or more frequently by a substantial majority (43%) of frontline healthcare professionals.

Table 22: Frequency of acute presentations of serotonin toxicity as reported by frontline healthcare professionals

Questionnaire item	N (%)
I see acute presentations of serotonin toxicity of any aetiology…	
Never or almost never	61 (32)
Yearly	23 (12)
Every few months	54 (28)
Monthly	23 (12)
Every few weeks	17 (9)
Weekly	7 (4)
Every few days	1 (1)
I see acute ecstasy-related presentations of serotonin toxicity…	
Never or almost never	77 (40)
Yearly	30 (16)
Every few months	49 (26)
Monthly	12 (6)
Every few weeks	16 (8)
Weekly	5 (3)

3.3.7 Resource development

In relation to the statement, 'I would use a resource on ecstasy and related drugs such as methamphetamine, cocaine, GHB and ketamine', the vast majority (94%) agreed overall and about one-third (35%) strongly agreed with the statement.

The majority of frontline healthcare professionals wanted to know more about each of the drugs asked about in the questionnaire (Table 23). There was, however, a greater demand for more information about GHB (71%) and methamphetamine (69%) than for ketamine (63%), cocaine (60%) or ecstasy (58%).

Table 23: Drugs frontline healthcare professionals wanted more information on

Which drugs would you like more information on?	N (%)
GHB	136 (71%)
Methamphetamine	132 (69)
Ketamine (in the context of illicit use)	121 (63)
Cocaine	115 (60)
Ecstasy	112 (58)
'Other' drug*	7 (4)

*Respondents specified cannabis, heroin, benzodiazepines and paramethoxyamphetamine (PMA)

When asked what information frontline healthcare professionals would find most useful in a resource on ERDs, the majority (81%) reported, 'management of ecstasy and related drug users' (Table 24). This was followed by the 'effects and harms of ecstasy and the concomitant use of pharmaceutical drugs' (67%). A minority (30%) of frontline healthcare professionals reported that they would find information on the 'prevalence of ecstasy and related drug use' most useful in such a resource. Other information specified to be most useful in a resource on ERDs was local market information and street terminology.

Table 24: Most useful information in a resource on ERDs as reported by frontline healthcare professionals

What information would you find most useful in a resource on ecstasy and related drugs?*	**N (%)**
Management of ecstasy and related drug users	155 (81)
Effects and harms of ecstasy and the concomitant use of pharmaceutical drugs	128 (67)
Effects and harms of ecstasy and related drug use	103 (54)
Referral of ecstasy and related drug users	96 (50)
Harm minimisation	92 (48)
What is ecstasy, methamphetamine, cocaine, GHB and ketamine	88 (46)
Trends in ecstasy and related drug use	74 (39)
Prevalence of ecstasy and related drug use	58 (30)

*More than one response was permitted

An 'internet or web-based' resource on ERDs was reported to be the most effective method of delivery by the majority (60%) of frontline healthcare professionals (Table 25). One-third (35%) of respondents reported 'Continuing Professional Development Program' (CPDP) as the most effective delivery method and the minority (7%) reported 'CD-ROM'.

Table 25: Most effective method of resource delivery as reported by frontline healthcare professionals

How would a resource be most effectively delivered?*	**N (%)**
Internet or web-based	115 (60)
CPDP	68 (35)
Publication or fact sheet	43 (22)
CPDP (online)	30 (16)
Seminar	25 (13)
CD-ROM	14 (7)

*More than one response was permitted

3.3.8 Presentation feedback

The vast majority of frontline healthcare professionals agreed overall that the ERDs presentation which was delivered improved their knowledge of ERDs (95%), was relevant to their work (95%) and was interesting (95%).

3.4 Discussion

Knowledge of ERDs and associated problems

A substantial majority of frontline healthcare professionals agreed they had a working knowledge of ecstasy, methamphetamine, GHB, cocaine and ketamine (in the context of illicit use). Subsequently, a large majority felt prepared to discuss the health risks associated with the use of these drugs. This is in stark contrast to the findings among GPs, where there was generally a lower self-reported level of knowledge of ERDs and associated problems. The increased frequency with which frontline healthcare professionals saw drug-related presentations may have necessitated greater expertise in illicit drugs and be one reason for this.

Frequency of ERDs-related presentations

ERDs-related presentations were seen with greater frequency in the hospital setting than in general practice. Among frontline healthcare professionals, acute presentations related to methamphetamine were most commonly reported, this was followed by ecstasy- and GHB-related presentations. Only a relatively small proportion of frontline healthcare professionals saw ERDs-related presentations on a daily basis, which, interestingly, is contrary to the portrayal of the frequency of these presentations in the popular media. Of the ERDs-related presentations asked about, only presentations related to methamphetamine and GHB were seen on a daily basis. Acute methamphetamine-related presentations were seen on a daily basis by frontline healthcare professionals in QLD (n=8), NSW (n=6) and WA (n=1). Acute GHB-related presentations were seen on a daily basis by one frontline healthcare professional in NSW.

As would be expected, acute presentations of serotonin toxicity were more commonly reported by frontline healthcare professionals at major hospitals than by GPs in their practice. In the hospital setting, one-quarter of health professionals saw such presentations monthly or more frequently, and one in twenty saw them at least weekly.

Resource development

Among frontline healthcare professionals, a large majority wanted to know more about the drugs GHB and methamphetamine, whereas the minority wanted to know more about ecstasy. This was not unexpected, given that frontline healthcare professionals saw acute presentations related to GHB and methamphetamine more often than those related to ecstasy. Information on the management of ERDs users was considered to be by far the most useful by this group. Information about the effects and harms of ecstasy and the concomitant use of pharmaceutical drugs was considered to be the second most useful. As with GPs, information about the prevalence of ERDs use was regarded as

least useful. Most frontline healthcare professionals preferred a resource on ERDs to be internet or web-based.

4 INTERVIEWS WITH ERDS USERS

Evidence that healthcare professionals in general practice and the hospital setting regularly manage patients with ERDs-related problems, suggests a need to explore, in more depth, the experiences of ERDs users when they use serotonergic drugs and substances.

4.1 Recruitment and procedure

In-depth interviews were conducted with 30 ERDs users who had recently combined ecstasy and antidepressant drugs. Participants were recruited between May 2006 and May 2007 through a purposive sampling strategy which included advertisements in entertainment street press, gay and lesbian newspapers and via internet websites. To a lesser extent, 'snowball' sampling procedures were used. This is where participants refer others who might be willing and able to participate.

Participants contacted the researcher by telephone and were screened for eligibility. To meet selection criteria they were required to:

- be at least 16 years of age,
- have visited a general practitioner within the previous six months,

and

- used antidepressant drugs as part of treatment for a current health condition and used ecstasy at least three times in the previous six months,

or

- intentionally used antidepressant drugs for non-medical purposes before, during or after ecstasy (to achieve a specific effect) at least three times in the previous six months.

All information provided was confidential and anonymous. The duration of interviews ranged from 60 to 90 minutes and the majority were conducted at the National Drug and Alcohol Research Centre, Sydney. A minority were conducted off-site at a public location (e.g. coffee shop). Where a face-to-face interview was not possible (e.g. the participant lived in a regional area or interstate) a telephone interview was conducted (n=7). Comprehensive notes were taken. All participants were volunteers and were reimbursed $30 for travel and related expenses. The nature and purpose of the study was explained to participants before informed consent was obtained. On completion of the interview, the potential harms of using ecstasy with other substances, in particular antidepressants, was explained and the participant was informed about where to access additional information (i.e. Alcohol and Drug Information Service) if they felt the need.

4.2 Measures

The in-depth interview incorporated structured and open-ended questions to identify patterns of illicit and prescribed drug use. The interview also explored participants' experience of combining ecstasy with pharmaceutical drugs and supplements, and any associated harms. In addition, the interview explored aspects of the sharing of prescription drugs with friends and participants' experiences when they visit a general practitioner and are prescribed pharmaceuticals. Where participants reported use of ecstasy on at least 48 days in the preceding six months (i.e. on average, at least two days per week in the preceding six months) a Severity of Dependence Score (SDS) scale (Gossop et al., 1995) was completed to asses the level of dependence. Each participant completed the Beck Depression Inventory (BDI) (Beck & Steer, 1990; Beck et al., 1996), a standardised measure of characteristic attitudes and symptoms of depression.

4.3 Results

In-depth interviews were conducted with 30 ERDs users and saturation of themes was achieved with this sample.

4.3.1 Sample description

The sample consisted of 30 ERDs users recruited between May 2006 and May 2007 (Table 26). The mean age of participants was 34 years (SD 9.8; range 18-59) and most (67%) were male. Just over three-quarters (77%) of the sample were Australian born. No participants reported being of Aboriginal or Torres Strait Islander origin. Twenty-eight (93%) participants lived in NSW, one in QLD and one in VIC. Most (70%) described the location where they lived as 'urban/inner city' and the remainder described it as 'suburban'. A majority (43%) of participants usually lived alone and 36% usually lived either with a spouse/partner, friend or other person (e.g. flatmate). Two-thirds (67%) of participants completed year 12 and the remainder completed year 11 (17%) or year 10 (17%). Since leaving school, 43% had completed a trade or technical course and one-third (33%) had completed a university or college course. Major areas of study varied considerably among participants and included commerce, IT, design, arts, law, nursing, psychology, nursing, welfare and pharmacy. Just less than one-third (30%) of the sample reported full-time employment at the time of interview; 27% were currently unemployed, 20% were studying full-time, 13% were employed part-time and 3% were studying part-time. Participants described their sexual identity as gay male (40%), heterosexual (30%), lesbian (17%), bisexual (10%) or 'other' (3%).

Table 26: Characteristics of ERDs users

	N (%)
Mean age in years (SD; range)	34 (9.8; 18-59)
Male	20 (67)
Australian born	23 (77)
State/territory of residence:	
NSW	28 (93)
QLD	1 (3)
VIC	1 (3)
Location of residence:	
Urban/inner city	21 (70)
suburban	9 (30)
Living with:	
Alone	13 (43)
Spouse/partner	4 (13)
Friend(s)	4 (13)
Parent(s)	3 (10)
Other person (e.g. flatmate)	3 (10)
Alone with children	1 (3)
Spouse/partner and children	1 (3)
Other relative(s)	1 (3)
Completed year 12 schooling	20 (67)
Courses completed since leaving school:	
Trade/technical	13 (43)
University/college	10 (33)
Current employment/study situation:	
Employed full-time	9 (30)
Unemployed	8 (27)
Studying full-time	6 (20)
Employed part-time	4 (13)
Studying part-time	1 (3)
Sexual identity:	
Gay male	12 (40)
Heterosexual	9 (30)
Lesbian	5 (17)
Bisexual	3 (10)
Other	1 (3)

4.3.2 Current health conditions and use of prescription drugs

The majority (57%) of participants reported a single current health condition which required the regular use of prescription drugs and just over one-third (37%) reported two or more. The most frequently reported current health conditions were depression (63%), anxiety (20%) and bipolar disorder (7%). Two (7%) participants reported that they did not have any current health conditions which required the regular use of prescription drugs. Current health conditions and the extent of use of prescribed antidepressant drugs are presented in Table 27.

Table 27: Current health conditions and use of prescribed antidepressant drugs among ERDs users

Current health conditions & prescribed antidepressant drugs	**N (%)**
One current health condition*	17 (57)
Two or more current health conditions*	11 (37)
No current health conditions*	2 (7)
Current health conditions reported:†	
Depression	19 (63)
Anxiety	6 (20)
Bipolar disorder	2 (7)
Obsessive compulsive disorder	2 (7)
Attention deficit hyperactivity disorder	1 (3)
Stress	1 (3)
Schizophrenia	1 (3)
Panic disorder	1 (3)
Dermatitis	1 (3)
Asthma	1 (3)
Peptic ulcer disease	1 (3)
Genital herpes	1 (3)
Opioid dependence	1 (3)
Mean age at diagnosis in years (SD; range) ‡	29 (8.7; 14-46)
Use of antidepressant drugs for a current health condition	26 (87)
SSRIs (i.e. citalopram, fluoexitine, escitalopram, sertraline)	15 (58)
Other antidepressants (i.e. mirtazapine, robexetine)	6 (23)
SNRI (i.e. venlafaxine)	3 (12)
TCAs (i.e. amitriptyline, prothiaden)	2 (7)

*A current health condition was defined as a condition requiring regular use of prescription drugs
†Some participants reported more than one current health condition
‡Only includes participants who reported a current health condition which required the regular use of antidepressant drugs (i.e. depression, anxiety, obsessive compulsive disorder, bipolar disorder, panic disorder)

The regular use of antidepressant drugs for a current health condition was reported by the majority (87%) of participants. Of these, most (58%) were prescribed SSRIs (i.e. citalopram, fluoexitine, escitalopram, sertraline), just less than one-quarter (23%) were prescribed 'other' antidepressants (i.e. mirtazapine, robexetine), 12% were prescribed the SNRI venlafaxine and the minority (7%) were prescribed TCAs (i.e. amitriptyline, prothiaden). No participants reported the regular use of MAOIs (e.g. moclobemide) or RIMAs (e.g. phenelezine, tranylcypromine) for a current health condition.

Participants who reported a current health condition which required the regular use of prescription antidepressant drugs (i.e. depression, anxiety, obsessive compulsive disorder, bipolar disorder, panic disorder) had a mean age at diagnosis of 29 years (SD 8.7; range 14-46). The regular use of methylphenidate (i.e. *Ritalin*) for a current health condition was reported by two (7%) of participants.

Depressive symptoms

The Beck Depression Inventory (BDI) was administered as a measure of severity of depressive symptoms. Prior to administering the measure, participants were asked how many days ago they last used ecstasy, how much ecstasy they had used on that occasion and how many days ago they last used antidepressant drugs (either for a current health condition or for non-medical purposes). The mean BDI score was 13.5 (SD 11.6; range 0-45), as presented in Table 28.

Table 28: Recent use of ecstasy and antidepressant drugs among ERDs users and mean BDI score

Median number of days ago last used ecstasy (range)	10 days (1-60)
Median amount of ecstasy used on that occasion (range)	2 tablets (0.5-5)
Median number of days ago last used antidepressant drugs (range)	0* (0-150)
Mean BDI score on day of interview (SD; range)	13.5 (11.6; 0-45)

*Indicates use on the day of interview

Slightly more than two-thirds (70%, n=21) of participants had BDI scores of below 17 indicating low levels of depressive symptoms. A minority (17%, n=5) had scores between 17 and 30 indicating moderate levels of depressive symptoms. The remaining four (13%) participants had scores of 31 or higher indicating high levels of depressive symptoms.

Among the four (13%) participants with BDI scores indicating high levels of depressive symptoms, all reported daily use of antidepressants for a current health condition and one of these participants reported also using antidepressant drugs intentionally for non-medical purposes with ecstasy. Three participants in this group reported use of ecstasy on 72, 60 and 15 days respectively in the preceding six months which was substantially above the median days of use for the entire sample. These three participants reported that they had last used ecstasy from one to four days prior to interview. The remaining participant reported use of ecstasy on four days in the preceding six months and had last used ecstasy 28 days prior to interview.

4.3.3 Patterns of drug use

Participants were asked about the use of a range of substances including illicit and prescribed drugs (Table 29).

Table 29: Patterns of drug use among ERDs users

Drug used*	Ever used N (%)	Used in last 6 months N (%)	Median days used in last 6 months (range)	Amount used in a 'typical' episode	Most frequently reported route of admin-istration	Mean age of first use (SD; range)
Ecstasy	30 (100)	30 (100)	8 (3-72)	1-4 tablets	swallow	26 (8.9; 15-54)
Methamphetamine powder	25 (83)	9 (30)	2 (1-4)	1 point-2 grams	snort	23 (9.0; 13-55)
Methamphetamine base	13 (43)	9 (30)	2 (1-20)	1 point-1 gram	swallow	29 (6.5; 16-37)
Crystal methamphetamine	17 (57)	16 (53)	6 (1-84)	1 point-20 pipes	smoke	33 (8.8; 18-56)
Cocaine	19 (63)	9 (30)	2 (1-24)	1 line-2 grams	snort	25 (9.1; 13-55)
GHB	12 (40)	11 (37)	2 (1-72)	1-2 vials	swallow	33 (6.4; 21-43)
MDA	14 (47)	4 (13)	2 (1-12)	2 points-1gram	swallow	27 (7.7; 17-46)
Ketamine	15 (50)	12 (40)	2 (1-72)	1-5 bumps	snort	31 (9.2; 19-54)
Cannabis	30 (100)	19 (63)	24 (1-168)	2 cones-10 joints	smoke	18 (4.6; 11-30)
LSD	21 (72)	3 (10)	5 (1-24)	0.5-3tabs	dissolve on tongue	-
Heroin	5 (17)	2 (7)	4 (2-6)	1-2 hits	inject	19 (2.7; 16-23)
Antidepressant drugs†	10 (33)	6 (20)	7 (3-14)	1-3 tablets	swallow	27 (12.9; 15-57)
Dexamphetamine/ methylphenidate †	4 (13)	2 (7)	1.5 (1-2)	1-3 tablets	swallow	23 (13.7; 13-43)
Benzodiazepines and sleeping tablets	23 (77)	15 (50)	6 (1-84)	1-5 tablets	swallow	27 (8.1; 16-43)
Sidenafil and other similar drugs	11 (37)	7 (23)	3 (1-27)	0.3-2 tablets	swallow	35 (8.1; 21-54)
Amyl nitrate	24 (80)	16 (53)	3 (1-40)	1-10 snorts	inhale	-
Nitrous oxide	9 (30)	3 (10)	3 (no range)	1-50 bulbs	inhale	-

†In the context of intentional use for non-medical purposes
*Excluding the drugs phencyclidine (PCP), dimethyltryptamine (DMT), codeine, morphine, benzylpiperazine (BZP) and dextromethorphan (DXM), each of which were reportedly ever used on one occasion

4.3.3.1 Illicit drug use

Ecstasy

Participants had used ecstasy on a median of eight days in the preceding six months (range 3-72) and one-fifth (20%) of participants had used ecstasy on at least one day per week. The median number of ecstasy tablets used in a 'typical' episode was two (range 1-4). Twelve (40%) participants reported that they typically used three or more tablets in a single use episode. When participants used ecstasy, the vast majority (94%) reported that they usually swallowed the tablet and the remainder (6%) reported that they usually shafted it. The mean age participants first used ecstasy was 26 years (SD 8.9; range 15-54).

Level of dependence on ecstasy

Three (10%) participants reported use of ecstasy on at least 48 days in the preceding six months and, therefore, these participants were asked to complete a Severity of Dependence Scale (SDS) (Gossop et al., 1995) for ecstasy use to assess the level of dependence. Possible SDS scores range from zero to 15, with higher scores indicating greater dependence. The median SDS score for ecstasy for these participants was six (range 5-9), well above published cut-off scores for dependence for a range of widely used illicit drugs(Dawe et al., 2002; Kaye & Darke, 2002; Ross & Darke, 1997). The validity and reliability of the SDS, however, has been established only for amphetamines, cannabis, cocaine and heroin. Interestingly, two of the three participants who had SDS scores which suggested higher levels of dependence on ecstasy also had BDI scores indicating high levels of depressive symptoms.

Methamphetamine powder

Eighty-three percent of participants had ever used methamphetamine powder ('speed') and just under one-third (30%) had used the drug in the preceding six months. Use was reported on a median of two days (range 1-4) in the preceding six moths. The amount used in a 'typical' episode ranged from one point (i.e. one-tenth of a gram) to two grams. Just less than half (48%) reported that they usually snorted the drug, 28% usually swallowed the drug and 24% usually injected it. The mean age of first use was 23 years (SD 9.0; range 13-55).

Methamphetamine base

Forty-three percent of participants had ever used methamphetamine base ('paste', 'pure') and just less than one-third (30%) had used the drug in the preceding six months. Use was reported on a median of two days (range 1-20) in the preceding six months. The amount used in a 'typical' episode ranged from one point to one gram. Just less than half (46%) reported that they usually swallowed the drug, 38% usually injected, 8% usually snorted and 8% usually smoked methamphetamine base. The mean age of first use was 29 years (SD 6.5; range 16-37).

Crystal methamphetamine

Fifty-seven percent of participants had ever used crystal methamphetamine ('crystal meth', 'ice') and just over half (53%) had used the drug in the preceding six months. Use was reported on a median of six days (range 1-84) in the preceding six moths. The amount used in a 'typical' episode ranged from one point to 20 pipes. Approximately half (53%) reported that they usually smoked the drug, 35% usually injected and 12% usually swallowed crystal methamphetamine. The mean age of first use was 33 years (SD 8.8; range 18-56).

Cocaine

Sixty-three percent of participants had ever used cocaine and just under one-third (30%) had used the drug in the preceding six months. Use was reported on a median of two days (range 1-24) in the preceding six months. The amount used in a 'typical' episode ranged from one line to two grams. The majority (79%) reported that they usually snorted the drug, 16% usually injected and 5% usually swallowed cocaine. The mean age of first use was 25 years (SD 9.1; range 13-55).

GHB

Gamma-hydroxybutyrate (GHB), otherwise known as 'liquid ecstasy' or 'fantasy', is a depressant drug with hallucinogenic properties. Forty percent of participants had ever used GHB and 37% had used the drug in the preceding six months. Use was reported on a median of two days (range 1-72) in the preceding six months. The amount used in a 'typical' episode ranged from two to four millilitres (i.e. one to two vials). All participants who used GHB usually swallowed the drug. The mean age of first use was 33 years (SD 6.4; range 21-43).

MDA

MDA (3,4-methylenedioxyamphetamine) is part of the phenethylamine family of substances. Like ecstasy, MDA is classed as a stimulant hallucinogen and has similar effects to ecstasy. Just under half (47%) of participants had ever used MDA and 13% had used the drug in the preceding six months. Use was reported on a median of two days (range 1-12) in the preceding six months. The amount used in a 'typical' episode ranged from 0.2 to one gram. Most (64%, n=9) participants reported that they usually swallowed the drug, 29% (n=4) usually snorted and 7% (n=1) injected MDA. The mean age of first use was 27 years (SD 7.7; range 17-46).

Ketamine

Ketamine ('K') is a disassociative anaesthetic. Half (50%) of the participants had ever used ketamine and 40% had used the drug in the preceding six months. Use was reported on a median of two days (range 1-72) in the preceding six months. The amount used in a 'typical' episode ranged from one to five bumps. Almost all (93%) of the participants who used ketamine reported that they usually snorted the drug. One (7%) participant reported that they usually injected it. The mean age of first use was 31 years (SD 9.2; range 19-54).

Cannabis

All participants had ever used cannabis and almost two-thirds (63%) had used the drug in the preceding six months. Use was reported on a median of 24 days (range 1-168) in the preceding six months. The amount used in a 'typical' episode ranged from two cones to 10 joints. All participants who used cannabis reported that they usually smoked the drug. The mean age of first use was 18 years (SD 4.6; range 11-30).

LSD

Lysergic acid diethylamide is commonly known as LSD, 'trips' or 'acid'. Just under three-quarters (72%) of participants had ever used LSD and 10% had used the drug in the preceding six months. Use was reported on a median of five days (range 1-24) in the preceding six months. The amount used in a 'typical' episode ranged from half a tab to three tabs. All participants reported that they usually dissolved the tab on their tongue.

Heroin

A minority (17%) of participants had ever used heroin and two (7%) participants had used the drug in the preceding six months. Among those who had used heroin, use was reported on a median of four days (range 2-6) in the preceding six months. The amount used in a 'typical' episode ranged from one to two 'hits' (0.1-0.2 grams). All participants reported that they usually injected heroin. The mean age of first use was 19 years (SD 2.7; range 16-23).

PCP

Phencyclidine (PCP) is an anesthetic agent used in veterinary medicine. The street name for phencyclidine is PCP or 'angel dust'. It is a psychoactive drug with CNS depressant, stimulant, analgesic and hallucinogenic effects. One (3%) participant reported ever use of PCP and stated that this was not in the preceding six months. Age of first use was 16 years.

DMT

Dimethyltryptamine (DMT) is a psychedelic tryptamine. DMT is a powerful psychoactive substance and can produce in users a sense of euphoria and intense visual hallucinations. One (3%) participant reported smoking DMT (crystalline form) on one day in the preceding six months. The amount used was approximately two points. The age of first use was 34 years.

4.3.3.2 Prescription drug use

Antidepressant drugs

Consistent with recruitment criteria, all participants reported ever use of antidepressant drugs. As mentioned earlier, the majority (87%) reported regular use of antidepressant drugs for a current health condition. One-third (33%), however, reported ever using antidepressant drugs intentionally for non-medical purposes (i.e. before, during or after

ecstasy use to achieve a specific effect) and one-fifth (20%) reported using antidepressant drugs in this way in the preceding six months. Use of antidepressant drugs intentionally for non-medical purposes was reported on a mean of seven days (range 3-14) in the preceding six months. The amount used ranged from one to three tablets. The mean age participants first used antidepressant drugs in this way was 27 years (SD 12.9; range 15-57).

Dexamphetamine and methylphenidate

Dexamphetamine and methylphenidate are frequently prescribed for ADHD. A minority (7%) of participants reported regular use of methylphenidate for a current health condition (e.g. ADHD). Four (13%) participants had ever used dexamphetamine ('dexies') or methylphenidate intentionally for non-medical purposes and two (7%) had used the drugs in this way in the preceding six months. Use for non-medical purposes was reported on a median of 1.5 days (range 1-2) in the preceding six months. The amount used ranged from one to three tablets. The mean age participants first used dexamphetamine or methylphenidate in this way was 23 years (SD 13.7; range 13-43).

Benzodiazepines and sleeping tablets

Participants were asked about the use of benzodiazepines and sleeping tablets. Just over three-quarters (77%) had ever used benzodiazepines and sleeping tablets and 50% had used these drugs in the preceding six months. Use was reported on a median of six days (range 1-84) in the preceding six months. The amount used ranged from one to five tablets. The mean age of first use was 27 years (SD 8.1; range 16-43).

Sidenafil and other similar drugs

Sidenafil, tadalafil (e.g. *Cialis*) and vardenafil (e.g. *Levitra*) are drugs used in the treatment of erectile dysfunction. More than one-third (37%) of participants had ever used sidenafil and other similar dugs, including one female, and 23% had used these drugs in the preceding six months. Use was reported on a median of three days (range 1-27) in the preceding six months. The amount used ranged from one-third of a tablet to two tablets. The mean age of first use was 35 years (SD 8.1; range 21-54).

Codeine

One (3%) participant reported use of codeine on 84 days in the preceding six months. The amount used ranged from 90 to 100 millilitres. The age of first use was 16.

Morphine

One (3%) participant reported having ever injected morphine and stated that this was not in the preceding six months. Age of first use was 35 years.

4.3.3.3 Other substance use

Amyl nitrate

Eighty percent of participants had ever used amyl nitrate ('amyl', 'poppers') and just over half (53%) had used the drug in the preceding six months. Use was reported on a median of three days (range 1-40) in the preceding six moths. The amount used in a 'typical' episode ranged from one to 10 snorts (i.e. inhalations). All participants who used amyl nitrate reported that they usually inhaled the drug.

Nitrous oxide

Thirty percent of participants had ever used nitrous oxide ('bulbs') and 10% had used the drug in the preceding six months. Use was reported on a median of three days in the preceding six months. The amount used in a 'typical' episode ranged from one to 50 bulbs. All participants who used nitrous oxide reported that they usually inhaled the drug.

Lighter gas

One (3%) participant reported having ever inhaled lighter gas and stated that this was not in the preceding six months. Age of first use was 13 years.

BZP

Benzylpiperazine (BZP) substances are derived from pepper plants and can also be synthetically produced. Preparations containing BZP are promoted by manufacturers as a legal alternative to the use of amphetamines. These products are not for sale in Australia, but are available over the counter in New Zealand and other countries. One (3%) participant reported ever using BZP and stated that this was not in the preceding six months. The amount used in a 'typical' episode was one-quarter of a gram. Age of first use was 16 years.

DXM

Dextromethorphan, often called DXM, is an active ingredient in some over the counter cough remedies. One (3%) participant reported use of DXM for non-medical purposes on one occasion and stated that this was not in the preceding six months. Age of first use was 17 years.

4.3.4 Ecstasy and the concomitant use of pharmaceutical drugs and supplements

Participants were asked a range of questions pertaining to ecstasy and the concomitant use of pharmaceutical drugs and supplements. Questions related to the awareness of associated health problems and, if relevant, what changes they made to the times or days they take their prescribed antidepressants if they planned on using ecstasy or had recently used ecstasy. Several questions asked about the use of antidepressant drugs and other substances for non-medical purposes with ecstasy (i.e. before, during or after ecstasy use to achieve a specific effect). Participants were also asked about any negative effects they may have experienced.

Pre-loading and post-loading

Participants were asked whether they were familiar with 'pre-loading' or 'post-loading'; these are 'street' terms for the deliberate use of a range of substances, including 5-HTP, and pharmaceutical drugs before or after ecstasy. Amongst the 30 participants interviewed, four (13%) mentioned they were familiar with these terms and two elaborated on what these terms meant to them:

> *Taking 5-HTP in the days before ecstasy, and taking5-HTP and vitamins after to avoid 'terrible Tuesdays'.*
>
> *Taking antidepressants before 'e' or after 'e' to get a more intense experience.*

Awareness of health problems

Participants were asked if they were aware of any health problems which can arise from combining ecstasy with pharmaceutical drugs and supplements. Half (50%) of the participants reported that they were aware of health problems associated with this practice and typical responses included:

> *Mixing some antidepressants that act on serotonin with ecstasy can be dangerous.*
>
> *You can get serotonin syndrome from using ecstasy with SSRIs or amphetamine.*
>
> *It's not recommended, but don't know why. You shouldn't take antidepressants with any drugs.*

4.3.4.1 Antidepressant drugs and the concomitant use of ecstasy

Experiences of participants who made changes to the times/days of regular prescribed antidepressant drugs due to planned ecstasy use

Of the 26 (87%) participants who reported regular use of antidepressant drugs for a current health condition, 15 (58%) participants made changes to the times or days they had taken their antidepressant drugs because they planned to use ecstasy or had recently used ecstasy.

Three participants stopped taking SSRIs before using ecstasy, and re-started again afterwards. Before using ecstasy, the length of time which participants stopped their antidepressant use ranged from 'a few days' to 'two weeks'. After using ecstasy, the

length of time which participants waited before re-starting antidepressant use ranged from 'a few days' to 'about a week'. One of these participants reported gradually reducing the dose of SSRI by one-quarter before stopping antidepressant use and taking ecstasy, and then gradually increasing the dose of SSRI by one-quarter (up to the prescribed dose) when re-starting the antidepressant drug after using ecstasy. Typical reasons given for these changes included:

It wouldn't be so dangerous.

To maximise the effect of the 'e'.

These participants all commented that when they had taken their antidepressant drugs at the prescribed time and used ecstasy the intensity of the ecstasy 'high' was significantly reduced or there was 'almost no high'.

One participant reported holding their SSRI dose the day before using ecstasy and one other reported taking half the prescribed antidepressant dose the day before using ecstasy. Typical reasons for these changes included:

To reduce the harm of using ecstasy with antidepressants.

Just being cautious about the drowsiness antidepressants can cause.

Two participants reported taking their SSRIs as prescribed on the day of using ecstasy but holding the dose the day after using ecstasy. The reasons stated were:

General concern about combining 'e' and antidepressants - fear of the unknown.

No need for antidepressants, as after 'e' I don't feel depressed.

One participant halved the dose of SSRI the day after ecstasy use and then began taking the prescribed dose on the following day. The reason given was:

If I take a full dose it keeps me going, boosts me too much.

Two participants reported holding their SNRI dose on the day they were planning to use ecstasy. They stated that this was because they:

Didn't want to be taking drugs on drugs.

The participants added that if they did not skip their dose on the day they used ecstasy the effects of ecstasy would be reduced.

One participant taking the TCA amitryptyline reported holding the dose on the day of using ecstasy to avoid the drowsiness associated with use of the antidepressant.

Two participants taking robexetine (i.e. *Edronax*) stated that they hold their dose up to three days before using ecstasy because if taken beforehand, "you don't feel the full effects of the 'e'". Two other participants taking robexetine and mirtazapine respectively, skipped the morning dose of antidepressant if still awake from a night on ecstasy stating that they:

Just didn't want to add to the chemical mix.

Don't want it to slow me down.

Experiences of participants who did <u>not</u> make changes to the times/days of regular prescribed antidepressant drugs due to planned ecstasy use

Of the 26 (87%) participants who reported regular use of antidepressant drugs for a current health condition, 11 (42%) did *not* make changes to the times or days they take

their antidepressant drugs because they planned to use ecstasy or had recently used ecstasy. The antidepressants which these participants regularly used for a current health condition were SSRIs (56%, n=5), 'other' antidepressants such as robexitine and mirtazapine (22%, n=2), the SNRI venlafaxine (11%, n=1) and the TCA prothiaden (11%, n=1). Most (82%, n=9) participants who did not make changes to the times or days they take their antidepressant drugs because they planned to use ecstasy or had recently used ecstasy reported never experiencing any negative effects.

A minority (18%, n=2) of participants, however, did experience negative effects when they had taken their antidepressants as prescribed and used ecstasy. In both these cases the antidepressant drug participants regularly used for a current health condition were SSRIs. The negative experiences they reported were:

> *The pills didn't work as well.*
>
> *The comedown was twice as bad.*
>
> *Weird dreams.*

Use of antidepressant drugs intentionally with ecstasy

Although the majority (87%, n=26) of participants reported regular use of antidepressant drugs for a current health condition, one-third (33%, n=10) reported using antidepressant drugs intentionally for non-medical purposes (i.e. before, during or after ecstasy use to achieve a specific effect). Among this group, a majority (40%, n=4) reported that the first time they had used antidepressant drugs in this way they had been prescribed them by a health professional (i.e. GP, psychiatrist) for a current medical problem, one-third (30%, n=3) had received them from friends and 20% (n=2) from their drug dealer. Note that five (17%) participants reported regular use of antidepressant drugs for a current medical condition and also had intentionally used antidepressants for non-medical purposes.

The antidepressants which participants reported intentionally using for non-medical purposes were SSRIs; the RIMA moclobemide; the SNRI venlafaxine; and 'other' antidepressants robexetine and mirtazapine (Table 30).

When participants were asked why they decided to use antidepressants with ecstasy in this way, typical responses included:

> *It helps with the comedown.*
>
> *Was led to believe [by a friend] it was a serotonin booster to avoid depression after 'e'.*
>
> *My dealer said that if you take antidepressants with the last pill of the night it works better and lasts longer.*

Before ecstasy use

Six participants who had intentionally used antidepressants for non-medical purposes reported that they had taken them *before* ecstasy use.

Three participants had used SSRIs in this way and reported taking 0.5 to two tablets about four hours before ecstasy. The reasons given for using the antidepressant drug with ecstasy in this way were:

> *To enhance and intensify the 'e' experience.*

To de-stress, sharpen awareness.

One participant had used SSRIs and robexitine (each separately) before ecstasy and stated that the reason for this was to, 'get a bit more energy to be in a good mood to take ecstasy'. One other participant used two to three tablets of an SNRI before ecstasy and reported that this was to increase the intensity and duration of the 'high'. The RIMA moclobemide was used before ecstasy by one participant who mentioned that the reason for this was to increase the effect of multiple ecstasy tablets. This participant remarked further that using moclobemide with ecstasy in this way delayed the onset of ecstasy and resulted in a bigger 'high' which lasted longer.

Among the six participants who had intentionally used antidepressants for non-medical purposes before ecstasy, one who had used SSRIs in this way reported that it reduced the effect of ecstasy and 'makes you depressed'.

Whilst under the influence of ecstasy

Four participants who had intentionally used antidepressants for non-medical purposes reported that they had taken them *whilst under the influence* of ecstasy (e.g. during the ecstasy 'high').

Two participants had used SSRIs and robexitine (not in combination) in this way and stated that the reason for this was, 'to give you another boost, more energy to dance'. The RIMA moclobemide was used whilst under the influence of ecstasy by two participants and the reasons given for this included:

To get the most effect out of the last pill for the night.

To reduce the comedown.

Among the four participants who had intentionally used antidepressants for non-medical purposes whilst under the influence of ecstasy, the participant who had used robexetine in this way experienced negative effects, and reported, "you can't communicate, you can't get a word out of yourself".

After ecstasy use

Three participants who had intentionally used antidepressants for non-medical purposes reported that they had taken them whilst 'coming down' *after* ecstasy use.

One participant reported doubling their prescribed SSRI dose in the morning after using ecstasy. One other participant, who was not prescribed antidepressants for a current medical condition, reported taking an SSRI daily for a few days after using ecstasy. A third participant who was prescribed mirtazapine 'nocte' took an additional dose in the morning when they got home after using ecstasy. Each of these participants mentioned that this was to reduce the after-effects of ecstasy and counteract the depression they would otherwise experience.

Among the three participants who had intentionally used antidepressants for non-medical purposes whilst 'coming down' after ecstasy use, only the participant who had used mirtazapine experienced negative effects. This participant mentioned that using antidepressants in this way was not relaxing and occasionally reported 'twitching' and 'electric fleas'.

Table 30: Intentional use of antidepressant drugs for non-medical purposes with ecstasy and reason for use/reported effect among ERDs users

	Antidepressant drug class used	Number of participants reporting use*	Reason for use/reported effect
Before ecstasy use	SSRI	4	*Enhance and intensify the 'e' experience* *De-stress, sharpen awareness* *Get a bit more energy and be in a good mood to take ecstasy* *It reduced the effect of ecstasy*
	Other†	1	*Get a bit more energy and be in a good mood to take ecstasy*
	SNRI	1	*Increase the intensity and duration of the 'high'*
	RIMA	1	*Increase the effect of multiple ecstasy tablets*
Whilst under the influence of ecstasy	SSRI	2	*To give you another boost, more energy to dance*
	Other†	2	*You can't communicate, you can't get a word out of yourself* *To give you another boost, more energy to dance*
	RIMA	2	*To get the most effect out of the last pill for the night* *To reduce the comedown*
After ecstasy use	SSRI	2	*Reduce the after-effects of ecstasy*
	Other†	1	*Twitching and electric fleas* *Reduce the after-effects of ecstasy*

*Several participants reported use of antidepressant drugs before, during and/or after ecstasy
†Antidepressants classified as 'Other' include mirtazapine and robexetine

4.3.4.2 Other drugs and supplements and the concomitant use of ecstasy

The majority (90%, n=27) of participants reported the use of a wide range of other drugs and supplements before, during and/or after ecstasy to achieve a specific effect (Table 31).

Table 31: Other drugs and supplements used with ecstasy and reason for use/reported effect among ERDs users

	Other drug or supplement used	Number of participants reporting use*	Reason for use/reported effect
Before ecstasy use	Sidenafil and other similar drugs	5	*To maintain an erection* *Priapism*
	5-HTP	3	*My friends said it would help me recover… and enhance my 'e'* *It builds up serotonin and maximises pills*
	Methylphenidate	3	*To counteract a smacky pill* *It can sometimes make me sick in the stomach* *To get a buzz*
	St. John's wort	1	*Resulted in an ecstasy 'high' of severely reduced intensity and duration*
	Benzodiazepines	1	*For relaxation and to slow down the effects of ecstasy*
	Iron tablets or multivitamins	2	*To stop anaemia after a night out*
Whilst under the influence of ecstasy	Sidenafil and other similar drugs	6	*Counteract reduced erectile function* *It kept things going a lot longer [female participant]*
	Dexamphetamine	2	*Wake you up* *Make you more alert and think clearly*
	5-HTP	1	*Build up serotonin to maximise the 'e' to keep going*
	Benzodiazepines	2	*To reduce the anxiety associated with ecstasy* *To bomb you out*
After ecstasy use	Benzodiazepines or sleeping tablets†	16	*For calming effect and to assist with sleep*
	Sidenafil and other similar drugs	5	*Maintain an erection*
	5-HTP	2	*To avoid the negative aspects of the comedown* *To make sure serotonin is up to scratch* *It physically makes me drowsy*
	St. John's wort	1	*Expecting an antidepressant effect, however, the participant reported that no such effect was experienced*
	Vitamin C, mulivitamins or paracetamol	9	*To re-charge* *To treat headache after ecstasy use*

*Several participants reported use of a range of other drugs and supplements before, during and/or after ecstasy

†Participants also reported the use of chlorpromazine (n=1), codeine (n=1), valerian (n=1) or melatonin (n=1) for their sedative properties

Before ecstasy use

Of those who had taken other drugs and supplements with ecstasy, nine reported using them *before* ecstasy. Participants frequently had used more than one drug or supplement during this period.

Five participants had taken sidenafil or other similar drugs before using ecstasy. The reason stated for this was to maintain an erection while engaging in sexual activity during ecstasy intoxication. Of these, one participant reported 'soreness' from being erect for an extended period of time (priapism) as an associated negative effect.

5-HTP was taken by three participants before using ecstasy. Typical reasons included:

> *My friends said it would help me recover… and enhance my 'e'.*
>
> *It builds up serotonin and maximises pills.*

Participants reported no negative effects from using 5-HTP with ecstasy in this way.

Methylphenidate was taken by two interviewees before ecstasy to provide more energy and one stated this was usually to 'counteract a smacky pill'. One participant mentioned that after combining methylphenidate with ecstasy in this way, 'it can sometimes make me sick in the stomach'. One participant reported taking one tablet of an unspecified type of prescription amphetamine, 'like what truck drivers use to stay awake', before using ecstasy 'to get a buzz'.

One other participant reported taking a 'double dose' of St. John's wort the morning before using ecstasy. This was done with the expectation of experiencing a stronger 'e', however, the participant reported that this had the opposite effect and resulted in an ecstasy 'high' of severely reduced intensity and duration.

Before ecstasy, benzodiazepines were used by one participant who mentioned this was for relaxation and to slow down the effects of ecstasy.

Other supplements taken by participants before ecstasy use were iron tablets, 'to stop anaemia after a night out', and multivitamins (e.g. *Berocca*).

Whilst under the influence of ecstasy

Of those who had taken other drugs and substances with ecstasy, eight reported using them *whilst under the influence* of ecstasy. Participants frequently had used more than one drug or supplement during this period.

Six participants had used sidenafil or other similar drugs whilst under the influence of ecstasy. Most stated that this was to counteract the reduced erectile function associated with ecstasy use. One female who had used sidenafil in this way reported that 'it kept things going a lot longer'.

One to two tablets of dexamphetamine (e.g. 'dexies') were taken by two participants whilst under the influence of ecstasy who reported this was to 'wake you up' and 'make you more alert and think clearly'.

One participant had used 10 to 15 milligrams of 5-HTP during ecstasy intoxication and mentioned this was to "build up serotonin to maximise the 'e' to keep going".

Whilst under the influence of ecstasy, benzodiazepines were used by two participants who mentioned this was to reduce the anxiety which is associated with ecstasy use and to 'bomb you out'.

After ecstasy use

Of those who had taken other drugs and supplements with ecstasy, twenty-five reported using them whilst 'coming down' *after* ecstasy use. Participants frequently had used more than one drug or supplement during this period.

Sixteen participants had taken benzodiazepines or sleeping tablets after ecstasy use. Typically the reason given for using benzodiazepines and sleeping tablets in this way was for their calming effect and to assist with sleep. The drugs chlorpromazine (e.g. *Largactyl*) (n=1), codeine (n=1), valerian (n=1) and melatonin (n=1) were used by a minority, also for their sedative effects.

Five participants had taken sidenafil or other similar drugs whilst 'coming down' after ecstasy use and reported that this was to help maintain an erection during sex in this period.

5-HTP was used after ecstasy by two interviewees, one who reported using 10 milligrams, the other reported doubling their regular morning dose (this participant was using 5-HTP daily for depression). The reasons mentioned for using 5-HTP in this way were:

> *To avoid the negative aspects of the comedown.*
>
> *To make sure serotonin is up to scratch.*
>
> *It physically makes me drowsy.*

One participant had taken one to two tablets of St. John's wort (on several occasions) after ecstasy expecting an antidepressant effect, however, the participant reported that no such effect was experienced.

Seven participants reported the use of vitamin C, multivitamins (i.e. *Berocca*) or 'rehydration sachets' whilst 'coming down' after ecstasy use. Two participants recounted using paracetamol (i.e. *Panadol*) and stated that this was to treat headache after ecstasy use.

Interestingly, dexamphetamine (i.e. 'dexies') was used whilst 'coming down' after ecstasy by one participant who stated the reason for this was to act as a 'pick-me-up'.

4.3.5 Experiences when visiting a general practitioner

Participants were asked a range of questions about their experiences when they visited a GP, in particular, on those occasions when they were prescribed pharmaceutical drugs such as benzodiazepines/sleeping tablets, sidenafil and other similar drugs, and antidepressants.

In the preceding six months, participants reported visiting a GP (for any reason) a median of six times (range 1-20). The majority (57%, n=17) mentioned that this was not typical of how often they would usually see a GP, and of these, 16 participants reported they would usually see a GP less often. Typical reasons for seeing a GP more often than what was usual during this period included:

> *I was on a [drug] trial.*
>
> *I was recently diagnosed with depression.*
>
> *I was unusually sick.*

Drug dependence issues.

The median number of different GPs participants reported visiting in the previous six months was two (range 1-8).

GP visitation: ecstasy use

Participants were asked to think about the GP who they had seen most often. Two-thirds (67%, n=20) reported that they had told this GP about their use of ecstasy and typical reasons for how this came about included:

I have a long-standing connection with my GP.

I was depressed and the doctor asked about my drug use.

My doctor's seen me out [clubbing] and we've chatted about it [at the night club].

I asked for help to stop using drugs.

Of the participants who had told the GP who they had seen most often about their use of ecstasy, the majority (n=17) mentioned that the GP responded in a very professional and non-judgemental way. Three participants reported that the GP responded somewhat negatively, for example:

He shook his head, asked how often I used, seemed uncomfortable to discuss it.

He gave me a 'disappointing' look.

One-third (33%, n=10) of participants mentioned that they had not told the GP who they had seen most often about their use of ecstasy, and typical reasons for this included:

I didn't want to be treated like a drug addict.

I wasn't using drugs at the time.

There's no need to, I don't have a problem with ecstasy.

He hasn't asked.

Participants who had not told the GP they had seen most often about their use of ecstasy were asked if they had ever told any other GP. Three participants responded that they had told an other GP, and the reasons for how this came about were:

I found a GP who I liked and trusted and disclosed everything.

I needed a medical certificate for days off work after a night on 'e'.

I was asked questions about drug use when I started on a [drug] trial.

If participants had questions about the effects and harms of ecstasy, two-thirds (67%, n=20) would feel comfortable raising them with the GP who they mostly see. The one-third (33%, n=10) who would not feel comfortable, typically reported that this was because:

The GP would advise against it [drug use].

I don't want to waste the doctor's time

I'd look on the internet first… or ask my friends or dealer.

Two participants who would not feel comfortable raising questions about the effects and harms of ecstasy with the GP they mostly see, stated they would, however, feel

comfortable raising these questions with a GP who is not the GP they mostly see. The reasons for this were:

> *I'd go to a GP on Oxford Street who might be a bit more liberal.*
>
> *I live in a very 'family' area, would feel more comfortable talking to an open-minded doctor.*

GP visitation: benzodiazepines and sleeping tablets

Half (47%, n=14) of the participants had ever visited a GP and received a prescription for benzodiazepines or sleeping tablets and 33% (n=10) had done so in the preceding six months. Participants were asked to think about the most recent time they were prescribed these drugs, which may not have been in the preceding six months.

A majority (n=11) of participants reported that the GP did not ask about their use of ecstasy at the time of this consultation. Several participants commented, however, that the GP already knew they were using ecstasy.

During the most recent consultation when participants were prescribed benzodiazepines or sleeping tablets, 10 participants reported that the GP did assess them for symptoms of anxiety or sleeplessness.

Six participants reported that the GP discussed alternatives to taking the benzodiazepines or sleeping tablets which were prescribed at the time. Examples of the alternatives discussed included cessation of illicit drug use, therapy and use of herbal supplements such as valerian. Two participants were referred to a specialist doctor (i.e. psychiatrist) at the time of this consultation. Four participants reported they were already regularly seeing a specialist doctor about their drug use or mental health problems.

GP visitation: sidenafil and other similar drugs

Just less than one-quarter (23%, n=7) of participants had ever visited a GP and received a prescription for sidenafil or other similar drugs and 17% (n=5) had done so in the preceding six months. Participants were asked to think about the most recent time they were prescribed these drugs, which may not have been in the preceding six months.

Of the seven participants who had recently been prescribed sidenafil or other similar drugs none reported that the GP had asked about their use of ecstasy during this consultation. Four participants, however, commented that the GP already knew they were using ecstasy.

During the most recent consultation when participants were prescribed sidenafil or other similar drugs, two participants reported that the GP did assess them for symptoms of erectile dysfunction. Participants reported that the questions the GP asked related to problems with premature ejaculation, getting an erection and any erectile dysfunction associated with antidepressant use.

Five participants commented that the GP did not assess them for erectile dysfunction. Of these, two stated that they had made the GP aware that the request for sidenafil or other similar drugs was related to symptoms of erectile dysfunction temporarily experienced during illicit drug use and that symptoms were not present at other times. One participant prescribed these drugs by a GP mentioned that the request for them was in the context of 'friendly experimentation'.

All participants reported that the GP did not discuss any alternatives to taking the sidenafil or other similar drugs which were prescribed.

Five out of the seven participants who had received a prescription for sidenafil or other similar drugs were also regularly using antidepressant drugs for a current health condition. One participant commented that their use of sidenafil or other similar drugs was to counteract the erectile dysfunction which is a frequently reported side-effect of antidepressant drugs.

GP visitation: antidepressant drugs

Most (70%, n=21) participants had ever visited a GP and received a prescription for antidepressant drugs and two-thirds (67%, n=20) had done so in the preceding six months. One participant who was regularly using antidepressant drugs for a current health condition, but had not visited a GP and received a prescription for antidepressant drugs in the preceding six months, mentioned that this was because they were using pharmaceutical drugs which had been issued on prescription to their partner (for their partner's current health condition). Four (13%) participants had never visited a GP and received a prescription for antidepressant drugs. Of these, none were regularly using antidepressant drugs for a current health condition, but all reported the intentional use of antidepressant drugs for non-medical purposes with ecstasy.

Where relevant, participants who had visited a GP and received a prescription for antidepressant drugs were asked to think about the first occasion this occurred. The majority (81%, n=17) of participants reported that at that time they were already using ecstasy. Thirteen participants reported that the GP did not ask about the use of ecstasy during the consultation, however, three of these participants mentioned that the GP was already aware of their illicit drug use. Nine participants reported that the GP did ask about the use of ecstasy, and questions typically related to the range and quantity of illicit drugs used and the participant's thoughts and feelings on drug use.

Reassuringly, twenty participants reported that on the first occasion they visited a GP and received a prescription for antidepressant drugs the GP did assess them for symptoms of depression. The questions asked typically related to how the participant was feeling, sleeping patterns, concentration, interaction with friends, changes in appetite and suicidal ideation. Only a single participant reported that the GP did not assess them for symptoms of depression.

The majority (n=16) of participants reported that the GP did not discuss any alternatives to taking the antidepressants which were prescribed on their first visit. The GP did, however, discuss alternatives with six participants, and these typically included counselling, use of St. John's wort and other natural therapies, exercise, diet and reducing alcohol consumption.

Fourteen (67%) participants commented that on the first occasion they visited a GP and received a prescription for antidepressants, the GP referred them to a specialist health professional. The referrals reported were to psychiatrists, psychologists or counsellors.

Eighteen (60%) participants had visited a GP and received a prescription for antidepressants on numerous occasions. These participants were asked to think about the most recent time they had visited a GP and received a prescription for these drugs.

Twelve participants reported that during the most recent visit to a GP when antidepressants were prescribed, the GP did not ask about their use of ecstasy. Five of these participants, however, noted that the GP was already aware of their ecstasy use. During this consultation, two participants were asked by the GP about their use of ecstasy and this was reportedly in the course of obtaining a drug use history.

Nine participants mentioned that at the time of this most recent visit, the GP did not discuss any alternatives to the antidepressants prescribed. Of these, four participants typically described having a long history of depression and reported that they mostly visited a 'regular' GP. During these visits, repeat prescriptions of antidepressants were obtained after the GP conducted a routine mental health assessment. Two other participants, when asked about whether the GP discussed alternatives to the antidepressants prescribed, made comments such as:

> *GPs just give you the repeat, very few ask questions before filling out the script.*
>
> *Just tell them what they want to hear, I say I've tried them before and they work.*

One participant reported that during the most recent visit to a GP when antidepressants were prescribed, the participant was referred to a psychiatrist. Seventeen participants commented that at the time of the most recent visit to a GP when antidepressants were prescribed, the GP did not make a referral. However, of these participants, fourteen recalled that they had been previously referred to a specialist health service or specialist health professional on a previous occasion.

Psychiatrist visitation: antidepressant drugs

Five (17%) participants who had received a prescription for antidepressants in the preceding six months had not visited a GP but had received a prescription from the psychiatrist they were seeing regularly.

These participants also reported that the first time they were prescribed antidepressant drugs, it was from a psychiatrist. Three participants stated that, at that time, they were not already using ecstasy. Two participants mentioned that the psychiatrist did not ask them about the use of ecstasy and one participant could not remember. In the case of one of these participants, the diagnosis of depression was made in the early 1990s, a time when the level of awareness of ecstasy as a drug may have been limited among health professionals. Two other participants who were prescribed antidepressant drugs for the first time by a psychiatrist noted that they were asked about their use of ecstasy. This was reportedly done by the psychiatrist in the course of obtaining a drug use history.

Participants who were regularly seeing a psychiatrist who prescribed their antidepressants were asked to think about the most recent time they were prescribed these drugs. Three participants commented that the psychiatrist did not ask about their use of ecstasy, but two of these participants added that the psychiatrist was already aware of their illicit drug use. One participant reported that the psychiatrist did ask about their use of ecstasy. The questions asked related to general drug use, frequency of use and how the participant managed the 'comedown' after using ecstasy.

4.3.6 Attainment of pharmaceutical drugs without prescription

Just under three-quarters (70%, n=21) of participants reported that they had ever attained pharmaceutical drugs without prescription and 53% (n=16) had done so in the preceding six months.

'Friends' were the main source of pharmaceutical drugs attained without prescription, and eighteen (60%) participants reported acquiring them through this means. Six (20%) participants mentioned that they had acquired pharmaceutical drugs through a drug

dealer. One (3%) participant had acquired pharmaceutical drugs over the internet, and one other reported that, to treat their own current health condition, they had regularly acquired a supply of pharmaceutical drugs from their partner.

Benzodiazepines (i.e. *Valium, Mogadon, Rivotril, Xanax*) (n=19) were the pharmaceutical drugs most frequently mentioned by participants as having been attained without prescription. Nine participants reported that they had attained sidenafil and other similar drugs (i.e. *Cialis*) in this way. Participants (n=9) also reported a range of antidepressants (i.e. *Lexapro, Efexor, Edronax, Prozac, Aurorix*) had been acquired without prescription. Six participants recalled they had attained sleeping tablets (i.e. *Stilnox, Temaze*). Other pharmaceuticals attained without prescription by a minority of participants were amphetamines (i.e. dexamphetamine, *Duramine*) (n=4), opioid analgesics (i.e. *Oxycodone*) (n=3), *Seroquel* (n=1) and *Normison* (n=1).

4.3.7 Cessation of ecstasy use

When asked about their use of ecstasy, slightly less than half (47%, n=14) of the participants had not ever thought about stopping. Typical comments included:

I don't see it as a problem.

I could easily stop.

I only use occasionally.

Slightly more than half (53%, n=16) of participants had ever thought about stopping their ecstasy use, and some typical reasons given were:

It's [ecstasy] not what it used to be.

I'm a mess on Tuesdays.

For health and financial reasons.

I've lost the connection with the people who sell it.

Of those who had thought about stopping their ecstasy use, three (19%) mentioned that they had tried to get help to stop in the past. These participants recalled that they had tried to get help to stop from drug and alcohol centres, counsellors and therapists.

Three quarters (75%, n=12) of those who had thought about stopping their ecstasy use had not ever tried to get help to stop. Some typical reasons stated for this were:

I can do it on my own.

I have stopped in the past.

Those participants who had not thought about stopping their use of ecstasy or had not tried to get help to stop, were asked where they thought they would go if they did want to get help. Some typical answers included:

A drug and alcohol service.

My GP or a counsellor.

My friends.

I'd go to my dealer and tell them I won't be buying from them anymore.

4.4 Discussion

Patterns of illicit and prescribed drug use

The patterns of drug use reported by ecstasy users in this study are of some concern. Participants reported the recent use of ecstasy and a wide range of other licit and illicit drugs, several of which have been implicated in serotonin toxicity. This pattern of polydrug use is not uncommon among ecstasy users (Dunn et al., 2007). Heavy ecstasy use (i.e. use on 48 days or more in the previous six months) was reported by several participants and their SDS scores suggested an increased dependence on ecstasy. The majority of participants had recently used the powdered ('speed') or crystalline ('ice') form of methamphetamine and all reported an extensive history of cannabis use.

Despite the awareness of health problems which could arise from combining ecstasy with pharmaceutical drugs, there was generally a high incidence of the use of prescription pharmaceuticals with ecstasy among participants. This included the use of antidepressant drugs for non-medical purposes to counteract the negative after-effects of ecstasy, and to a much lesser extent, the use of antidepressants putatively to intensify and lengthen the ecstasy 'high'.

Approximately half of the participants who regularly used antidepressants for a current health condition reported that they did make changes to the times or days they had taken their antidepressants if they planned on using ecstasy or had recently used ecstasy. Typically, these changes included stopping antidepressant use in the days leading up to using ecstasy and re-starting again afterwards. The reasons frequently stated for making these changes suggest a proportion of ecstasy users are adopting this as a harm reduction strategy, to minimise the harms associated with using ecstasy together with pharmaceutical drugs. For a proportion of users, however, the reason for making these changes is to avoid the chemical interaction between ecstasy and some antidepressants which results in a reduced ecstasy 'high'.

An almost equal proportion reported that they did *not* make any changes if they planned on using ecstasy or had recently used the drug. Interestingly, only a minority of this group experienced any negative effects and typically these were noted to be a significantly diminished ecstasy 'high' or a worse 'comedown'. The noticeable lack of serious negative health consequences is not surprising given that most participants were regularly using SSRIs, SNRIs or other antidepressants for their current health condition which, when used with ecstasy, were of relatively low risk to health (Silins et al., 2007). Among participants, none had been prescribed the older generation antidepressants such as MAOIs or RIMAs which, when used with ecstasy, are more likely to result in serious elevations in serotonin. This is in keeping with reports that these antidepressants represent a relatively small percentage of total antidepressant sales in Australia (Mant et al., 2004).

A minority reported using antidepressant drugs intentionally for non-medical purposes before, during or after ecstasy to achieve a specific effect. Typically this included increasing the prescribed dose of SSRIs the morning after using ecstasy to counteract the depressed mood associated with the 'comedown'. It was not uncommon for SSRIs to be used with ecstasy for the effect of potentiating the ecstasy 'high'. This purported effect, however, is somewhat at odds with that described in the literature, which suggests SSRIs are likely to reduce the intensity but prolong the duration of ecstasy intoxication (Liechti et al., 2000). There was no evidence that SSRIs were taken before ecstasy use for their protective effects.

The use of RIMAs with ecstasy to intensify and prolong intoxication, a potentially risky practice, was not widely reported which is keeping with other studies that report this behaviour (Copeland et al., 2006). Furthermore, those who reported combining RIMAs with ecstasy tended to be the older, more experienced users who were already aware of the risks associated with this practice. From this study, there was little evidence to suggest that the intentional use of antidepressants with ecstasy was widespread among this group of drug users. Findings do highlight, however, that among those taking antidepressants for a current health condition and using ecstasy, there is a need for more information about the risks of concomitant use. Additionally, this group ought to be better informed of the potential problems which can arise from altering the prescribed dosage of antidepressant drugs without consulting a health professional.

Benzodiazepines (e.g. *Valium*) or sleeping tablets were typically used with ecstasy to assist with sleep during the 'comedown' period. Sidenafil (e.g. *Viagra*) and other similar drugs were frequently used with ecstasy to counteract the erectile dysfunction secondary to ecstasy use. A small proportion of ecstasy users combined sidenafil and other similar drugs with ecstasy for their supposed aphrodisiac properties. This practice is of some concern as the use of sidenafil and other similar drugs in this way may lead to an increased likelihood of sexual risk-taking while intoxicated. A number of participants commented that the reason for their recent use of sidenafil and other similar drugs was to moderate the erectile dysfunction which was a side-effect of regular antidepressant use. Serious negative health consequences from using these pharmaceutical drugs with ecstasy were not reported.

5-HTP was taken before, during and after ecstasy use to enhance the ecstasy 'high' and/or to ease the recovery period. Amongst participants using 5-HTP with ecstasy, none reported any negative consequences. There is, however, conflicting evidence about the potential harms associated with using 5-HTP with ecstasy (Enlighten, 2006; Juhl, 1998).

Depressive symptoms

Participants, on average, reported low levels of depressive symptoms. However, about one in three had BDI scores indicating they had experienced moderate to high levels of depressive symptoms in the two weeks prior to interview. Among these, most were regularly taking antidepressant drugs for a current health condition and reported relatively heavy use of ecstasy. As several participants had reported recent use of ecstasy between one to four days prior to interview, ecstasy-related depression may partly account for the elevated BDI scores.

Attainment of pharmaceutical drugs without prescription

It was not uncommon for pharmaceutical drugs to be attained without prescription, and in accordance with other studies of ecstasy users (Copeland et al., 2006), friends were the main source of prescription drugs attained in this way. Interestingly, the second most common source of pharmaceutical drugs was from drug dealers. Benzodiazepines, sidenafil and antidepressants were the drugs most commonly acquired from these sources.

GP visitation

The majority of participants had told their GP about their use of ecstasy, and reassuringly, the GP's response in most cases was reported to be professional and non-judgemental. For many, the nature of the therapeutic relationship was such that they would feel comfortable raising questions about ecstasy and other drugs with the GP they saw regularly. The findings generally support previous research that doctors are well positioned to respond to patients with drug-related issues because of their accessibility and credibility (Copeland et al., 2006; Deehan et al., 1998; Dunn et al., 2007; Roche, 1993; Sanson-Fisher et al., 1986).

During consultations where participants were prescribed pharmaceutical drugs such as antidepressants, sidenafil, benzodiazepines and sleeping tablets, few mentioned that the GP asked them about their use of ecstasy, however, in many cases, the GP already knew of their ecstasy use. Based on participants' experiences when they visited a GP, prior to being prescribed benzodiazepines, sleeping tablets or antidepressants, most were assessed for symptoms of anxiety, sleeplessness or depression respectively. When prescribed sidenafil and other similar drugs, however, only a small minority reported being screened for erectile dysfunction. Worth noting is that some participants reported the GP was aware that their request for sidenafil was related to erectile dysfunction secondary to illicit drug use. In cases where GPs prescribed benzodiazepines and sleeping tablets, it was encouraging to find that they frequently discussed with patients possible alternatives to taking the pharmaceuticals prescribed.

Cessation of ecstasy use

The majority of participants had, at times, thought about stopping their use of ecstasy. Many of these commented that they had stopped in the past and would be able to stop again without assistance. Participants did, however, mention that if they needed help to stop they would approach a GP, counsellor or drug and alcohol service. A minority mentioned they would approach their friends for help.

5 GENERAL DISCUSSION

The view that serotonin toxicity, commonly known as serotonin syndrome, is a drug-induced toxic state caused by an excess of serotonin within the central nervous system has been well supported over several decades. A growing body of research alludes to the concept of serotonin toxicity as a spectrum of serotonin-related side-effects progressing to toxicity; where the extent of toxicity depends on the type and quantity of substances ingested. A comprehensive review of the literature reveals that numerous substances have been implicated in serotonin toxicity including a range of illicit drugs (e.g. ecstasy, methamphetamine, cocaine, LSD), antidepressants (e.g. *Nardil, Prozac, Aurorix, Efexor*), opiate analgesics (e.g. tramadol), migraine medications (e.g. dihydroergotamine) and supplements (e.g. St. John's wort, 5-HTP).

When these substances are used with ecstasy, there is a demonstrated potential for increased toxicity. Substances which inhibit serotonin reuptake (e.g. SSRIs, TCAs, SNRIs) are less likely to lead to life-threatening elevations in serotonin when used with ecstasy. This is because these drugs differ from other serotonergic drugs in that they compete with ecstasy at the serotonin receptor site and, therefore, diminish the effects of ecstasy. On the other hand, high doses or repeated use of stimulants such as methamphetamine, cocaine and methylphenidate (e.g. *Ritalin*) with ecstasy increase the risk of serotonin toxicity, as a result of their serotonin-releasing effects. Serotonin precursors, which give rise to serotonin after a metabolic process (e.g. 5-HTP), also influence the course of serotonin toxicity when used with ecstasy. Particular attention, however, must be drawn to substances which inhibit serotonin metabolism (e.g. MAOIs, RIMAs), as these are most likely to lead to serious increases in serotonin when used with ecstasy (Silins et al., 2007). For several substances implicated in serotonin toxicity, the risk of their use with ecstasy is somewhat unknown (e.g. LSD, St. John's wort, anti-migraine drugs, lithium).

In Australia, over the four year period 2001-2004, the National Coroners Information System (NCIS) identified approximately 45 ecstasy-related deaths where drug toxicity was found to be the cause (Kinner et al., 2005). However, to what extent other drugs played a part in these fatalities is unclear. Generally, the incidence of ecstasy-related fatalities is considered to be relatively low in comparison to the likely frequency of its use (Gowing et al., 2002; White et al., 1997).The findings from the survey of frontline healthcare professionals tends to be in keeping with this; slightly more than half saw acute presentations of ecstasy-related serotonin toxicity yearly or much *less* frequently and just 3% saw such presentations on a weekly basis. Among GPs, such presentations were very rarely seen at all.

It is by no means a surprise to find that healthcare professionals from hospital settings generally reported greater knowledge of ERDs and associated problems than those in general practice. More experience in managing relatively frequent and acute drug-related presentations is a likely reason for greater expertise in illicit drugs among frontline healthcare professionals. Nevertheless, among GPs and frontline healthcare professionals, there was a strong demand for resource materials on ERDs. There were, however, marked differences between the specific needs of each group in relation to the content and method of delivery of such a resource.

The patterns of drug use reported by ecstasy users in this study were of some concern. Generally, they were heavy users of ecstasy and a wide range of other illicit drugs.

Despite an awareness of health problems which could arise from combining ecstasy with pharmaceuticals, there was, overall, a high incidence of the use of prescription drugs with ecstasy. Many ecstasy users who were taking antidepressants for a current health condition made changes to the times or days they would take their antidepressants if they knew they were going to be using ecstasy or had recently used ecstasy. Although this may reduce the risks associated with combining antidepressants with ecstasy, the negative impact these changes may have on management of an individual's depression, or other health condition, can not be ignored. Reassuringly, the risky practice of using antidepressants to intensify the ecstasy 'high' was not widely reported. The experiences of ERDs users when they visit a GP suggest that screening for ecstasy use occurred infrequently when antidepressants were prescribed. Other pharmaceuticals and supplements which were typically used to counteract the effect of ecstasy in one way or another were benzodiazepines, sleeping tablets, sidenafil (and other similar drugs) and 5-HTP. In cases where benzodiazepines and sleeping tablets were prescribed, it was encouraging to find that patients frequently reported GPs had discussed alternatives to using these pharmaceutical drugs.

6 RECOMMENDATIONS

This study highlights that a wide range of drugs and supplements have serotonergic properties and have been implicated in serotonin toxicity. When used with ecstasy, many of these substances have a demonstrated potential for increased toxicity, this is particularly the case with some antidepressants. As perhaps would be expected, ERDs-related presentations were found to be more common in the acute hospital setting than in general practice. Nevertheless, in both settings there was a strong demand for ERDs-related resource materials. There is convincing evidence that, among GPs, screening patients for ecstasy use is rarely carried out. In-depth interviews with ERDs users revealed a group of polydrug users potentially at risk of serious health consequences. In regard to the findings presented here, a number of recommendations are enunciated below:

General practitioners

It is important that GPs are well informed of the effects of ERDs and the harms associated with their use. A strong demand for such information has been demonstrated and resources which focus on the following are likely to be of benefit to GPs:

- Management of ERDs users in general practice
- Referral of ERDs users
- Effects and harms of ERDs
- Effects and harms of ERDs and the concomitant use of pharmaceutical drugs
- Harm minimisation strategies for ERDs users
- Specific information on ecstasy, methamphetamine, GHB and ketamine
- Screening of patients who present to GPs with symptoms related to ERDs use

Methods of resource delivery which are likely to be effective in the general practice setting may include:

- Pamphlets and booklets
- Fact-sheets and bulletins
- Continuing Professional Development Programs (CPDP)
- Internet-based resources (e.g. *Medical Director*)
- Seminars/workshops

Collaboration with organisations such as the Fellowship of the Royal Australian College of General Practitioners (FRACGP) or the Australian Medical Association (AMA) would help facilitate the development and implementation of a series of ERDs-related seminars or workshops specifically tailored to the needs of GPs.

In addition, information may be disseminated through existing publications for medical practitioners (e.g. *Medical Observer, Australian Medicine*). This could be in the form of a series of ERDs-related articles appearing over several weeks or months. Consideration

should also be given to purchasing space within these publications where bulletins or fact-sheets pertaining to ERDs can be published.

GPs are ideally placed to respond to people who present with drug-related problems. There is evidence that screening for ecstasy use was limited among GPs. This strongly suggests a need to increase awareness among GPs of the importance of screening for ERDs use, especially among younger patients, and to develop a screening tool that will improve the screening of patients who present to GPs with ERDs-related symptoms.

There is also scope for developing an ERDs-related training module suitable for graduate medical programs. Collaboration with tertiary institutions may help to facilitate this.

Frontline healthcare professionals

Frontline healthcare professionals have a set of needs in relation to resources on ERDs which vary somewhat from those of GPs. For this group, resources which focus on the following are likely to be of benefit:

- Clinical management of ERDs users in the acute care setting
- Referral of ERDs users
- Effects and harms of ERDs
- Effects and harms of ERDs and the concomitant use of pharmaceutical drugs

An internet or web-based resource would be easily accessible to frontline healthcare professionals who frequently work in a busy clinical environment. A resource with a focus on the clinical management of ERDs users in the hospital setting would be particularly well received. Attention should be paid to providing information on methamphetamine and GHB, as acute presentations to hospitals are frequently associated with these drugs.

The development of a brief intervention, with proven efficacy, which can be administered by frontline healthcare professionals prior to the discharge of a patient who has presented with ERDs-related problems is essential. Such a brief intervention may also help to increase the referral of people with ERDs-related problems to drug and alcohol treatment services. Developing a brief intervention for people who have presented to hospital after GHB overdose is a priority.

Given the success of the ERDs presentations delivered to frontline healthcare professionals as part of this study, consideration should be given to the development of a formal series of ERDs-related presentations that could be delivered to healthcare professionals in the hospital setting.

Potential also exists to adapt the Ecstasy and Related Drug Trends Bulletin, published quarterly by NDARC as part of the Ecstasy and Related Drug Reporting System (EDRS), for GPs and frontline healthcare professionals and distribute it to interested clinicians.

Ecstasy and related drug users

The use of a wide range of licit and illicit substances by ERDs users is of concern. There is a need to more clearly delineate strategies which will inform users of the potential harms of this practice. It is crucial that resources targeting ERDs users, and young people who may be more likely to experiment with ERDs, be developed which focus on the following:

- Strategies to prevent ERDs use
- Harms associated with ERDs use
- Potential harms of combining ERDs with pharmaceutical drugs
- Strategies to minimise the harms associated with ERDs use
- Accessing drug and alcohol treatment services

The following approaches are likely to be effective in accessing ERDs users:

- Pamphlets and booklets
- Internet and web-based sites aimed at young people
- Internet and web-based sites aimed at ERDs users
- Fact-sheets (linked to internet and web-based sites)

Forming partnerships with organisations that maintain existing, popular, youth-oriented internet sites (e.g. *Enlighten*) may be a way to further disseminate relevant health information to ERDs users.

Peer-led education interventions play an important role in propagating health messages to young people about the harms associated with ERDs use. Collaboration with established peer-led education organisations (e.g. *KIS*, Manly Drug Education and Counselling Centre, NSW; *Save-a-mate*, Red Cross, Australia) is vital.

There is scope to develop ERDs-related learning modules specifically for peer-led organisations. These modules could then be offered to peer-led education organisations and subsequently integrated into the training these organisations provide for their peer educators on ERDs.

In addition, collaboration with relevant government departments (e.g. Department of Education, Science and Training; DEST) will aid the development and implementation of best practice policies in education and training related to ERDs. For example, findings from this study could be used to enhance school-based resources such as the Resilience Education and Drug Information (REDI) resources, part of the National School Drug Education Strategy (NSDES), which focuses on preventing and reducing drug related harm in young people.

Further ERDs-related research

As large gaps still remain in knowledge about the effects of ERDs and their potential to interact with pharmaceuticals, supplements and each other further research into this area is essential. There is a pressing need to explore the long-term effects of ERDs use and a prospective study, preferably utilising a large cohort of ERDs users, would be valuable and contribute greatly to current knowledge.

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