Novel Psychoactive Treatment UK Network

NEPTUNE

Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances

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Inspiring Improvement

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Chapter 10

Ecstasy (MDMA, 3,4-methylene-dioxymethamphetamine) and drugs with similar effects

Drug group: stimulant

This chapter uses the term 'ecstasy' to refer to illicit drug products that contain MDMA (3,4-methylenedioxy-N-methylamphetamine) as their only, or primary, psychoactive component. Despite some changes in the prevalence of its use, MDMA has been a popular drug for many decades in the UK.

MDMA is structurally similar to both amphetamine-type stimulants and to mescaline-type hallucinogens, but is pharmacologically different from other substance classes.[1] In addition of their stimulant and hallucinogenic effects, MDMA and similar substances share properties that are sometimes referred to as 'entactogenic'[2,3] or empathogenic.[4,5] This has been defined as combining a psychostimulant effect with highly unusual changes in consciousness, leading to euphoria and an intense love of self and others.[5] MDMA presents a good example of the difficulties in drawing clear distinctions between empathogens and stimulants, as it combines both properties.[6]

This chapter also addresses issues pertaining to the consumption of MDMA-like novel psychoactive substances (NPS),[6] which include other substituted amphetamines (see Table 10.1). Some cathinones and benzofurans also mimic the effects of MDMA (see Chapter 9), although there are subtle differences in their psychic effects.[6]

Users of 'ecstasy' may use the term strictly to mean MDMA, or generically to mean any substance with a similar effect. Users may deliberately acquire and consume one of the named entactogens listed in Table 10.1, or may consume them unknowingly[7,8] in products they obtain as 'ecstasy'.

There are significant variations in the compounds found in products sold on the market as 'ecstasy'. Studies have shown variations in the purity of MDMA over time and location, and variations in the compounds found in tablets sold as ecstasy,[8–12] Over the years, the latter have included non-MDMA products such as MDA, benzofuran, methylone,[13] piperazines such as BZP[14] and, more recently, PMA and PMMA.

There are also significant variations in the potency of tablets, even among those sold as the same product or 'brand' and containing MDMA as the main active ingredient. In a study carried out from November 2013 to July 2014, 24 separate groups of tablets sold as 'ecstasy' in the Glasgow area were analysed to quantify their MDMA content, to determine the common dose and to identify any other drugs in the tablets. There

Table 10.1. *Entactogens MDMA and MDMA-like novel psychoactive substances:*

Chemical name		Street names (these come and go, and other names may be used locally)
Substituted methylenedioxyphenethylamines[18]		
3,4-methylenedioxy-N-methylamphetamine	**MDMA**	Ecstasy, E, Molly, Mandy, MD,
3,4-methylenedioxy-N-ethylamphetamine	MDEA, MDE	Eve
1,3-benzodioxolyl-N-methylbutanamine *(N-methyl-1,3-benzodioxolylbutanamine)*	MBDB[19]	Eden, Methyl-J
3,4-methylenedioxyamphetamine	MDA	Tenamphetamine, love drug,[8] Sass
Other substituted amphetamines[2]		
4-methylthioamphetamine	4-MTA[19]	Flatliners[20]
para-methoxyamphetamine 4-methoxyamphetamine	PMA, 4-MA (note that another drug, 4-methylamphetamine, shares this name)	Dr Death, Death
para-methoxy-N-methylamphetamine *4-methoxy-N-methylamphetamine*	PMMA, 4-MMA	Dr Death Death

Table 10.2. *Other substances used for their entactogenic properties*

Chemical name		Street name
3,4-methylenedioxy-N-methylcathinone bk-3,4-methylenedioxymethamphetamine	bk-MDMA (MDMC, methylone)	Methylone MDMC, bk-MDMA, or 'Molly'
β-keto-N-methylbenzodioxolylbutanamine B1	bk-MBDB (beta-ketone-MBDB)	Butylone

was a 5.7-fold difference in the lowest to the highest concentration found. Variations were even found between tablets that carried the same logo and looked identical.[15]

A small number of samples analysed by a Welsh drug testing service demonstrate that methylone and MDA have been recently sold in the UK as 'ecstasy' or under their own names.* Only two samples were tested by this service that were presented as MDAI and contained MDAI; a further 6 samples presented as MDAI contained other drugs, in line with evidence of the misrepresentation of MDAI purchased online.[16] Four samples presented as other drugs contained MDAI. Benzofuran derivatives, such as 5- and 6-APB, were certainly available for purchase and in use since around 2011, but their use was not widely reported in surveys.[17]. Whether they remain in use following the 2014 ban, or whether they are replaced by vendors with other entactogen NPS, remains to be seen.

* This paragraph refers to the Welsh Emerging Drugs and Indentification of Novel Substances (WEDINOS), whose website (http://www.wedinos.org) was searched in September 2014 using the keyword search 'methylone', 'MDA' and 'MDAI'.

A number of other substances are also used for their entactogenic properties, including some cathinones (particularly those which are also beta-keto analogues of methylenedioxyphenethylamines[21]). They are listed in Table 10.2

Some benzofurans derivatives, indanylalkylamine derivatives and aminoindane derivatives are also used recreationally for similar effects. They are addressed briefly at the end of this chapter.

10.1. Street names

Street names used at the time of publication include the ones listed in Tables 10.1 and 10.2. Other street names may be used locally.

10.1.1. Tablets, pills and capsules

The term 'ecstasy' (often shortened to 'E', 'XTC' etc.) is most often used for pressed tablets or capsules ('pills', 'beans', 'Es', 'bickies' 'bangers' etc.) containing a dose of MDMA. Users may also refer to such products by the variable 'branding' colour, shape, imprinted logo with which manufacturers make them distinguishable (e.g. 'White Doves', 'Yellow Superman', 'Apples', 'Pink Hexagons').

10.1.2. Crystals and powders

Ecstasy powders and crystals are often referred to by users as 'MDMA' or 'pure MDMA' as opposed to the tablet form, which is referred to as 'ecstasy'.

Specific names include Mandy, MD, Mad Dog and Molly (the term currently used in US pop culture, so more likely to be adopted by a younger generation of users). A dose wrapped in tissue or cigarette paper for swallowing may be called a 'bomb' or 'parachute'.

10.2. Legal status

MDMA is a Class A drug under the Misuse of Drugs Act 1971. Other entactogens are controlled across the classes (Table 10.3). New entactogenic substances that fall outside legal control may emerge.

Table 10.3. *Legal status of entactogens (as of February 2015)*

Classification under Misuse of Drugs Act 1971	Drug
Class A	**MDMA**, MDEA, MDA, MBDB, 4-MTA, PMA, PMMA
Class B	bk-MDMA (methylone), bk-MBDB (butylone), 5-APB, 6-APB, 5-APDB, 6-APDB, 5-MAPB, 6-MAPB, 5-EAPB, 5-APDI[22]
Class C	MDAI (Isle of Man)
Uncontrolled ('legal highs')	MDAI (excluding Isle of Man), 5-IAI

10.3. Quality of research evidence

Although much more is known about MDMA than other club drugs, the evidence is limited on its acute and chronic harms, and on the management of those harms particular. Much of the clinical evidence is derived from individual case reports and case series and a small number of prospective observational studies, retrospective audits and analysis of patient records.

A number of reviews of the evidence have been carried out,[23–25] but there is still no consensus on some of the harms among leading ecstasy researchers.[26,27] For example, Parrott emphasises the accumulation of literature detailing the harms of the drug, particularly chronic neurotoxic effects.[24,25] However, his conclusions have been contested.[26] A recent review by Cole takes a more critical approach to the evidence base, emphasising the lack of certainty about many of the harms putatively attributed to ecstasy. He suggests that the number of clinical presentations relating to ecstasy is far smaller than would be expected, given the high prevalence of its use.[27]

As with other NPS and club drugs, the reliability of case reports is inconsistent. Many lack toxicological confirmation. Some authors have suggested that such case studies fail to convince that ecstasy use is, on balance, the most plausible explanation for the clinical observations.[28,29] However, despite these limitations, these sources have built up a consistent picture of common patterns of acute ecstasy toxicity.

The evidence relating to specific NPS analogues of MDMA, used for entactogenic effects, is much more limited, consisting of a small amount of animal and in vitro research on their pharmacology and some case studies of acute toxicity. However, reports of their effects and toxicity generally fall within the range described in the larger literature on ecstasy,[18] and on amphetamine-type stimulants (ATS), so useful inferences can be made from the existing literature.

10.4. Brief summary of pharmacology

MDMA and other ecstasy-type drugs have phenethylamine-derived molecular structures, and can be thought of, pharmacologically, as atypical ATS. MDMA has multiple actions at different targets: it is a releaser and reuptake inhibitor of the monoamines serotonin, dopamine and noradrenaline.[30,31] It also has an MAOI effect and acts directly as an agonist at receptors, including the $5HT_{2A}$ receptor, the serotonin receptor responsible for psychedelic effects.[30] Its action on the noradrenaline transporter appears to explain much of the euphoric psychostimulant effect,[32] with the powerful serotonergic action being chiefly responsible for its pharmacological divergence from typical psychostimulants.[33,34]

However, among the stimulant and psychedelic drugs, the risk–effect profiles of ecstasy-like drugs are unique, and comparison with drug classes with divergent properties can misguide as much as inform, so they have been increasingly seen as neither classical hallucinogens nor classical stimulants.[2]

In addition to its stimulant effects (such as increased energy, euphoria) and cardiovascular effects common to ATS and cocaine, MDMA-produces characteristic alterations

of mood and perception, particularly increased empathy, feelings of emotional well-being, sociability and sensuality.[2,35] This has led to MDMA being described as intermediate between (or combining some properties of) stimulants and psychedelic hallucinogens.[2]

This family of drugs with shared MDMA-like emotional and behavioural effects are known as 'entactogens',[1,36] although this word has not gained universal use. The word 'empathogen' has also been used to describe drugs sharing the psychoactive properties of MDMA.[4] These drugs have been described as capable of inducing a reversible controlled alteration of consciousness in humans characterised by emotional relaxation, feelings of happiness and empathy with other persons[2] that has been called the 'entactogenic syndrome'.[37] MDMA induces altered states of consciousness characterised by increase empathy with others[38] and an 'open mind' state, characterised by heightened self-acceptance and openness for communication, and a decrease of fear responses, without psychedelic-like effects.[2] Other typical entactogen effects, including subjective 'relaxation',[39] 'peacefulness',[36] 'closeness to others'[40] and 'empathy',[40] may diverge from the effects expected from ATS.

There is uncertainty regarding the pharmacology specific to the 'entactogenic' effects of MDMA and related drugs. In addition to the direct serotonergic effects on mood, the serotonin transporter (SERT), upon which MDMA and its analogues act, appears to mediate the release of the neuropeptide hormones oxytocin and prolactin.[41] The action of MDMA on SERT are hypothesised to contribute to its pro-social, entactogenic effects.

Doses or serum concentrations of MDMA and related drugs are often not closely associated with the level of acute harm observed, and lifetime dosage may not be closely associated with the degree of chronic harm either. One suggested explanation is that genetic polymorphisms affecting the hepatic metabolism of MDMA play a mediating role in toxicity.[34] The metabolism of MDMA (via steps which include pharmacologically active and toxic metabolites) is affected by the pattern of dosing,[42] with the metabolism of subsequent doses being inhibited by the limited availability of the cytochrome P450 (CYP2D6) enzyme.[30,43]

Paramethoxyamphetamine (PMA) and paramethoxymethamphetamine (PMMA) are potent noradrenaline and serotonin transporter inhibitors and releasers of these monoamines. They are associated with higher morbidity and mortality, particularly attributable to hyperthermia.[44,45] They have a potential for causing greater serotonin toxicity. PMA, PMMA and 4-MTA are often characterised by severe hyperthermia, probably resulting from severe serotonin toxicity arising from the combined effects of marked serotonin release and strong monoamine oxidase inhibition.[46–51] Their hyperthermic properties are stronger than those of MDMA.[52] In combination with MDMA and other serotonergic drugs, this risk is multiplied further.[53]

MDMA is rapidly absorbed. It typically takes 20–60 minutes to take effect, reaching peak effects between 60 and 90 minutes, and lasting up to 5 hours.[54] The half-life of a typical dose of 100 mg is around 8–9 hours.[30] While actively partying on ecstasy, saliva levels of cortisol can rise to more than eight times baseline levels.[55]

The onset of the effects of similar substances varies. User reports suggest the effects of MDAI are felt within 10–12 minutes of oral consumption. The duration of its effects has also been reported by users as varying considerably between individuals, with effects peaking after 30–45 minutes, to up to 3 hours,[56] a variability that has been attributed partially to products containing substances other than MDAI.[57]

The onset of the effects of PMA is significantly later. This has caused concern, especially when users take it thinking it is MDMA. Users may take another dose, thinking that the first one has had no effect. There is, therefore, the risk of overdose, including fatal overdose.

10.5. Clinical uses

MDMA is a Schedule 1 drug with no well supported and no licensed clinical uses. However, prior to being classified and scheduled, MDMA was used to facilitate psychotherapy.[58]

In recent years, some research into its psychotherapeutic use has continued, despite the legal barriers to this, and MDMA has now reached phase II clinical trials as an adjunct to psychotherapy for treatment-resistant post-traumatic stress disorder (PTSD). The first small-scale pilots have demonstrated good preliminary results with minimal adverse effects, but larger trials are needed.[59]

MDMA is hypothesised to support and enhance psychotherapy by increasing the subject's access to emotionally upsetting material, modulating the associated level of arousal and strengthening the therapeutic alliance.[60] MDMA is known to have major effects on serotonergic neurotransmission, but a downstream consequence of its effects on serotonin is the release of oxytocin and vasopressin, which may have relevance to producing trust and may reduce the threat response of being asked to revisit traumatic memories.[61]. Brain imaging studies show reduced amygdala activity after MDMA administration, plus changes in the response to angry and happy facial expressions.[4] Nonetheless, marked differences of view are apparent among experts,[26,62] with other scientists believing that the evidence of MDMA's toxicity is already sufficient to conclude that 'there are no safe clinical applications for MDMA'.[63]

10.6. Prevalence and patterns of use

The recreational use of ecstasy has well established in the UK for a number of decades. Prevalence has varied over time but data from the Crime Survey for England and Wales (CSEW)[64] shows that in 2013/14 it was the third most prevalent illicit drug after cannabis and cocaine, with 1.6% of adults aged 16–59 and 3.9% of young adults (16–24) having used it in the last year. While this represents one of the highest rates of use in Europe, last-year use in England and Wales had fallen overall from a high of 2.1% in 2001/12 (6.8% among 16–24s).[64]

Much less is know about the use of other MDMA-like NPS. Prevalence estimates of the use of PMA/PMMA are unavailable, but an Australian study reported that a majority

of patients presenting with severe symptoms following the use of what had been sold as 'ecstasy' had in fact consumed PMA.[47] Deliberate use of PMA and PMMA is negligible to non-existent.[47]

The 'reliability' of ecsasy, determined by users in terms of the substance sold containing a significant quantity of MDMA as the primary active compound, has been variable,[65] and may be linked to changing patterns of use over the years. Between 2012/13 and 2013/14 there was a significant rise in use of ecstasy again,[64] although not to 2001/12 levels. This is possibly linked to the apparent increase in ecstasy products containing 'reliably' large amounts of MDMA,[66] which appears once again to be the norm in the UK,[66] following a dip in quality around 2008/09. It has been argued that this dip may have helped drive the emergence of mephedrone as a club drug.[67] In the most recent available data, the average seized tablet contained around 100 mg of MDMA;[66] such tablets correspond to user preferences, having the optimal ratio of desired to unwanted effects.[68]

In the early years of ecstasy's emergence as a recreational drug, it was strongly associated with underground raves, 'acid house' and associated dance subcultures. As use has become more widespread, settings of use and types of users have diversified.[69] Clubs, parties and festivals remain the key locations for use, accompanying music and dancing.

Ecstasy has been reported as the favourite drug of surveyed club-goers, and the drug has been described as central to the culture of the British club scene.[70] Data from 2013/14 suggest that ecstasy use in the last year was around 15 times higher among those who had visited a nightclub at least four times in the past month (11.9%) compared with those who had not visited a nightclub in the past month (0.8%).[64]

Those frequenting certain clubbing environments, differentiated for example by dance music genres, may show even higher rates of use. A majority may have a history of recent ecstasy use,[71,72] and use 'ever' can be almost ubiquitous, as high as 96% of respondents of a 1999 survey of readers of *Mixmag*, a clubbing culture magazine.[73].

Although the use of ecstasy is linked to the use of the night-time economy, use in other settings, such as homes, is not unusual.[74,75] The number of deaths among drug-dependent solitary users may suggest that non-clubbing users could be over-represented among the clinical population.[23]

The CSEW finds that students were twice as likely to use ecstasy than people in employment (who are more likely to use cocaine than students).[64] Over the three years of data to 2013/14, people who self-identify as gay or bisexual were far more likely to be last-year users of ecstasy (5%) than heterosexual people (1.3%), although this is likely simply to reflect the higher overall prevalence of all drug use in this group. Asian/Asian British people (0.1%) and Black/Black British people (0.3%) were less represented among users of ecstasy than White people (1.6%) or people of mixed ethnicity (2.3%).[64] As with other drugs, men were more likely to have used ecstasy than women (2.3% versus 0.9% respectively in 2013/14). Ecstasy is used by people across the socioeconomic spectrum.[64]

Most people who try ecstasy will not escalate to regular or sustained use.[24] A Dutch study recruited ecstasy-naïve subjects who said they were probably going to try the drug. Of the 64 who did so in the next one to two years, more than half consumed only one tablet or less.[76] Ecstasy is typically used occasionally.[24] CSEW data show that 86% of last-year ecstasy users took it less frequently than monthly, 10% monthly, and 4% more regularly than monthly.[64]

While CSEW data show only a minority (4%) of last-year users use ecstasy more than once a month,[64] using ecstasy on many or most weekends is not uncommon among users sampled at clubs and raves.[77] Use of ecstasy several times a week, or even daily,[78] has been recorded, although this is exceptional and very likely to be linked to comorbidities.[78–80] One case has been reported of a poly-drug user who self-reported the consumption of 40,000 ecstasy tablets between the ages of 21 and 30, before ceasing use following several collapses.[81] Bingeing for up to 48 hours and using up to 25 tablets has been reported,[24] but there is a lack of recent evidence, and the number of tablets is an imprecise guide to the total dose taken.

The tendency is for tolerance to the positive effects of ecstasy to build up with use,[82] leading to diminishing returns from consumption. This may be protective against sustained heavy use or addiction.[24] It has been suggested that regular users often follow a trajectory of discovering and strongly liking MDMA, using it most weekends, sometimes with escalating dosages, for a year or two, suffering increasing adverse effects with decreasing enjoyment ('losing the magic') and then reducing or ceasing use spontaneously.[83] This pattern of decline has been described as almost unique among recreational drugs.[83]

A minority of ecstasy users will develop problems and will access drug treatment services, especially when no other problem drugs were also involved. Between 2006/07 and 2011, adults over the age of 18 years in England and Wales receiving treatment for drug use, which included problematic ecstasy use, use fell from 2138 to 1018.[66,84] In 2013/14, only 201 people (less than 0.1%) cited it as their main problem drug; but 964 people presented to treatment and cited ecstasy as one of their problem drugs.[85]

Ecstasy users are highly likely to be poly-drug users.[86,87] The CSEW does not record poly-drug use annually; 2012 data[88] show that ecstasy was commonly taken simultaneously with alcohol almost all of the time (95%) and with other illicit substances about half of the time (49%). When used simultaneously with other illicit drugs, the most common co-intoxicant was cannabis (64%), followed by cocaine (44%) and amphetamines (18%).[88] Poly-use was shown elsewhere. In a large Australian sample of regular ecstasy users, 62% said they usually consumed more than five 'standard drinks' (equivalent to more than 6 UK alcohol units) when they took ecstasy.[89]

Ecstasy users have higher levels of consumption of alcohol, cigarettes and cannabis than non-ecstasy users, but while they may combine ecstasy with alcohol and other drugs, ecstasy intoxication itself may not increase the likelihood of using other drugs at times where ecstasy is not used.[90]

However, among ecstasy users, heavy and frequent users are significantly more likely to use other stimulants and psychedelics at higher intensities than lighter ecstasy

users.[86] Studies suggest that the heavier an individual's ecstasy use, the heavier and more varied their poly-drug use will be.[86] This could reflect the fact that people with higher levels of use may also be more likely to use other drugs with stimulant and hallucinogenic properties. Scholey et al. suggest that this may represent a greater need (on the part of people with high levels of use) to boost drug effects as they become tolerant to the effects of MDMA.[86]

10.7. Forms, routes of ingestions and frequency of dosing

Ecstasy is available in a number of forms, mainly as powder/crystals or as pills, tablets and capsules. Currently in the UK, powder and crystals are most commonly used. In the Global Drug Survey 2014 UK sample, MDMA powder/crystals were twice as commonly used as tablets.[91] It is unclear whether this current dominance of crystals and powders is a universal or reflects the preference for these as a 'premium' product[70] among the Global Drug Survey sample – the crystals in particular are reputed among users to be a purer and more reliable product than tablets.[70] That form first became widespread against the backdrop of unreliable or low-dose tablets sold in 2009 and after. However, as of 2012, the average dose in seized tablets was much higher (102 mg) than in the 'poor quality' ecstasy sold in preceding years.[66] However, powder and crystals are no longer necessarily less adulterated or misrepresented than tablets. Indeed, a small but significant proportion of 'MDMA' crystals currently analysed are in fact methylone.[92]

Ecstasy is typically taken orally,[18] including in its powder/crystal form, which can be 'bombed' (wrapped in a cigarette paper or tissue and swallowed).[24] Some users consume ecstasy by licking a finger and dipping it into powder[93] or through 'dabbing' on gums.

When not consumed orally, it may be insufflated,[91] which is particularly common among experienced users.[69] User forums[94] report that the insufflation of ecstasy is painful and gives a shorter high, but with a rapid onset. According to the Global Drug Survey, oral ingestion remains the preferred method of administering MDMA, with only 15% of users snorting it.[91] Insufflation may be used as an alternative to oral use,[18] or sometimes as an additional route of administration for a boost, following oral ingestion.[95] Rectal[18] ('plugging' or 'booty bumping') and injecting are uncommon.[24,80] The latter has been described as 'too intense to enjoy', leading to reversion to oral use.[96] Other entactogens, such as 5-APB and 6-APB,[97], are also most often used orally.

The reported MDMA content of a single ecstasy tablet or capsule of powder has varied from no MDMA content at all to doses as high as 245 mg or 270 mg.[98,99] The higher doses are likely to cause toxicity, being well above the dose that seems associated with the best ratio of wanted to unwanted effects (about 100 mg).[68,100] Similarly, in a case of a fatality linked to consumption of two capsules thought to be 'ecstasy', a further single capsule from the batch was found to contain 422 mg bk-MDMA (methylone) and 53 mg bk-MBDB (butylone), far higher than typical reported doses.[7]

As mentioned in section 10.1, even tablets of the same 'brand', can vary between batches, or can be easily mimicked in an uncontrolled market. Tablets of the same appearance may not deliver a consistent dose, or even contain the same psychoactive substance. In 1999, identical-looking 'Dove' tablets were shown to range in dose from 19 mg to 140 mg of MDMA.[100] More recently, when two 'Yellow Rockstar' tablets from Glasgow were analysed, one contained 82 mg of MDMA, lower than doses administered to healthy humans in a recent research study,[101] and the other contained PMA and PMMA, along with caffeine.[15]

Doses consumed by the 'bombing' method (powder, typically wrapped in cigarette paper and swallowed) may be higher than average tablet doses.[24] There was an apparent increase in 2013 of the number of ecstasy users who accessed emergency treatment, according to reports to the Global Drug Survey. Users linked this to the current dominance of high-purity MDMA powder over pills, with Winstock suggesting that users may lack awareness of how to dose with powder.[91]

A naturalistic study of Australian users found that doses consumed in a session usually fell in the 50–150 mg range, but rose as high as 280 mg. Users took 0.5–5 tablets and these varied in dose from 0 mg to 245 mg.[98] American adolescent users in one study rarely took more than one pill per session.[102] Evidence from a web survey suggests that the dose users choose is linked to their level of experience. None of the 109 novice users (<10 lifetime uses) reported taking more than one or two tablets in one session, but 38% of 37 experienced users (>100 lifetime doses) described doing this.[86] When asked what their record highest ever intake was, heavy users in one sample had taken an average highest ever dose of 10.9 tablets,[103] but this may say more about variability in tablet quality,[27] as the same heavy user sample took 3.7 tablets during an average session.[103]

In audits of emergency department presentations in Switzerland and London, 15.4% and 20% of patients respectively had taken more than two tablets.[104] In a small American sample, three-quarters of users took just one dose in a session, usually between 8pm and 2am on a Friday or Saturday night. A minority took a further dose, usually within the first 2 hours, suggesting the additional dose constitutes a top-up if the initial effects are not satisfactory, rather than a typical stimulant dosing pattern of extending the high and avoiding the come-down.[90]

10.8. Desired effects for recreational use

The unique combination of desired effects elicited by ecstasy has been roughly summarised as the '3 Es' – energy, euphoria and empathy.[105] MDMA's continued presence as the key ingredient in ecstasy pills has been ascribed to its singular properties, combining unique desired effects with relatively low adverse effects at optimal doses.[68] MDMA topped a novel 'net pleasure index' among a large self-selected sample (22,000 people). In this index, subjective ratings of adverse effects were subtracted from ratings of desired effects to give a mean score that could be used to rank a range of drugs.[106] MDMA was also considered the best value drug overall by its users.[106]

Questionnaire evidence from people currently on ecstasy in a naturalistic party setting allowed ter Bogt and Engels to identify a hierarchy of motives for taking ecstasy.[77] Energy and euphoria were the leading motivations for a majority of users (as captured by users endorsing statements like 'dance all night' and 'feel absolutely great'). These were followed by sociability and flirtatiousness (e.g. 'flirting easier'), sexiness (e.g. 'sex better') and coping (e.g. 'forget my problems'); conformity (e.g. 'be cool') was the least important motivating factor.[77] When they contain MDMA, 'ecstasy' tablets are a relatively reliable producer of subjective pleasure.[68] Commonly reported positive effects, such as 'calmness', however, contrast sharply with paradoxical adverse effects that clinicians may encounter, such as agitation and anxiety.[35]

Pure MDMA usually elicits highly 'liked' effects, even in the research environment. However, in keeping with its intermediate position between typical stimulants (where positive mood change occurs reliably) and psychedelic hallucinogens (where setting powerfully mediates mood changes), positive effects may fail to appear in a context that is particularly unconducive to them (as observed in a research setting which was poor in social stimulation).[107]

Increased sensual awareness, love, feeling of connection, desire, sexual intensity and satisfaction are also reported,[77] but paradoxically this may be coupled with erectile dysfunction in men and delayed orgasm in both sexes.[108,109] It has been hypothesised that this is due to release of prolactin and oxytocin, such that ecstasy mimics the emotionally close but sexually impaired features of the post-orgasmic refractory period.[110] Female heterosexual ecstasy users, interviewed in one study, did not generally think that ecstasy increases the likelihood of high-risk sexual activities, although noted that they sometimes chose to engage in behaviours such as anal sex while intoxicated which they otherwise may not have engaged in.[109] Roger et al.'s systematic review, which includes a meta-analysis, shows that ecstasy use is linked to small to moderate increases in sexual risk.[23] However, ecstasy is not one of the drugs most linked to 'chemsex' and associated risks.[111]

Ecstasy was found in one case to give temporary dramatic relief from the symptoms of Parkinson's disease;[112] this discovery, corroborated in animal studies, has led to drug development.[113]

Although not widespread, it has been reported that some individuals may use ecstasy in an attempt to self-medicate, for example to manage current stresses and lifetime traumas,[114] including PTSD symptoms.[80] In the US, there appears to be some 'underground' use of ecstasy for therapeutic purposes.[115]

Some NPS have been reported to produce similar subjective effects to those reported by MDMA users,[13,116] especially an 'entactogenic syndrome',[2] but evidence from studies in humans is limited. In combination with animal research, some anecdotal evidence supports the existence of subtle[18] to significant differences, with some entactogens producing the empathogenic effects and serenity associated with ecstasy but with less of the stimulant and euphoriant effect.[117]

Whereas many NPS are selected by users because they wish to experience a new drug, this is not necessarily the case with PMMA and PMA, as these are typically not

taken deliberately as such. For example, none of the 22 people seen with PMA toxicity in an Australian emergency department reported deliberately taking the drug; rather, they had all intended to take ecstasy.[47]

In fact, there is no evidence that PMA and PMMA have any prominent desired effects,[68,118] although their serotonergic pharmacology suggests that they could have 'entactogenic' effects. A study linking the pharmacological content of a tablet consumed and its subjective effects on users reported that desired effects were nearly absent with tablets containing MDMA adulterated with PMMA (odds ratio of 0.05 relative to desired effects from MDMA-only tablets).[68]

10.9. Unwanted effects

The use of MDMA is associated with a number of unwanted effects. For example, a study reported that typical side-effects as experienced by more than half of a sample of users included jaw clenching (trismus, 'gurning'), dry mouth, tachycardia and sweating, with a minority having experienced urinary retention, dizziness, nausea and vomiting, and decreased libido.[119]

It has been argued that common side-effects, such as nystagmus, trismus, mild confusion and feeling hot, are the low end of a spectrum of serotonergic overactivity that has at the higher end serotonin syndrome and death.[120] Other adverse reactions include feeling cold and shivering.[120]

Unwanted effects could be associated with MDMA and/or adulterants and other compounds found in tablets sold as ecstasy. In one study, adverse drug effects were reported by 16% of 924 users who had handed in 'ecstasy' for testing by the Dutch recreational drug testing service, DIMS.[68] The testing revealed that where adulterated or counterfeited 'ecstasy' had been handed in, a much greater proportion of users had complained of adverse effects. Products containing MDMA alone (at widely varying doses) were reported to have been associated with adverse effects 8% of the time and desired effects 74% of the time. Adverse effects reported from tablets containing MDMA included nausea (most common), headache, hallucinations, dizziness, 'allergic reactions' (note, however, that this term may not have been used by users in its medical sense) and, more rarely, palpitations, hyperthermic seizures, agitation and abdominal cramps.[68]

In addition to unwanted acute side-effects, MDMA may have long-lasting effects. Users have described 'mid-week blues' appearing three to five days after the use of ecstasy. These 'blues' appear to increase in intensity and incidence[120] as users persist with the drug.[119] Novice users may suffer fatigue, depressed mood and decreased appetite in the days after use. The majority of experienced users have experienced additional symptoms, such as nightmares and difficulty with memory and concentration.[119] The subacute effects are associated with depleted serotonin, so the worsening effects in experienced users,[83] especially when not associated with higher doses,[119] may indicate chronic serotonergic dysfunction, with heightening sensitivity to depletion.[121] Depressed mood following use is not universally found

after administration of MDMA and other entactogens in a therapeutic or research setting, and a positive mood change may even occur, as seen in a study with MDEA,[3] suggesting that the combined effect of the drug and environmental and behavioural stressors in typical use is important.[122]

One study of Dutch 'ravers', including 103 women, suggested that females may suffer a greater incidence of adverse effects, such as nausea, headache, dizziness and feeling faint.[77]

PMA and PMMA seem to have pronounced unwanted effects. The Dutch testing service found that tablets containing MDMA adulterated with PMMA had caused adverse effects in the majority of users (56% vs. 8% for MDMA-only tablets).[68] There is limited evidence on the detail, but self-experimentation by Shulgin and Shulgin et al. found that PMA (called 4-MA in their book) produced a sudden robust rise in blood pressure at 60 mg, and a feeling of 'druggedness' rather than a 'high' at 70 mg.[123] PMMA was not liked either, as it produced tachycardia, eye-muscle twitch and compulsive yawning, and no enjoyable subjective effects.[124] The relative lack of desired ecstasy-like effects combined with a slow onset is thought to lead to users believing they have taken weaker ecstasy, taking more and suffering greater toxicity.[118]

10.10. Mortality

In England and Wales, MDMA or ecstasy was mentioned on the death certificate in 43 cases in 2013,[125] representing a steep year-on-year rise from a recent low of 8 in 2010, but a fall from a peak of 58 in 2005. There have been concerns about the recent availability of some 'super-strength' formulations, with reports of MDMA content 2–2.5 times higher than the 'standard' dose.[126]

PMA and PMMA have been associated with a significant number of deaths. Compared with MDMA, they appear to have a high potential to cause life-threatening toxicity.[47]

The emergence of PMA[47] and PMMA[44] on the ecstasy market internationally dates as far back as 1973, when PMA appeared in Canada, leading to fatalities.[127] In the UK, the number of PMA-associated deaths was 1 in 2011 but then 20 in 2012. In 2013, PMA or PMMA was mentioned on 29 death certificates in total, on 14 as the sole drug and on 2 with alcohol.[125] PMA-related deaths in the UK at first seemed to be concentrated in Scotland, but more recently clusters have also been reported in Suffolk and eastern England more generally.[128]

Deaths in England and Wales related to other NPS are not listed separately, but several fatalities associated with substances with entactogenic effects (e.g. MDAI,[56] 5-APB and 6-APB[17]) have been reported from the UK and internationally in recent years.

10.11. Acute harms

A minority of users of ecstasy will present to hospitals from 'raves'[129] or nightclubs.[130] In a retrospective review of patients from nightclubs attending a hospital emergency

department between 1997 and 1998, ecstasy was the second most common drug cause of presentation, after alcohol.[131]

There is no clear fatal blood concentration level of MDMA. One study showed that the levels recorded at autopsy in 13 deaths by ecstasy toxicity alone overlapped considerably with MDMA levels recorded from 24 cases where the drug was detected post-mortem but trauma was the cause of death.[132]

There are difficulties in disaggregating the harmful effects specific to MDMA toxicity from the confounding effects of analogues, co-intoxicants and environmental and individual factors.[133] It is not yet clear how much of the overall ecstasy-related harm is attributable to the toxicity of MDMA in isolation.[23]

As with other club drugs, mixed intoxications (from deliberate poly-drug use, alcohol or from ecstasy adulteration) are typical in general use and in presentations to acute clinical settings.[130] Poly-drug use appears to be associated with life-threatening outcomes at lower blood concentrations, as shown by a study which reported a mean post-mortem MDMA blood concentration of 2.90 mg/l in 22 ecstasy poly-drug deaths, whereas it was 8.43 mg/l in 13 cases where only MDMA was found.[130]

There is evidence that some adverse side-effects may be gender-specific. A study reported that women experienced more intense psychological effects, while men showed a greater increase in physiological measures, particularly systolic blood pressure. Although body weight may play a part, it also appears that there are pharmacokinetic and/or pharmacodynamic differences between genders.[134] Adverse effects may be dose-dependent as well as gender-specific. In the analysis of clinical studies by Lietchi et al., increasing dose was correlated with greater self-reporting of hallucinogen-like perceptual effects, in women in particular, and with greater reported dysphoric states in women alone. However, increasing dose was not associated with increases in measures of desired effects.[134]

10.11.1. Features of acute ecstasy toxicity

Table 10.4 provides information on acute MDMA toxicity. In addition, MDMA (as well as NPS such as PMA and PMMA) causes severe serotonin syndrome and sympatho-mimetic effects. Death can follow sudden collapse and cardiac arrest, or can result from disseminated intravascular coagulation, protracted seizures and multiple organ failure. Many of these result from extreme hyperthermia.

When acute toxicity has occurred following the use of other NPS, patterns of harms are similar to the broad spectrum of acute harm associated with MDMA and are described below.[18,47,135] However, the severity of symptoms may tend towards the higher or lower end of the spectrum seen with MDMA.

PMA and PMMA are particularly associated with severe and life-threatening symptoms, such as seizures and coma.[23,45] A study from Norway, for example, reported 12 fatalities and 22 recoveries from a series PMMA intoxications.[44]

Table 10.4. *Features of acute ecstasy toxicity*

Reported effects associated with 'ecstasy' or MDMA	Other NPS with similar reported effects
CNS, neurobehavioural and psychiatric	
Dilated pupils, mydriasis[136] **Common**[104,130]	bk-MDMA (methylone), bk-MBDB (butylone),[7] 5-APB, 6-APB[97]
Feeling unwell/weak/dizzy **Common**[104]	
Restlessness **Common**[74]	MDEA,[3] PMA/PMMA[137]
Nystagmus	bk-MDMA (methylone),[13] 4-MTA,[20] PMA/PMMA[45]
Euphoria	bk-MDMA (methylone), bk-MBDB (butylone)[7]
Anxiety[136]	5-APB, 6-APB,[138] MDEA[3]
Panic[104]	MDEA[3]
Agitation[136] **Common**[74,104,129]	6-APB,[139] MDEA[140]
Disorientation/confusion[136] **Common**[74,104]	Bk-MDMA (methylone),[13] 4-MTA[20]
Psychosis[136]	6-APB,[139] MDEA[3]
Paranoid ideation, delusions[136]	6-APB,[139] MDEA[3]
Delirium	PMA/PMMA[141]
Sleepiness	PMA/PMMA[141]
Collapse, loss of consciousness **Common**[74,104]	PMA/PMMA[44,137]
Self-injury	6-APB[139]
Convulsions, seizures[136] **Common**[129]	bk-MDMA (methylone), bk-MBDB (butylone),[7] 4-MTA,[49] PMA/PMMA[137,141]
Amnesia (one case without analytic confirmation[142])	4-MTA[20]
Hallucinations[136]	4-MTA,[48] MDEA,[3,140] PMA/PMMA[45]
Coma[74]	bk-MDMA (methylone), bk-MBDB (mutylone),[7] PMA/PMMA[141]
Trism, bruxism,[143] increase in jaw/facial tension	Bk-MDMA (methylone),[13] MDEA,[3] PMA/PMMA[45]
Thirst[104]	4-MTA[20]
Headache[136] **Common**[74,104]	
Brian oedema[74]	
Cardiovascular effects	
Tachycardia **Very common**[104,129,130,144]	5-APB, 6-APB,[97,138] bk-MDMA (methylone), bk-MBDB (butylone),[7] MDEA,[3] PMA/PMMA[45]
Hyperthermia **Common**[74,104]	bk-MDMA (methylone), bk-MBDB (butylone),[7] 4-MTA,[20,49] MDEA,[140] PMA/PMMA[44,45]
QT prolongation[145,146]	5-APB, 6-APB[138]
Palpitations[104]	5-APB, 6-APB,[97] MDEA[3]
Hypertension **Common**[74,104])	bk-MDMA (methylone), bk-MBDB (butylone),[7] 5-APB, 6-APB,[97,138] PMA/PMMA[45]
Disseminated intravascular coagulation (DIC)[104]	bk-MDMA (methylone), bk-MBDB (butylone),[7] MDEA,[135,140] PMA/PMMA[137]
Arrhythmias[147] (atrial fibrillation[148])	MDEA[3]
Myocardial infarction[149]	
Cyanosis secondary to methaemoglobinaemia, one report[150]	

Gastrointestinal effects	
Nausea, vomiting[104]	bk-MDMA (methylone),[13] 4-MTA,[20,49] MDEA,[3] PMA/PMMA[137]
Stomach cramps	4-MTA[49]
Dry mouth	MDEA[3]
Respiratory effects	
Tachypnoea[130]	bk-MDMA (methylone), bk-MBDB (butylone),[7] MDEA 'hyperventilation'[3]
Pneumomediastenum, causing subcutaneous crepitation,[151] emphysema with neck/chest swelling[152,153] (3 reports)	
Shortness of breath, dyspnoea, breathing difficulty[104,151,153]	4-MTA,[49] MDEA[140]
Chest pain[104,151]	
Respiratory failure, acute respiratory distress	MDEA,[3] PMA/PMMA[44]
Musculoskeletal effects	
Rhabdomyolysis[74]	bk-MDMA (methylone),[13] MDEA,[140] PMA/PMMA[137]
Hyperreflexia	bk-MDMA (methylone), bk-MBDB (butylone)[7]
Shivering[105], [130]	bk-MDMA (methylone), bk-MBDB (butylone),[7] 5-APB, 6-APB,[97] 4-MTA,[20,48]
Shaking **Common**[74]	4-MTA[48,49]
Tremor[104,136]	bk-MDMA (methylone), bk-MBDB (butylone),[7] 5-APB, 6-APB[97]
Muscle spasms	MDEA,[140] PMA/PMMA[45]
Myoclonus[104]	bk-MDMA (methylone), bk-MBDB (butylone)[7]
Increased muscle tone, muscle rigidity	Bk-MDMA (methylone), bk-MBDB (butylone),[7] PMA/PMMA[45]
Inability to stand	4-MTA,[49] MDEA[140]
Collapse	4-MTA[49]
Hyperactivity ('hrashing around')	PMA,[127,154] 4-MTA[155]
Other effects	
Metabolic acidosis	bk-MDMA (,ethylone)[156]
Sweating, diaphoresis,	bk-MDMA (methylone), bk-MBDB (butylone),[7] 5-APB, 6-APB,[97] 4-MTA,[20,48,49] MDEA[140]
Fever	5-APB, 6-APB[97]
Foaming at the mouth	4-MTA,[49] MDEA[140]
Acute kidney injury/ acute kidney failure[157]	

Data from the National Poisons Information Service (NIPS) provides some information about harms in the UK. In 2012/13, among telephone enquiries relating to psychoactive illicit drugs, those about MDMA were the second highest in number (131), after cocaine, and in terms of the number of times the NIPS's TOXBASE® website was accessed (4778), it came third, after cocaine and mephedrone.[158]

The majority of presentations are managed in hospital emergency departments; they are mild or moderate in severity and self-limiting.[23,130] In a recent Australian study, the median duration of stay in the emergency department was 3 hours.[75]

Studies from accident and emergency units show that the most common presentations after consuming ecstasy include collapse and/or loss of consciousness, as well as 'feeling 'unwell', 'strange', 'weak' or 'dizzy'; nausea, vomiting and palpitations are also common.[23,130] Most of those presenting have come from a club, rave or party; among a series of presentations to a London emergency department, 67% had co-used other substances.[104,130] Similar and higher rates of co-intoxication were found in more recent reviews internationally, with alcohol, amphetamines and cocaine being common co-intoxicants.[23,104]

Severe acute harm following use of ecstasy usually falls into the categories described below,[105,159] although the clinical picture is often complicated by concomitant drug use,[104] and a single case may have symptoms from more than one category:

- hyperthermia/hyperpyrexia and secondary manifestations;
- serotonin syndrome (a cause of hyperthermia[105]);
- dilutional hyponatraemia and hyponatraemic encephalopathy**.** Hyponatraemia is particularly a cause of ecstasy fatalities in women;[129]
- acute psychiatric presentations, including symptoms of anxiety, panic or psychosis;
- other isolated physiological syndromes, including cardiac events, liver failure and pneumomediastenum.

It has been suggested that hypoglycaemia, hyperkalaemia[160] and QRS elongation[47] may be features specific to PMA poisoning. However, all these signs have a been observed occasionally in cases of severe ecstasy toxicity not linked to PMA.[161–163]

10.11.2. Hyperpyrexia/hyperthermia and consequences

Ecstasy use can promote the development of hyperthermia in two principal ways:[105] by adding to heat load and by reducing heat dissipation. It promotes a hypermetabolic state pharmacologically,[162] and behaviourally, often leading to muscular exertion through hours of dancing.[104] Moreover, hot, overcrowded dance floors are a typical setting for its use.[164,165] Heat dissipation can be impaired by peripheral vasoconstriction, at least in rats,[166] or by dehydration. Many ecstasy-using dancers who suffer adverse effects display typical symptoms of heat illness, such as feeling unwell and collapsing in an exhausted state.[104,130,165] Some will move to a 'chill-out' room to recover at the dance venue, or be treated on site. Some will present to hospital, mostly with self-limiting symptoms, requiring minimal intervention beyond correcting dehydration and allowing rest. However, more severe symptoms have been reported.[130]

The overheating associated with ecstasy use can produce harms across a spectrum of severity; a minority of patients present with a severe hyperpyrexia that will not resolve spontaneously with rest in a cooler environment. This has been attributed

to an idiosyncratic drug reaction causing a pharmacologically mediated central and peripheral thermogenesis.[23,167]

Hyperpyrexia associated with MDMA can appear across a broad dosage range.[23] A vicious cycle of positive feedback from agitation, clonus and seizures can all contribute to heat generation. The hyperpyrexia and serotonin syndrome seen in association with MDMA and related serotonergic drugs are clinically distinct from malignant hyperthermia and neuroleptic malignant syndrome.[105,168,169]

Hyperpyrexia is one of the predominant life-threatening adverse reactions to ecstasy and is the underlying cause of many acute ecstasy-related deaths. It is also a cause of severe chronic harm resulting from secondary complications such as liver failure and brain damage.[23,167] Compartment syndrome has been reported as a complication at least twice,[170] and was in one further case associated with ecstasy injection in the absence of hyperpyrexia.[171]

There may be considerable overlap between serotonin syndrome and this form of acute ecstasy-related toxicity. Serotonin syndrome can be a trigger for uncontrolled hyperpyrexia, but hyperpyrexia can also occur without serotonin syndrome.[105] Acute kidney injury occurs as a consequence of the myoglobinurea seen with rhabdomyolysis, but may be compounded by a number of factors, which include a direct toxic effect of the drug in the kidney and volume depletion from dehydration.[157]

10.11.3. Serotonin syndrome/serotonin toxicity

MDMA is a powerful releaser of serotonin and as such is linked to serotonin syndrome. Further information on the features and management of serotonin toxicity can be found in Chapter 7.

Ecstasy can be a cause of serotonin syndrome alone, or in combination with other factors that increase serotonin to toxic levels, including many recreational and pharmaceutical drugs,[172] such as MAOIs, SSRIs, tricyclics, tramadol and linezolid (see TOXBASE®). In one Australian study, some ecstasy users reported deliberately taking these and other pharmaceuticals to magnify the effects of MDMA.[173]

The risks of serotonin syndrome associated with MDMA are boosted by several classes of serotonergic drug.[53,174] A recent fatality was associated with 6-APB and mirtazapine.[22] Some NPS entactogens inhibit monoamine oxidase.

PMA/PMMA poses a particular threat of severe serotonin toxicity.[44] It has been suggested that it may simultaneously promote serotonin toxicity in several ways – by causing serotonin release, inhibiting reuptake and inhibiting CYP2D6 metabolism.[45] Symptoms commonly seen in reports of severe PMA and PMMA toxicity are consistent with serotonin syndrome and hyperthermia. Serotonergic and sympathomimetic features may include bruxism, agitation, confusion, convulsions, rhabdomyolysis, coagulopathy, organ failure, coma and death.[47,160,175] One case series of eight fatal PMMA intoxications showed different presentations depending on dose; those with lower blood concentrations of the drug had delirious hypertalkativity and convulsions, but higher blood concentrations were associated with drowsiness and coma,[141] symptoms consistent with severe serotonin syndrome.

10.11.4. Dilutional hyponatraemia and hyponatraemic encephalopathy

Ecstasy has been described as causing a 'perfect storm' of effects that can precipitate dilutional hyponatraemia. Women make up more than 85% of symptomatic cases in the literature, despite more males being users of MDMA.[129,157,176] MDMA has the potential to directly affect water balance via a syndrome of inappropriate anti-diuretic hormone (SIADH) secretion, at least in women.[176]

The drug and the typical contexts of use promote exertion and sweating (resulting in loss of sodium). Hyponataemia can occur when these effects are combined with the consumption of excessive quantities of low-electrolyte fluids such as beer and water.[143] The psychoactive effects of ecstasy may encourage this, perhaps promoting obsessional repetitive behaviour, and masking awareness of emerging symptoms of hyponatraemia, such as confusion.[23,177] Furthermore, mistaken, or misunderstood, harm-reduction information has allegedly led to excessive drinking of water to avoid dehydration and heatstroke.[177]

Mild, asymptomatic hyponatraemia has recently been shown to be a common effect of ecstasy use in a typical electronic dance music context. Women are more vulnerable than men, as they are more likely to have lower serum sodium levels before MDMA use. They are more likely to become mildly hyponatraemic while using, more likely to develop symptomatic hyponatraemic encephalopathy, and more likely to die as a result.[23] Fatalities are almost exclusively in women under 21, although men have suffered hyponatraemia so the possibility of male cases should not be ignored.[23]

In contrast to other acute syndromes caused by ecstasy, dilutional hyponatraemia often follows a uniform course, with symptoms mostly resulting from the progression of cerebral swelling. Initial headache, vomiting and disturbed mental state are followed by seizures, drowsiness, disorientation and muteness, progressing to coma, hypoxia and death, often due to tentorial herniation.[23] Patients may already be comatosed upon admission to hospital.[178]

Relatively low doses, including single tablets, are not unusual in cases of hyponatraemia.[23] Also, the excess water intake required to cause symptomatic hyponatraemia, in the context of ecstasy intoxication, is not extreme; 1700 ml and 1200 ml have been cited in case reports;[157,178] 3500 ml was drunk in a case related to bk-MDMA (methylone) and ethcathinone.[13] Genetic variation in the function of alleles coding for the CYP2D6 enzyme and the COMT enzyme may predispose some individuals to ecstasy-induced hyponatraemia.

10.11.5. Acute psychiatric presentations

Anxiety and panic are common presentations among users seeking medical help.[23] Ecstasy is an ATS, and is widely used, yet evidence linking it to psychosis is limited to a relatively small number of case reports and case series.[23] Collectively, these suggest that ecstasy does occasionally act as a stressor that precipitates acute psychosis, but at a much lower rate than amphetamine, its molecular relative.[136]

Psychotic symptoms can result from poly-drug use involving ecstasy or, on occasion, from ecstasy alone, particularly in vulnerable individuals.[23,136] No single characteristic pattern emerges from the evidence base; putative cases include previously healthy people experiencing sudden onset of psychosis after taking a single pill,[179] as well as chronic poly-drug users with complex vulnerabilities taking up to four tablets of ecstasy *daily* before admission with acute symptoms.[79] As with psychosis linked to other drugs, the prognosis varies from rapid resolution within hours (perhaps in those with a low intrinsic propensity to psychosis) to months or years as an inpatient (perhaps in those with a high vulnerability).[23,180]

The evidence base includes several cases where there is no toxicological evidence of ecstasy consumption[29,179] and, in most cases, deliberate or unintended co-intoxication with other drugs linked to psychosis cannot be excluded as a factor.[79] It remains unclear whether the tendency for ATS to precipitate psychosis is more a direct pharmacological action or toxicity, or more an indirect product of severe psychological stress, such as that caused by sleep deprivation and bingeing behaviour.[180,181] In either case, ecstasy is an exception among ATS, with lesser effects on dopamine and use typically confined to weekends, rather than multi-day binges, as may occur with methamphetamine and cocaine. Two cases of ecstasy-induced psychosis occurred in individuals who were 'spiked' with the drug without their knowledge and consent.[23,181] This may indicate a substantial influence of psychological 'set' in determining the response to intoxication. A case control study in a subacute population of males undergoing treatment for their first-episode psychosis found that those who had a recent history of ecstasy use showed significantly different symptoms from those who had not used ecstasy, including shorter hospitalisation, less bluntening of affect but increased hostility.[182]

10.11.6 Suicidal ideation and suicide

Ecstasy users have an increased risk of suicide attempts,[183] but it is uncertain how much of this association is causal, how much may relate to acute use and how much to chronic effects. Recent ecstasy use has been linked to suicidal thoughts and behaviour, in some case reports in the context of acute psychosis as described above, or subacutely, possibly triggered by the ecstasy 'come-down' (for example one case followed a three-day session of injecting ecstasy).[23] Ecstasy overdose has been employed as a mechanism of suicide or suicide attempt,[184,185,186] as has bk-MDMA (butylone).[187]

10.11.7. Acute and subacute cardiac events

Ecstasy alone, and in mixed intoxication, has been associated with acute cardiac events, including myocardial ischaemia and infarction.[23,188] It can also unmask underlying cardiac dysfunction. Myocardial infarction probably results from coronary artery spasms, similar to those observed in cocaine users. A series of three cases of acute coronary syndrome and ST elevation myocardial infarction (STEMI) demonstrates that, as with cocaine-induced heart problems, they may emerge long after plasma

drug concentrations have peaked.[188] Hyperkalaemia could also contribute to cardiac arrhythmias. There is a single case report of severe dilated cardiomyopathy accompanying hepatic damage.[189]

Cardiac arrests occasionally occur without being precipitated by hyperpyrexia or serotonin syndrome.[104] When patients present with chest pain and other symptoms, concomitant use of other drugs should be considered, especially cocaine, which is well known for provoking cardiac dysfunction.[23]

10.11.8. Pulmonary harms: pneumothorax, pneumomediastenum

One study has reported that ecstasy has been associated (through uncertain mechanisms) with at least 23 cases of pneumomediastenum,[152] and a smaller number of pneumothorax cases are also reported in the systematic review by Rogers et al.[23] Patients usually present with pain of the chest and neck and shortness of breath, but subcutaneous emphysema and resultant swelling may also be apparent.[152] Sometimes presentations may be delayed, days after consumption. It is hypothesised that the muscle tension caused by ecstasy, combined with exertion from dancing, jumping or sex,[153,190] could lead to air pressure against a closed glottis, similar to the Valsalva manoeuvre, raising alveolar pressures and causing ruptures.[152] This can result in air being forced out into spaces in the mediastinum.[191] One case with an alternative mechanism featured a tear in the oesophagus, allowing air into the mediastinum.[105]

10.11.9. Intracranial haemorrhage

Ecstasy use has been associated with intracranial haemorrhage, even in the apparent absence of co-intoxicants.[23,192] Pre-existing aneurysms, or arteriovenous malformations, may rupture as a result of the acute surge in blood pressure caused by ecstasy, similar to the mechanisms seen with cocaine.

10.11.10. Liver failure

Ecstasy may cause liver failure in two ways. According to a review of the evidence, one group develop acute liver failure secondary to a severe hyperthermic reaction to ecstasy. The other group appear to suffer, isolated hepatotoxicity without any hyperthermia. This is generally a subacute effect which may emerge over the days following use, in contrast to the rapid onset of organ failure in the hyperthermic patients.[23] Despite its rarity, this constitutes one of the more common causes of liver failure in this young age group. Patients may present in a critical condition, with hepatic encephalopathy, and some will require transplantation.[193] It has been suggested that ecstasy may cause a greater amount of 'silent' liver damage than is recognised.[23]

10.11.11. Diabetic ketoacidosis

A small number of case reports demonstrate that people with diabetes can suffer ketoacidosis and associated symptoms following ecstasy use combined with exertion.[194,195]

10.11.12. Poly-drug use and drug interactions

As discussed above, MDMA is commonly used with other psychoactive drugs and this can increase harm. For example, cocaine co-ingested with ecstasy seems to increase the risk of severe anxiety. In an audit of 52 acute ecstasy-related admissions, 13 with co-use of cocaine, 4 of the 7 patients who suffered panic reactions were among the 13 cocaine users.[104] When MDMA is co-ingested with stimulants in general, the potential for toxicity is likely to be raised.[196] Co-intoxication with caffeine increases the risk of hyperpyrexia in rats.[197] PMMA and PMA produce greater toxicity in combination with stimulants.[45]

Poly-drug use commonly confuses the clinical picture of ecstasy intoxication, and can lead to paradoxical features that are not those expected from intoxication with ecstasy alone. In a Swiss emergency department audit, hypothermia was, paradoxically, one of the most commonly recorded features, and brachycardia, coma, pupil constriction and hypotension were also noted.[104] These were associated with the co-use of substances, including GHB and opiates.[23] Consuming alcohol with ecstasy is associated with a higher rate of l harm. Concomitant alcohol use was implicated in 75% of cases of ecstasy-related presentations in an Australian emergency department.[75]

In terms of drug interactions, MDMA and related drugs are substrates and inhibitors of CYP2D6, so combining them with other drugs or pharmaceuticals which compete for, inhibit or block CYP2D6 may cause greater unwanted effects or toxicity. For example, people taking the antiretroviral drug ritonavir are likely to be at particular danger from ecstasy toxicity.[198] Similar reactions may be possible with any drug sharing ritonavir's capacity to compete with MDMA as a substrate of CYP2D6 and inhibit the enzyme. Other drugs linked to apparent cases of adverse interactions include dextromethorphan (DXM), fluoxetine, paroxetine and moclobemide.[18,43] Drugs which could theoretically cause similar problems include haloperidol, thioridazine and quinidine.[18] CYP3A4 is also involved in the metabolism of MDMA and its derivatives, and co-ingestion of ritonavir has been linked with several cases of toxicity.[18] There may be risks associated with many other substances which affect CYP3A4.[18,199]

Importantly, MDMA is metabolised by CYP2D6 and inhibitors of this metabolic pathway may therefore increase its level and consequently toxicity. Among the antiretrovirals, the new booster cobicistat (used to optimise concentrations of the integrase inhibitor elvitegravir or of the protease inhibitors atazanavir and darunavir) has been reported to be a CYP2D6 inhbitor.[200,201] While ritonavir at low doses (as administered to boost HIV protease inhbitors) is not a CYP2D6 inhibitor but is a strong CYP3A4 inhbitor, its role may be important if CYP2D6 metabolisers use CYP3A4 as a compensative metabolic pathway of MDMA, as the latter would be inhibited and lead to increase concentrations of MDMA and toxicity. This would add to the already discussed wide inter-individual variability in responses to MDMA.

For up-to-date guidance on the management of ecstasy/MDMA acute toxicity, it is recommended that information be sought from the National Poisons Information Service (NPIS), specifically the NPIS 24-hour telephone service and the poisons information database TOXBASE®:

http://www.toxbase.org/Poisons-Index-A-Z/M-Products/MDMA2/

It is recommended that relevant clinicians and departments are registered to receive these facilities.

Non-UK readers should consult their local or national guidelines.

10.12. Clinical management of acute toxicity

Admissions following ecstasy use often occur at peak times and therefore put pressure on resources.[75] PMA and PMMA may account for many cases of severe 'ecstasy' toxicity encountered in an emergency department.[44,47]

In an Australian emergency department, 14% of people presenting to hospital after ecstasy consumption required admission.[75] The most common interventions required are clinical monitoring, observation and reassurance, and symptomatic treatment, including fluids.[104] The average duration of hospital stay reported by the Australian study was three hours.[75] TOXBASE® recommends observation of asymptomatic patients for at least four hours.

Dehydration should be addressed. Following ecstasy-related presentation to a hospital emergency department, intravenous fluids were administered to 31% of patients in a UK study,[130] and to 71% of cases in a Swiss study,[104] but it is important to note that symptoms following ecstasy use range from severe dehydration to severe hyponatraemia; the latter patients require fluid restriction, so it is dangerous to give hypotonic fluids or normal saline to patients prior to proper assessment.[143,157]

There is no evidence to support gastric decontamination with activated charcoal, but it may be appropriate for cases of presentation within 1 hour of ingestion. Gastric lavage was used in a case with a positive outcome following an attempted suicide with 30 tablets.[184]

10.12.1. Hyperpyrexia and hyperthermia

Patients presenting with body temperatures above 39°C need aggressive cooling measures, such as icebaths or internal cooling, and benzodiazepine sedation. It has been suggested that dantrolene may be considered when hyperthermia persists. However, this has been contested by some. No clinical trials have been conducted but a review has reported better survival rates for patients with temperatures above 40° C who received dantrolene, with minimal adverse effects.[202] However, a 2011 evaluation of options in MDMA-induced hyperthermia recommended against the use dantrolene and antipyretics.[203]

10.12.2. Acute psychiatric presentations

The most of the common features observed in acute patients can be at least partially attributable to anxiety, agitation and panic (e.g. dizziness, palpitations, hyperthermia, hypertension). Some features (e.g. tachycardia) act as internal stimuli to anxiety and panic attacks through positive feedback. TOXBASE® notes that controlling agitation with benzodiazepines may relieve hypertension.

Many cases are resolved in a preclinical setting, or upon reassurance during the initial assessment. Agitation, anxiety and panic can be managed as they would be in the absence of a drug trigger, but cardiac monitoring is a higher priority.[130] Reassuring patients that they are not likely to be in physical danger may be sufficient, but benzodiazepines are the first-line pharmacological treatment. One study reported that they were administered to a quarter of all patients presenting following ecstasy use at a Swiss emergency department.[104,105] Some suggest that haloperidol is contraindicated as a second-line option, because of possible dangerous interactions with MDMA and related drugs.[18]

10.13. Harms associated with chronic use

While the association between ecstasy consumption and several types of acute harm is relatively clear, current understanding of the chronic harm caused by ecstasy use is limited, due to incomplete and disputed evidence.

Chronic use of ecstasy has been linked to serotonergic neurological damage and dysfunction, which some researchers have suggested may be responsible for a broad range of neuropsychiatric symptoms and cognitive impairments. A meta-analysis shows these to be predominantly small, subclinical effects.[23] Significant trends indicating impairment are typically not identified in samples of ecstasy users who have taken the drug on fewer than 50 occasions.[204]

Other harmful chronic consequences that have been attributed to use of ecstasy include cardiovascular damage, particularly serotonergic valvular heart disease.

Evidence of long-term effects of NPS use is not available, and so the potential for each of these to cause harm remains unknown. Chronic use of an NPS product (called 'Pink Panthers') containing MDAI and 2-AI (the latter of which appears to be more amphetamine-like than MDMA-like) has been linked to one case of cyanosis caused by methemoglobinaemia. Such effects may also result from chronic use of the many NPS products containing benzocaine as a cutting agent.[205]

10.13.1. Neurotoxicity

Differences in the serotonergic function of ecstasy users, compared with controls, have been observed in neuroimaging studies.[206–211] Observed differences in markers of serotonergic function have been interpreted as indicating the degeneration and loss of serotonergic neurons and their terminals, i.e. 'neurotoxicity'.[209] Correlations have been demonstrated between presumed markers of toxicity seen in users and

functional deficits in memory.[212,213] This supports the hypothesis that serotonergic neurotoxicity is the cause of the cognitive deficits and worsened neuropsychiatric status of ecstasy users.[25]

The idea that MDMA is neurotoxic in typical human users is supported by some animal research,[206] but some experts do not consider the evidence to be conclusive.[27,214] Some have argued that the observations in such studies may be consistent with changes and loss of serotonergic markers, without loss of the neurons themselves (i.e. serotonergic dysfunction occurs but this may or may not amount to 'neurotoxicity').[215,216] Other authors highlight limitations in the predominantly retrospective and non-randomised studies supposedly indicative of 'neurotoxicity', claiming that current evidence is insufficient to exclude non-causal explanations,[214] such as pre-existing lower levels of serotonergic markers in the brains of ecstasy users.[27,217] While poly-drug use in virtually all ecstasy users has been cited as a confounding factor, recent investigations comparing ecstasy users with LSD users[218] and other poly-drug users[219] add weight to the evidence for ecstasy-specific neurotoxicity.

High lifetime intake may not necessarily be required for neurotoxicity to occur. One prospective study found evidence indicative of some brain changes in new users with an average lifetime intake of only six tablets. These changes did not, though, include losses in serotonin transporter density, which is the marker of toxicity most commonly observed. The authors concluded that it is possible that MDMA is neurotoxic even in small quantities.[76]

Studies have found evidence consistent with some recovery[220] and adaptation of the altered serotonin system,[211] but, conversely, other results indicate the persistence of serotonergic dysfunction following cessation of ecstasy use.[207]

The degree of any lasting dysfunction or neurotoxicity caused by MDMA is thought to be a function of the bioenergetic stress undergone during acute intoxication.[221] This theory has led to the hypothesis that there are mediating factors for the bioenergetic stress experienced, and thus the vulnerability or resilience an individual may have to neurotoxicity, beyond the MDMA dose per session and frequency of use. These factors include: ambient temperature and level of exertion (increases of each may promote neurotoxicity), poly-drug use (with stimulants likely to promote neurotoxicity[222,223]) and others ranging from users' genetics and nutritional status to how well rested they are.[224]

A recent study suggests that people's age when they first used ecstasy may be strongly linked to brain changes brought about by ecstasy, with those first exposed while their brains were still developing showing greater apparent deficits. The authors suggest that these age-related differences may reflect differences in the maturation stage of the 5-HT projection fields at the time of first exposure and enhanced outgrowth of the 5-HT system due to 5-HT's neurotrophic effects.[225]

Some entactogenic NPS, for example 4-MTA,[49] have been referred to in the literature as 'non-neurotoxic' analogues of MDMA,[226,227] and some were developed for this purpose.[228] However, these assessments were based on pre-clinical evidence, and evidence from long-term human use is not available to confirm that these drugs do

not cause serotonergic neurotoxicity. Animal and in vitro evidence suggests that among MDMA-like drugs, some are likely to be more neurotoxic (e.g. MDA) and some less neurotoxic (e.g. MDEA) than MDMA.[18]

10.13.2. Cognitive deficits

A number of studies have compared the performance of community samples of ecstasy users (current or past) against that of matched controls on many standard tests of cognitive performance. Weaker performance in certain domains has been identified in the ecstasy users, with the greatest and most consistent effects seen on aspects of memory and recall,[23] such as verbal memory[213] and visual paired associate learning.[229]

One explanation for the poorer performance of the ecstasy users is typically considered to be serotonergic neurotoxicity associated with the drug (see above). However, there is no consensus on this,[26] with many findings open to alternative, non-causal, interpretations, such as confounding cannabis use, or tendencies towards impulsivity and boredom leading to both ecstasy use and poorer performance on tests.[230]

The weaker performance of ecstasy users remains within 'normal' limits, according to some,[230] and deficits appear to be specific to certain domains rather than general, with one meta-analysis finding general intelligence unaffected and no impairments seen in simple cognitive functions like basic attention and reaction times.[23]

Deficits in verbal memory have been identified, whereas deficits in executive function and visual memory have been identified in some studies but not others.[230] The performance of users typically overlaps substantially with the performance of controls, and uncertainty and controversy remain over the clinical significance and real-world impact of the apparent deficits identified in these samples.[25,27]

A relatively high intensity of use may be necessary to produce significant deficits. In one study, which excluded anyone with significant poly-drug or alcohol use from the ecstasy-user sample, and which used controls who also shared the 'rave' lifestyle, no marked deficits were found. The authors argued that the confounding influences of poly-drug use and lifestyle may lead to overestimation of the harm associated with ecstasy.[231] However, in response it has been argued that this study was nonetheless consistent with the serotonergic neurotoxicity of ecstasy causing cognitive deficits, since it was not highly powered enough (with fewer than 50 users) to show subtle deficits associated with an average lifetime history of use.[204]

10.13.3. Psychiatric symptoms and harms

Community samples of current or past ecstasy users have been compared with matched controls on measures of psychiatric and psychological health. A study has shown poorer results among ecstasy users on several of these indices.[232] MDMA acutely increases cortisol levels, especially when the bioenergetic stress is magnified by behaviour and environment, but recent studies have also associated ecstasy use with more chronic increases in cortisol and related dysfunction of the

hypothalamic–pituitary–adrenal axis. This is in turn has been linked in chronic users to symptoms of distress, anxiety, aggression[233] and impaired coping.[234,235]

A meta-analysis in 2005 of 25 studies found a small but significant link between ecstasy use and depressive symptoms. However, the authors noted several methodological limitations and showed that publication bias may have occurred. They concluded that any effect of ecstasy on depression is unlikely to be clinically significant.[236] More recently, in a sample of 3880 disadvantaged Canadian adolescents, those who self-reported ecstasy use were more likely to have elevated depression symptoms one year later (odds ratio 1.5) and those who used MDMA with methamphetamine had even higher rates (odd ratio 1.9).[237] However, studies have shown that circumstances such as a deprived home environment can provide a partial or even complete explanation for the higher incidence of depressive symptoms in ecstasy users.[238,239]

A US study using a national sample reported that suicide risk appears to be elevated among adolescent users of ecstasy, almost twice that of users of other illicit drugs and nine times the risk among non-users.[183]

A number of factors may be associated with long-term harms. A study by Soar et al. found that the 57 people who reported their ecstasy use as having caused them problems (such as increased depression, somatisation and anxiety) did not differ from those who reported no harm in the duration of their use of ecstasy. However, those who reported problems also reported higher doses, in a pattern the authors call 'binge consumption', without further defining this.[240]

Concomitant use of other drugs is a confounding factor[133] that may explain much of the apparent heightened prevalence of various markers of psychopathology, such as depression and anxiety experiences.[241] Cannabis use, for example, has been found to mediate this relationship.[242] Early onset of cannabis use,[239] and tobacco use, have been shown to correlate with greater anxiety among ecstasy users, where neither lifetime nor recent ecstasy use did.[239] However, in one sample of 30 users, the users were not more likely than controls to report pre-existing depression or anxiety symptoms.[243]

The come-down period after ecstasy use is characterised by low mood and serotonin depletion, and it is possible that, for people vulnerable to depressive symptoms, this could exacerbate symptoms or cause suicidality.[23]

In an experimental set-up, 12 male ecstasy users performed a laboratory task involving monetary rewards. They were more 'aggressive' and 'irritable' than controls towards fictional co-players. It is not possible to exclude personality factors that pre-existed ecstasy use, and it is uncertain how this 'aggression' would translate to real-world face-to-face interactions.[233]

In addition to this evidence of poorer mental health in samples of ecstasy users, mostly relating to subtle, subclinical differences, there is evidence from case reports of more profound psychiatric disturbances and disorders in individual users. One paper detailed two case studies of severe obsessive-compulsive disorder developing in chronic heavy users of ecstasy, leading, in one case, to depression with psychotic features, and, in the other, to psychosis.[244] The former patient (a 16-year-old female

who took four or five tablets per week for a year) was judged to have vulnerabilities to mental disorder, but the second patient did not (a 23-year-old male who took one or two tablets a week for more than two years). Both cases resolved with treatment. The authors conclude that causation cannot be determined, but is suggested by the case histories.

10.13.4. Dependence and withdrawal

While ecstasy is generally considered to have some potential for dependence,[3] use is often self-limiting and focused around weekend activities.[3] Reasons suggested for the low dependence potential include the relatively long period of recovery after one dose.[24]

It has been argued that although the physiological basis of MDMA dependence is relatively weak in comparison with some other drugs, other factors related to the behavioural and psychological aspects of reward and dependence may have a relatively greater contribution to dependence for ecstasy than for other drugs.[245]

Users may fulfil dependence criteria,[246–251] develop problematic chronic use patterns, have concerns about their use and seek treatment.[245] Several studies have demonstrated some features of dependence among ecstasy users, such as worrying about use, thinking use was out of control and finding it difficult abstain.[245,247]

A number of studies have shown that approximately one in five users have been found to be potentially dependent,[73,249,252,253] although studies which carried out detailed investigation of withdrawal symptoms have shown higher rates, as much as 43% in a US study of adolescents and young adults,[248,250] and as high as 64% in a study using DSM-IV criteria for amphetamines dependence.[253]

Some studies have suggested that how ecstasy is used, rather than how often, may be of key importance in ecstasy dependence, with 'binge' use and higher doses being associated with dependence.[247] Users who 'binge', who use ecstasy more frequently, and who experience more social and physical harm are more likely to become dependent users.[96]

Ecstasy 'craving' does not tend to follow the pattern typical with other drugs, as a symptom of dependence, but instead resembles anticipation of an enjoyed activity, typically being low during the week, but rising in the hours before weekend use.[90]

A withdrawal syndrome with ecstasy has been reported. However, it has been argued that the wide between-study variations in the incidence of withdrawal symptoms indicate the need for improved distinction between the short- and the long-term effects of MDMA in standardised assessment tools, despite recent advances. As with other stimulants, the period following acute use is marked by a number of phases: an initial dysphoric 'crash', followed, in chronic users, by an extended 'withdrawal' phase, marked by anhedonia and anergia.[254] It has been argued that the application by some studies of withdrawal criteria related to the ecstasy come-down may have led to inflation of estimates of rates of potential dependence and withdrawal.[255] While 'true' withdrawal symptoms lead to users taking more of the drug to relieve them, adverse

effects following an episode of ecstasy use have been seen as one reason why heavy users sometimes spontaneously quit ecstasy.[83]

Some animal studies have shown that chronic use can lead to ecstasy acting increasingly like an addictive stimulant. If chronic use of MDMA causes significant serotonergic damage but little or no dopaminergic damage (as supported by brain imaging[212]), then the dopaminergic effects may become more prominent than the serotonergic ones, similar to amphetamines with greater addictive potential.[256] This is partially supported by user experiences; many report 'losing the magic'[83] of the serotonergic effects with overuse and, outside the academic literature, users of drugs fora note how, after overuse, MDMA feels more typically amphetamine-like.[257]

Ecstasy dependence presents unique features.[247] In an online survey promoted to users of a dance-music website, ecstasy users were *more* likely than users of cocaine, ketamine or mephedrone to endorse three or more DSM-IV criteria, yet reported less harm, more pleasure and less desire to seek help than users of these other club drugs.[246]

Ecstasy is rarely reported as an individual's principal problem drug,[247] with 201 people presenting to drug treatment services in England (fewer than 0.1%) in 2013/14 citing ecstasy as the main problem drug they used.[84] Although ecstasy is rarely a primary problematic drug, users of ecstasy are more likely than other drug users to have experienced substance use disorders in the past year involving drugs other than ecstasy.[258] This was the case for 7 out of 10 ecstasy users in an American population sample.[258]

10.13.5. Sleep problems

A history of ecstasy use has been linked to poorer sleep in some studies but other studies have found no differences.[23,259,260] Dysfunctional sleep processes may be involved in the memory deficits associated with ecstasy use.[261]

10.13.6. Vascular problems

The typical surge in blood pressure that ecstasy causes may, over time, damage the blood vessels, in particular the walls of aneurysms and arteriovenous malformations.[23] This could lead to haemorrhage.[262] Therefore, patients with aneurysms, or any other history of vascular disorders, should be strongly advised of the risks from any drug with a hypertensive effect.

10.13.7. Heart disease

A link between heavy, chronic MDMA use and valvular heart disease has been proposed, due directly to its serotonergic effects.[263,264] Activation of the 5-HT_{2B} receptor in heart valves by (now obsolete) serotonergic pharmaceuticals such as fenfluramine and ergotamine have been demonstrated to cause cell proliferation, fibrotic thickening and valve dysfunction.[265] There is some limited evidence that ecstasy may be capable

of causing such reactions in chronic, heavy users. A blinded study using echocardiography to identify abnormalities reported that MDMA may lead to mild to moderate valvular heart disease and valvular strands.[264]

A 33-year-old male smoker with an exceptionally high level of lifetime ecstasy use (several pills per week since the age of 17)[266] reported shortness of breath and chest pain. He had severe mitral valve disease, with fibrotic thickening of the leaflets and resulting severe regurgitation, necessitating a valve replacement. It was suggested that the lack of reports of similar cases may be explained by the typically short 'ecstasy career' of most users, and the potential reversibility of the valve damage.[263]

In addition to valvular heart disease, chronic ecstasy use has been linked to cardiomyopathy more generally,[263] although the evidence remains inconclusive. A retrospective analysis of autopsy records shows that the hearts of people who had MDMA in their bodies at post-mortem were more likely to have enlarged hearts, consistent with myocardial hypertrophy, as seen in users of cocaine and methamphetamine. However, this study did not appear to be controlled in a way that could exclude the confounding factor of poly-drug use.[267] A single case study of dilated cardiomyopathy associated with ecstasy has been reported.[189]

10.14. Management of chronic harms

10.14.1. Treatments for harmful use and dependence

As with other ATS, the treatment of harmful ecstasy use is primarily psychosocial. No specific guidelines for psychosocial intervention have been described and validated for chronic ecstasy users, but for general guidance on treatment options see Chapter 2.

In most cases, chronic ecstasy users will be poly-drug users, and existing interventions would be unlikely to focus on ecstasy in isolation. For example, an intervention in the form of 45–60 minutes of structured motivational discussion was trialled in young stimulant users, most of whom had recently used ecstasy and cocaine, and most of whom were also regular users of cannabis and alcohol.[268] This discussion included exploration of the individual's pattern of use, 'good' and 'bad' effects of use, plans for behaviour change, likely outcomes of this and, for users with no immediate plans to change behaviour, reflection on what future scenarios would lead to a change (boundary setting).[268] In this study, the majority (59%) of participants did report making efforts to reduce or cease their stimulant use following the intervention, but 41% of the control group did as well. Average number of days with ecstasy use in the previous 90 days fell from around 18 at baseline to around 8 at 6-month follow-up, and average dose fell from more than 2 tablets per session to around 1.5, with no significant difference seen between intervention and control groups.[268] Both the intervention and the control groups participated in baseline self-assessment and read health information, so the authors speculate that while there was no additional benefit from the intervention, contact with personnel and actions that focus attention on substance use may be enough to change behaviour.[268]

Similar results were found in a trial aiming to reduce ecstasy use among Australian university students. A 50% reduction in use and a 20% reduction in reported severity of harm were recorded 24 weeks after 'motivational enhancement therapy', but the same changes followed the control condition, a 15-minute information session.[269] Another brief intervention for regular users did not produce significant reductions in quantity or frequency of use compared with the control condition (assessment only), but did significantly reduce reported symptoms of dependence, and a greater proportion (16%) achieved abstinence, although the study was underpowered to show whether this was statistically significant.[270]

It has been noted that ecstasy users may not always accurately assess the harm that their drug use may be causing. The degree of apparent subclinical cognitive impairment in users appears to correlate not with the users' own assessments of how problematic their use is, but with the cumulative dose.[271]

However, most ecstasy users are aware that there are risks associated with the drug, and will have reflected upon, contextualised and rationalised that risk.[272,273] Reducing risk of harm by encouraging ecstasy users to cease use (especially early in their career[268]) may be difficult because acute harm may be perceived as rare, and chronic harm too subtle to motivate behavioural change.[274]

Consequently, it has been suggested that the best approach to reducing the risk of harm may be to encourage users to minimise their intake as much as possible.[274] This can be attempted by exploring users' experiences of the common unpleasant side-effects during and following use, and the disruption to other areas of life.[274]

This approach may be supported by sharing the evidence that lighter users tend to maintain the positive effects from ecstasy, without the negative effects increasing much over time, whereas heavy users tend to find that the positive effects reduce sharply and unpleasant effects rise over time, to the point where they outweigh the enjoyment.[83] Furthermore, typical user ratings of the positive effects from MDMA, as a function of dose, peak at around 100 mg (matching the content of a single average pill, as of 2012). Doses higher than one average pill, or equivalent, are more likely to decrease the positive effects, with adverse effects rising steeply above 120 mg.[66,68]

10.14.2. Treatment of depression in the context of MDMA use

It is recommended that clinicians prescribing antidepressants ask about recreational drug use and discuss the risk of drug interactions with those who use MDMA.[53]

One study has reported that citalopram strongly reduces the desired effects of MDMA, and other SSRIs would be likely to act similarly.[275] Despite this reduction in enjoyment, it is possible that SSRIs or SNRIs could increase the risks of MDMA toxicity.[53,172] In rats, some effects of MDMA, including hyperthermia, are not diminished by citalopram, suggesting that if human users attempt to compensate for diminished enjoyment with higher doses, the risk of acute harm could be increased.[276] Furthermore, the pharmacological effects of these drugs involve multiple actions on serotonin release and reuptake, and this complexity may allow for unexpected interactions, including serotonin syndrome.

MAOIs are strictly contraindicated in those who are unlikely to be able to abstain from ecstasy, because the combination has a high risk of causing serotonin syndrome.

10.15. Public health and harm reduction

Taking precautions and limiting dose were not found to be associated with experiencing a lower rate of adverse effects in a sample of 159 ecstasy poly-drug users, although most of this sample did not associate their use with adverse effects.[277]

Ecstasy users sometimes believe that MDMA itself is virtually risk-free when it is 'clean',[278] i.e. that adulteration is responsible for most or all of the adverse effects, minor and severe. It may be beneficial to tell patients that while adulteration certainly does contribute to the risks, pure MDMA can cause harm and death,[278] especially in high doses and in environments that contribute to overheating and overexertion.[99]

The principles for the reduction of the harms of ecstasy are similar to those for the reduction of ATS harms in general. In addition:

- Ecstasy users should be made aware that not all ecstasy pills contain the same dose, and that some tablets sold as ecstasy may contain other drugs, like PMA, which can be stronger, take longer to take effect and have higher risks.
- Users should be advised to start with a small dose (half or quarter of a tablet) to test a tablet to make sure there are no bad effects. They should be made aware that taking more than one pill at once might not increase the effect, but can make a come-down worse and increase the risk.
- Users should be advised take regular breaks from dancing and be sensitive to the possibility of exhaustion or overheating.
- Users should be advised to stay hydrated, but not to over-drink. It is best to take regular small sips of water and to drink no more than one pint per hour if dancing in a hot environment and half a pint if not dancing.
- Users should be advised to avoid mixing ecstasy with alcohol and other drugs, as this increases the risks.
- Users should be aware that serotonin syndrome is dangerous and that they should watch out for anyone who looks red hot and rigid and call 999 immediately. A person on antidepressants who also takes ecstasy pills will be at greater risk of serotonin syndrome.

10.16. Benzofurans

Other substances used for their 'emphathogenic', and well as their stimulant effects, include benzofurans, principally 6-(2-aminopropyl)benzofuran (6-APB) and 5-(2-aminopropyl)benzofuran (5-APB), but also the other substances listed in Table 10.5.

Benzodifurans include a group also known as the 'fly' drugs (for example, bromo-dragon fly, 2C-B-fly). They are hallucinogens and are discussed in Chapter 12.

Table 10.5. *Benzofuran derivatives*[17]

Chemical name		Street names or product brands (other names may be used locally)
5-(2-aminopropyl)benzofuran	5-APB[19]	Benzofury
6-(2-aminopropyl)benzofuran	6-APB[19]	Benzofury
5-(2-aminopropyl)-2,3-dihydrobenzofuran	5-APDB	Benzofury
6-(2-aminopropyl)-2,3-dihydrobenzofuran	6-APDB	Benzofury
1-(benzofuran-5-yl)-N-methylpropan-2-amine	5-MAPB	Benzofury
1-(benzofuran-6-yl)-N-methylpropan-2-amine	6-MAPB	Benzofury
1-(benzofuran-5-yl)-N-ethylpropan-2-amine	5-EAPB	Benzofury
Indanylalkylamine derivative[19]		
5-(2-aminopropyl)-2,3-dihydro-1H-indene	5-APDI IAP[19]	
Aminoindane derivatives[279]		
5,6-methylenedioxy-2-aminoindane	MDAI	Sparkle, Mindy[56]
5-iodo-2-aminoindan	5-IAI[116]	

In 2013, temporary legislation was passed relating to a number of benzofurans, indanylalkylamines and some 'NBOMe' compounds. Then in 2014, benzofurans were classified as Class B drugs under the 1971 Misuse of Drugs Act.

Benzofurans are ring-substituted amphetamine derivatives. Similar compounds have also appeared on the market in recent years, including 5- and 6-APB and their *N*-methyl derivatives. It was found that when these two materials were subjected to standard analytical techniques, it was not possible to distinguish between them. It is therefore very unlikely that those selling these drugs will know which form they are selling.[22]

Benzofurans were initially sold as 'legal highs', initially sometimes as 'legal ecstasy'. They were also sold as psychoactive substances in their own right, as 'Benzofury'. A study of internet sites showed that when mephedrone became controlled, the vendors aggressively promoted the sale Benzofury, as well as other new compounds (e.g. NRG-1 and NRG-2).[280] It has been reported that after the temporary drug order on these two substances, some websites no longer offered them, but described the ethyl analogue 5-EAPB (1-(benzofuran-5-yl)-*N*-ethylpropan-2-amine) as a legal alternative to 5- or 6-APB.22

The term Benzofury was originally applied to 6-APB; however, the name was later used interchangeably for 5-APB and 6-APB, as differentiation of the two isomers even in laboratory analysis is difficult.

10.16.1. Pharmacology

Understanding of benzorurans remains limited. Both 5- and 6-APB are phenethylamine-type materials and are related to methylenedioxyphenethylamines, such

as MDMA and MDA.[22] They are potent inhibitors of the reuptake of noradrenaline, dopamine and serotonin with a potency on monoamine transporters similar to that of MDMA.[281] An animal study has shown that 5-APB and 6-APB are potent full agonists at 5-HT_{2B} receptors.[282]

10.16.2. **Patterns of use, modes of ingestion**

It is not possible to determine the prevalence of use of benzofurans in the UK, but there was confirmation of its use in 2012, through analyses of pooled urine from London and north-west England.[283,284] There are also police reports of the use of 5- and 6-APB across north Scotland, with anecdotal evidence that they are more prevalent in remote areas. Their use in open prisons was reported by Avon and Somerset police. The 2013 reportfrom the Advisory Council on the Misuse of Drugs (ACMD) refers to anecdotal evidence that they were one of the most popular products sold in 'legal high' shops.[22] However, there was no evidence of significant use from the 2013 Global Drug Survey (only 3.2% of UK respondents reported use at some point in their lives and 2.4% use in the past year). Enquiries to the NPIS about benzofuran compounds are also infrequent.[97]

Similarly, in a personal communication from Professor F. Measham to the ACMD, she suggests that the prevalence of 5- and 6-APB use is very low in surveys conducted in night clubs and festivals.[22]

As with other substances, benzofurans are used as part of a wider drug repertoire. Information about 5 and 6-APB toxicity collected by the NPIS (prior to the ban) found that co-used substances (9 cases) included aMT (alpha-methyltryptamine, a tryptamine), etizolam (a thienodiazepine currently not controlled nor licensed as a medicine in the UK), 5-iodo-2-aminoindane (5,IAI) and 5,6-methylenedioxy-2-aminoindane (MDAI) (phenythelamines; aminoindane derivatives[97]).

Benzofurans are typically sold as a white powder, or in the form of pellets.[285] The ACMD review reports that in 2013 it was claimed by sellers on the web that pellets contained a 120 mg dose (sold at approximately £10 a pellet, with reductions for multiple purchases), while powder was sold for approximately £35 per gram.[22]

There are reports from police seizures from around the UK, as well as from the Serious Organised Crime Agency (SOCA) in 2011 and 2012, that many of the 'Benzofury' products did not in fact contain benzofurans, but rather piperazines, cathinone derivatives, benzocaine, D2PM or caffeine.[22]

10.16.3. Desired effects

Users report that the effects of 5-APB and 6-APB are comparable to those of MDMA but more intense.[286] and that they have mood-enhancing, emphathogenic and stimulant effects; they suggest that 5-APB is stronger than 6-APB.[22]

10.16.4. Clinical uses

A patent application has been made for benzofuran compounds and their use as antidepressants and anxiolytics The compounds inhibit serotonin reuptake, exhibit serotonin agonistic and antagonistic properties and are claimed to be suitable as antidepressants, anxiolytics, antipsychotics, neuroleptics and/or antihypertonics.[287]

10.16.5. Mortality

Analysis of data collected by NPSAD from 1977 to 2012 showed that there were 10 cases in 2011 and 2012 in which 'Benzofury' was identified at post-mortem, with the drug directly implicated in eight of these deaths. In nine cases, other drugs were also detected at post-mortem.[288]

10.16.6. Acute harms

Very little information has been published on the acute harms of benzofuran. It is suggested that such compounds produce clinical features similar to those of amphetamine, MDMA and mephedrone. Acute toxicity is characterised by serotonergic and sympathomimetic toxidrome, with nausea, agitation, anxiety, dizziness and hyperthermia.[289]

Adverse effects include nausea, sympathomimetic stimulation and agitation.[286] Stimulant features of acute intoxication with benzofurans are most common, followed by mental health disturbances.[97] A study of NPIS patient-specific telephone enquiries and user sessions for TOXBASE® from March 2009 to August 2013 was conducted, focusing on (2-aminopropyl)-2,3-dihydrobenzofurans. These data were compared with those of mephedrone collected over the same period. Ingestion of benzofuran was associated with similar toxic effects to those of amphetamines and cathinones. However, mental health disturbances and stimulant features were reported more frequently following reported ingestion of benzofuran compounds than after ingestion of mephedrone. However, there are limitations to these findings, resulting from a number of factors, including lack of analytical confirmation.[97]

Comparing the 57 patients who reported ingesting benzofuran compounds alone with 315 patients ingesting mephedrone alone, benzofurans were more often associated with stimulant features, including tachycardia, hypertension, mydriasis, palpitation, fever, increased sweating and tremor (72% v. 38%) and mental health disturbances (58% v. 38%). Other features reported after benzofuran compound ingestion included gastrointestinal symptoms (16%), reduced level of consciousness (9%), chest pain (7%) and creatinine kinase elevation (5%).[97]

One case report describes agitation and paranoia, but as a number of other drugs were ingested it is possible that another substance – or all – contributed to acute psychosis.[139]

It has been argued that the serotonin agonism of benzofuran raises the possibility that chronic use of this compound could be associated with valvular heart disease similar to that caused by fenfluramine and ergoline derivatives.[290,291]

For up-to-date guidance on the management of benzofuran acute toxicity, it is recommended that information be sought from the National Poisons Information Service (NPIS), specifically the NPIS 24-hour telephone service and the poisons information database TOXBASE®:

http://www.toxbase.org/Poisons-Index-A-Z/B-Products/Benzo-Fury/

It is recommended that relevant clinicians and departments are registered to receive these facilities.

Non-UK readers should consult their local or national guidelines.

10.16.7. Management of acute harms

A case with severe psychotic symptoms after use of 6-APB was successfully managed with benzodiazepines alone.[139]

10.16.8. Harm reduction

The harm reduction advise given for ATS and for MDMA is applicable here.

References

1 Nichols DE. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. *J Psychoactive Drugs.* 1986;18:305–13.

2 Sáez-Briones P, Hernández A. MDMA (3, 4-methylenedioxymethamphetamine) analogues as tools to characterize MDMA-like effects: an approach to understand entactogen pharmacology. *Current Neuropharmacology.* 2013;11(5):521.

3 Hermle L, Spitzer M, Borchardt D, Kovar KA, Gouzoulis E.Psychological effects of MDE in normal subjects. Are entactogens a new class of psychoactive agents? *Neuropsychopharmacology*. 1993 Feb;8(2):171–6.

4 Bedi GD. Is ecstasy an 'empathogen'? Effects of MDMA on prosocial feelings and identification of emotional states in others. *Biol Psychiatry.* 2010;68(12):1134–40.

5 Iversen LL. *Speed, Ecstasy, Ritalin: The Science of Amphetamines*. Oxford University Press, 2006.

6 Iversen L, White M, Treble R. Designer psychostimulants: pharmacology and differences. Neuropharmacology. 2014 Dec;87:59–65. doi: 10.1016/j.neuropharm.2014.01.015.

7 Warrick BJ, Wilson J, Hedge M, Freeman S, Leonard K, Aaron C. Lethal serotonin syndrome after methylone and butylone ingestion. *J Med Toxicol.* 2012 Mar;8(1):65–8. doi: 10.1007/s13181-011-0199-6.

8 Kalasinsky KS, Hugel J, Kish SJ. Use of MDA (the 'love drug') and methamphetamine in Toronto by unsuspecting users of ecstasy (MDMA). *J Forensic Sci.* 2004 Sep;49(5):1106–12.

9 Parrott AC. Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. *Psychopharmacology.* 2004;173:234–41.

10 Cole JC, Bailey M, Sumnall HR, Wagstaff GF, King LA. The content of ecstasy tablets: implications for the study of their long-term effects. *Addiction.* 2002;97:1531–6.

11 Cheng WC, Poon NL, Chan MF. Chemical profiling of 3,4-methylenedioxymethamphetamine (MDMA) tablets seized in Hong Kong. *J Forensic Sci.* 2003;48:1249–59.

12 Tanner-Smith EE. Pharmacological content of tablets sold as 'ecstasy': results from an online testing service. *Drug Alcohol Depend*. 2006 Jul 27;83(3):247–54.

13 Boulanger-Gobeil C, St-Onge M, Laliberté M, Auger PL. Seizures and hyponatremia related to ethcathinone and methylone poisoning. *J Med Toxicol.* 2012;8(1):59–61.

14 Elliott S, Smith C. Investigation of the first deaths in the United Kingdom involving the detection and quantitation of the piperazines BZP and 3-TFMPP. *J Analytic Toxicol.* 2008;32(2):172–7.

15 O'Connor LC, Torrance HJ, McKeown DA, Simpson K. Analysis of 'ecstasy' tablets from Police Scotland in the Glasgow area – November 2013 to July 2014.

16 Gallagher CT, Assi S, Stair JL, Fergus S, Corazza O, Corkery JM, Schifano F. 5,6-methylenedioxy-2-aminoindane: from laboratory curiosity to 'legal high'. *Hum Psychopharmacol Clin Exp.* 2012;27:106–12.

17 Advisory Council on the Misuse of Drugs (ACMD). *6-APB and 5-APB: A Review of the Evidence of Use and Harm*. 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/204808/J_TCDO_report_on_5-6APB_and_NBOMe_compounds.pdf (accessed 5 September 2014).

18 Freudenmann, Roland W, Spitzer M. The neuropsychopharmacology and toxicology of 3,4-methylenedioxy-N-ethyl-amphetamine (MDEA). CNS Drug Reviews 2004;10(2):89–116.

19 King LA. New phenethylamines in Europe. Drug Test Analysis. 2014;6:808–18.

20 Winstock AR, Wolff K, Ramsey J. 4-MTA: a new synthetic drug on the dance scene. Drug *Alcohol Dependence.* 2002;67(2):111–15.

21 Zaitsu K, Katagi M, Tatsuno M, Sato T, Tsuchihashi H, Suzuki K. Recently abused β-keto derivatives of 3, 4-methylenedioxyphenylalkylamines: a review of their metabolisms and toxicological analysis. *Forensic Toxicol.* 2011;29(2):73–84.

22 Advisory Council on the Misuse of Drugs (ACMD). Benzofu*rans: A Review of the Evidence of Use and Harm. 2013*. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/261783/Benzofuran_compounds_report.pdf (accessed 6 September 2014).

23 Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, Zawada A, Somerville M. The harmful health effects of recreational ecstasy: a systematic review of observational evidence. *Health Technol Assess*. 2009 Jan;13(6). doi: 10.3310/hta13050.

24 Parrott AC. Human psychobiology of MDMA or 'ecstasy': an overview of 25 years of empirical research. *Hum Psychopharmacol.* 2013 Jul;28(4):289–307. doi: 10.1002/hup.2318.

25 Parrott AC. MDMA, serotonergic neurotoxicity, and the diverse functional deficits of recreational 'ecstasy'users. *Neurosci Biobehav Rev.* 2013 Sep;37(8):1466–84. doi: 10.1016/j.neubiorev.2013.04.016.

26 Doblin R, Greer G, Holland J, Jerome L, Mithoefer MC, Sessa B. A reconsideration and response to Parrott AC (2013) 'Human psychobiology of MDMA or "ecstasy": an overview of 25 years of empirical research'. *Hum Psychopharmacol Clin Exp.* 2014;29:105–8. doi: 10.1002/hup.2389.

27 Cole JC. MDMA and the 'ecstasy' paradigm. *J Psychoactive Drugs.* 2014;46(1):44–56.

28 Bombe A, Dave-Momin N, Shah N, Sonavane S, Desousa A. MDMA dependence: a case report from urban India. *History.* 2013;3(9):32–3.

29 Potash MN. Persistent psychosis and medical complications after a single ingestion of MDMA 'ecstasy': a case report and review of the literature. *Psychiatry (Edgmont).* 2009;6(7):40.

30 De la Torre RM. Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition. *Therapeutic Drug Monitoring.* 2004;26(2):137–44.

31 Docherty JR, Green AR. The role of monoamines in the changes in body temperature induced by 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and its derivatives. *Br J Pharmacol.* 2010 Jul;160(5):1029–44. doi: 10.1111/j.1476-5381.2010.00722.x.

32 Hysek CM, Simmler LD, Ineichen M, Grouzmann E, Hoener MC, Brenneisen R, Huwyler J, Liechti ME. The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA ('ecstasy') in humans. *Clin Pharmacol Ther*. 2011 Aug;90(2):246–55. doi: 10.1038/clpt.2011.78.

33 Roiser JP. Association of a functional polymorphism in the serotonin transporter gene with abnormal emotional processing in ecstasy users. *Am J Psychiatry.* 2005;162(3):609–12.

34 Pardo-Lozano R, Farré M, Yubero-Lahoz S, O'Mathúna B, Torrens M, Mustata C, Pérez-Mañá C, Langohr K, Cuyàs E, Carbó Ml, de la Torre R. Clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): the influence of gender and genetics (CYP2D6, COMT, 5-HTT). *PLoS ONE*. 2012;7(10):e47599.

35 Baylen CA. A review of the acute subjective effects of MDMA/ecstasy. *Addiction.* 2006;101(7):933–47.

36 Gouzoulis-Mayfrank E. Differential actions of an entactogen compared to a stimulant and a hallucinogen in healthy humans. *Heffter Rev Psychedelic Res.* 2001;2:64–72.

37 Shulgin AT. History of MDMA. In: Peroutka SJ, ed *Ecstasy: The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA*, pp. 1–20. Kluwer Academic, 1990.

38 Greer GR, Tolbert R. The therapeutic use of MDMA. In: Peroutka SJ, ed *Ecstasy: The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA*, pp. 21–36. Kluwer Academic, 1990.

39 Sessa B. Is there a case for MDMA-assisted psychotherapy in the UK? *J Psychopharmacology.* 2007;21(2):220–4.

40 Harris DS, Baggott M, Mendelson JH, Mendelson JE, Jones RT. Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology (Berl).* 2002 Aug;162(4):396–405. Epub 2002 Jun 27.

41 Dumont GJ. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3, 4-methylenedioxymethamphetamine) administration. *Social Neuroscience.* 2009;4(4):359–66.

42 Peiró AM. Human pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) after repeated doses taken 2 h apart. *Psychopharmacology.* 2013;225(4):883–93.

43 Yubero-Lahoz SRM. Sex differences in 3,4-methylenedioxymethamphetamine (MDMA; ecstasy)-induced cytochrome P450 2D6 inhibition in humans. *Clinical Pharmacokinetics.* 2011;50(5):319–29.

44 Vevelstad M, Oiestad EL, Middelkoop G, Hasvold I, Lilleng P, Delaveris GJ, et al. The PMMA epidemic in Norway: comparison of fatal and non-fatal intoxications. *Forensic Sci Int*. 2012;219:151–7.

45 Lurie Y, Gopher A, Lavon O, Almog S, Sulimani L, Bentur Y. Severe paramethoxymethamphetamine (PMMA) and paramethoxyamphetamine (PMA) outbreak in Israel. *Clin Toxicol (Phila)*. 2012;50:39–43.

46 Hill SL, Thomas SHL. Clinical toxicology of newer recreational drugs. *Clin Toxicol.* 2011;49:705–19.

47 Ling LH, Marchant C, Buckley NA, Prior M, Irvine RJ. Poisoning with the recreational drug paramethoxyamphetamine ('death'). *Med J Australia.* 2001;174:453–5.

48 De Letter EA, Coopman VAE, Cordonnier JACM, Piette MHA. One fatal and seven non-fatal cases of 4-methylthioamphetamine (4-MTA) intoxication: clinico-pathological findings. *Int J Legal Med.* 2001;114:352–6.

49 Elliot SP. Fatal poisoning with a new phenethylamine: 4-methylthioamphetamine (4-MTA). *J Anal Toxicol.* 2000;24:85–9.

50 Felgate HE, Felgate PD, James RA, Sims DN, Vozzo DC. Recent paramethoxyamphetamine deaths. *J Anal Toxicol.* 1998;22:169–72.

51 Lamberth PG, Ding GK, Nurmi LA. Fatal paramethoxy-amphetamine (PMA) poisoning in the Australian Capital Territory. *Med J Australia*. 2008;188:426.

52 Daws LC, Irvine RJ, Callaghan PD, Toop NP, White JM, BochnerF. Differential behavioural and neurochemical effects of para-methoxyamphetamine and 3,4-methylenedioxymethamphetamine in the rat. *Prog Neuropsychopharmacol Biol Psychiatry.* 2000;24:955–77.

53 Silins E, Copeland J, Dillon P. Qualitative review of serotonin syndrome, ecstasy (MDMA) and the use of other serotonergic substances: hierarchy of risk. *Aust NZ J Psychiatry*. 2007 Aug;41(8):649–55.

54 Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'). *Pharmacological Reviews.* 2003;55(3): 463–508.

55 Parrott AC, Lock J, Adnum L, Thome J. MDMA can increase cortisol levels by 800% in dance clubbers. *J Psychopharmacology.* 2013;27(1):113–14.

56 Corkery JM, Elliott S, Schifano F, Corazza O, Ghodse AH. MDAI (5,6-methylenedioxy-2-aminoindane; 6,7-dihydro-5Hcyclopenta[f][1,3]benzodioxol-6-amine; 'sparkle'; 'mindy') toxicity: a brief overview and update. *Hum Psychopharmacol Clin Exp.* 2013;28:345–55.

57 Brandt SD, Sumnall HR, Measham F, Cole J. Analyses of second generation 'legal highs' in the UK: initial findings. *Drug Test Anal.* 2010;2(8):377–82.

58 Greer GR, Tolbert R. A method of conducting therapeutic sessions with MDMA. *J Psychoactive Drugs.* 1998 Oct-Dec;30(4):371–9.

59 Oehen PR. A randomized, controlled pilot study of MDMA (±3, 4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorder (PTSD). *J Psychopharmacology*. 2013;27(1):40–52.

60 Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, Yazar-Klosinski B, Michel Y, Brewerton TD, Doblin R. Durability of improvement in posttraumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3, 4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *J Psychopharmacol.* 2013 Jan;27(1):28–39. doi: 10.1177/0269881112456611.

61 Johansen PØ, Krebs TS. How could MDMA (ecstasy) help anxiety disorders? A neurobiological rationale. *J Psychopharmacol*. 2009 Jun;23(4):389–91. doi: 10.1177/0269881109102787.

62 Parrott AC. The potential dangers of using MDMA for psychotherapy. *J Psychoactive Drugs* 2014; 46(1):37–43.

63 Capela JP. Molecular and cellular mechanisms of ecstasy-induced neurotoxicity: an overview. *Molecular Neurobiology.* 2009;39(3):210–71.

64 Office for National Statistics. *Drug Misuse: Findings from the 2013 to 2014 CSEW* (2nd edition). Home Office, 2014. https://www.gov.uk/government/statistics/drug-misuse-findings-from-the-2013-to-2014-csew (accessed 10 September 2014).

65 Schifano FJ. Ecstasy (MDMA, MDA, MDEA, MBDB) consumption, seizures, related offences, prices, dosage levels and deaths in the UK (1994–2003). *J Psychopharmacology.* 2006;20(3):456–63.

66 Davies C, Murray R, eds. *United Kingdom Drug Situation: Annual Report to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 2013.* United Kingdom Focal Point at Public Health England, 2013.

67 McElrath K, Van Hout MC. A preference for mephedrone: drug markets, drugs of choice, and the emerging 'legal high' scene. *J Drug Issues.* 2011;41(4):487–507.

68 Brunt TM, Koeter MW, Niesink RJ, van den Brink W. Linking the pharmacological content of ecstasy tablets to the subjective experiences of drug users. *Psychopharmacology (Berl).* 2012 Apr;220(4):751-62. doi: 10.1007/s00213-011-2529-4.

69 Hansen DB. 'Weddings, parties, anything…': a qualitative analysis of ecstasy use in Perth, Western Australia. *Int J Drug Policy*. 2001;12(2):181–99.

70 Smith ZK, Moore K, Measham F. MDMA powder, pills and crystal: the persistence of ecstasy and the poverty of policy. *Drugs Alcohol Today.* 2009;9(1):13–19.

71 Deehan A. *Calculating the Risk: Recreational Drug Use Among Clubbers in the South East of England.* Home Office, 2003.

72 Breen CL. Alcohol use and risk taking among regular ecstasy users. *Substance Use Misuse.* 2006;41(8):1095–109.

73 Winstock AR. Drugs and the dance music scene: a survey of current drug use patterns among a sample of dance music enthusiasts in the UK. *Drug Alcohol Dependence*. 2001;64(1):9–17.

74 Halpern P, Moskovich J, Avrahami B, Bentur Y, Soffer D, Peleg K. Morbidity associated with MDMA (ecstasy) abuse – a survey of emergency department admissions. *Hum Exp Toxicol.* 2011 Apr;30(4):259–66. doi: 10.1177/0960327110370984.

75 Horyniak D, Degenhardt L, Smit de V, Munir V, Johnston J, Fry C, Dietze P. Pattern and characteristics of ecstasy and related drug (ERD) presentations at two hospital emergency departments, Melbourne, Australia, 2008–2010. *Emerg Med J.* 2014 Apr;31(4):317–22. doi: 10.1136/emermed-2012-202174.

76 de Win MM. Sustained effects of ecstasy on the human brain: a prospective neuroimaging study in novel users. *Brain.* 2008;131(11):2936–45.

77 ter Bogt TF, Engels RC. 'Partying' hard: party style, motives for and effects of MDMA use at rave parties." *Substance Use Misuse.* 2005;40(9-10):1479–502.

78 Miller JM, Vorel SR, Tranguch AJ, Kenny ET, Mazzoni P, van Gorp WG, Kleber HD. Anhedonia after a selective bilateral lesion of the globus pallidus. *Am J Psychiatry*. 2006 May;163(5):786–8.

79 McGuire P, Fahy T. Chronic paranoid psychosis after misuse of MDMA ('ecstasy'). *BMJ*. 1991 Mar 23;302(6778):697.

80 Jansen KLR. Ecstasy (MDMA) dependence. *Drug Alcohol Dependence.* 1999;53(2):121–4.

81 Kouimtsidis CF. Neurological and psychopathological sequelae associated with a lifetime intake of 40,000 ecstasy tablets. *Psychosomatics*. 2006;47(1):86–7.

82 Kirkpatrick MG, Baggott MJ, Mendelson JE, Galloway GP, Liechti ME, Hysek CM, de Wit H. MDMA effects consistent across laboratories. *Psychopharmacology (Berl)*. 2014 Oct;231(19):3899–905. doi: 10.1007/s00213-014-3528-z.

83 O'Sullivan A, Parrott AC. Deteriorating cost–benefit ratios for ecstasy/MDMA with repeated usage. *Open Addiction J.* 2011;4:38–9.

84 Public Health England. *Drug Statistics from the National Drug Treatment Monitoring System (NDTMS): 2012-2013.* PHE, 2013.

85 Public Health England. *Drug Statistics from the National Drug Treatment Monitoring System (NDTMS): 2013-2014.* PHE, 2014.

86 Scholey AB, Parrott AC, Buchanan T, Heffernan TM, Ling J, Rodgers J. Increased intensity of ecstasy and polydrug usage in the more experienced recreational ecstasy/MDMA users: a WWW study. *Addictive Behaviors.* 2004;29(4):743–52.

87 Wu L-TA. The variety of ecstasy/MDMA users: results from the National Epidemiologic Survey on alcohol and related conditions. *Am J Addictions*. 2009;*18(6):*452–61.

88 Office for National Statistics. *Drug Misuse Declared: Findings from the 2011/12 Crime Survey of England and Wales* (2nd edition). Home Office, 2013. https://www.gov.uk/government/statistics/drug-misuse-declared-findings-from-the-2011-to-2012-crime-survey-for-england-and-wales-csew-second-edition (accessed 10 September 2014).

89 Kinner SA, George J, Johnston J, Dunn M, Degenhardt L. Pills and pints: risky drinking and alcohol-related harms among regular ecstasy users in Australia. *Drug Alcohol Review*. 2012;31:273–80.

90 Hopper JW. Incidence and patterns of polydrug use and craving for ecstasy in regular ecstasy users: An ecological momentary assessment study. *Drug Alcohol Depend.* 2006;85(3):221–35.

91 Winstock A. *The Global Drug Survey 2014 Findings*. Global Drug Survey, April 2014. http://www.globaldrugsurvey.com/facts-figures/the-global-drug-survey-2014-findings.

92 Personal communication, John Ramsey.

93 Pearson G. Normal drug use: ethnographic fieldwork among an adult network of recreational drug users in inner London. *Substance Use Misuse.* 2001;36(1–2):167–200.

94 Drugs-Forum. MDMA - Snorting vs Oral, 2005. https://www.drugs-forum.com/forum/showthread.php?t=26751(accessed 2 July 2014).

95 Drug-Forum. (2009) MDMA Opinions - Insufflation vs Ingestion of MDMA. http://www.drugs-forum.com/forum/showthread.php?t=74402 (accessed 2 July 2014).

96 Topp L, Hando J, Dillon P, Roche A, Solowij N. Ecstasy use in Australia: patterns of use and associated harm. *Drug Alcohol Depend.* 1999;55:105–15.

97 Kamour A, James D, Lupton DJ, Cooper G, Eddleston M, Vale A, Thompson JP, Thanacoody R, Hill SL, Thomas SH. Patterns of presentation and clinical features of toxicity after reported use of ([2-aminopropyl]-2,3-dihydrobenzofurans), the 'benzofuran' compounds. A report from the United Kingdom National Poisons Information Service. *Clin Toxicol (Phila).* 2014 Dec;52(10):1025–31. doi: 10.3109/15563650.2014.973115.

98 Morefield KM. Pill content, dose and resulting plasma concentrations of 3,4-methylendioxymethamphetamine (MDMA) in recreational 'ecstasy' users. *Addiction.* 2011;106(7):1293–300.

99 Armenian PT. Multiple MDMA (ecstasy) overdoses at a rave event: a case series. *J Intensive Care Medicine*. 2013;28(4):252–8.

100 Sherlock K, Wolff K, Hay AW, Conner M. Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department. *J Accident Emergency Medicine.* 1999;16(3):194–7.

101 Carhart-Harris RL, Murphy K, Leech R, Erritzoe D, Wall MB, Ferguson B, Williams LT, Roseman L, Brugger S, De Meer I, Tanner M, Tyacke R, Wolff K, Sethi A, Bloomfield MA, Williams TM, Bolstridge M, Stewart L, Morgan C, Newbould RD, Feilding A, Curran HV, Nutt DJ. The effects of acutely administered 3, 4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level–dependent resting state functional connectivity. Biol Psychiatry. 2014 Jan 10. pii: S0006-3223(14)00005-5. doi: 10.1016/j.biopsych.2013.12.015.

102 Singer LT, Linares TJ, Ntiri S, Henry R, Minnes S. Psychosocial profiles of older adolescent MDMA users. *Drug Alcohol Depend*. 2004;74(3):245–52.

103 Fox H, Parrott AC, Turner JJD. Ecstasy/MDMA related cognitive deficits: a function of dosage rather than awareness of problems. *J Psychopharmacology.* 2001;15:273–81.

104 Liechti ME, Kunz I, Kupferschmidt H. Acute medical problems due to ecstasy use. *Swiss Medical Weekly.* 2005;135(43-44): 652–7.

105 Hall AP, Henry JA. Acute toxic effects of 'ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management. *Br J Anaesthesia* 2006;96(6):678–85.

106 Winstock A. *Drug Pleasure Ratings*. Global Drug Survey, April 2014. http://www.globaldrugsurvey.com/facts-figures/the-net-pleasure-index-results.

107 Parrott AC. MDMA and methamphetamine: some paradoxical negative and positive mood changes in an acute dose laboratory study. *Psychopharmacology*. 2011;215(3):527–36.

108 Zemishlany ZD. Subjective effects of MDMA ('ecstasy') on human sexual function. *European Psychiatry*. 2001;16(2):127–30.

109 Kennedy KE. Ecstasy and sex among young heterosexual women: a qualitative analysis of sensuality, sexual effects, and sexual risk taking. *Int J Sexual Health*. 2010;22(3):155–66.

110 Passie T, Hartmann U, Schneider U, Emrich HM, Krüger TH. Ecstasy (MDMA) mimics the post-orgasmic state: impairment of sexual drive and function during acute MDMA-effects may be due to increased prolactin secretion. *Med Hypotheses*. 2005;64(5):899–903.

111 Bourne ARD. *The Chemsex Study: Drug Use in Sexual Settings Among Gay and Bisexual Men in Lambeth, Southwark and Lewisham, London*. Sigma Research, London School of Hygiene and Tropical Medicine, 2014.

112 Concar D. Ecstasy has dramatic effect on Parkinson's symptoms. *New Scientist*. 2002;17(2368):14.

113 Johnston TH, Millar Z, Huot P, Wagg K, Thiele S, Salomonczyk D, Yong-Kee CJ, Gandy MN, McIldowie M, Lewis KD, Gomez-Ramirez J, Lee J, Fox SH, Martin-Iverson M, Nash JE, Piggott MJ, Brotchie JM. A novel MDMA analogue, UWA-101, that lacks psychoactivity and cytotoxicity, enhances l-DOPA benefit in parkinsonian primates. *FASEB J*. 2012 May;26(5):2154–63. doi: 10.1096/fj.11-195016.

114 Moonzwe LS, Schensul JJ, Kostick KM. The role of MDMA (ecstasy) in coping with negative life situations among urban young adults. *J Psychoactive Drugs*. 2011;43(3):199–210.

115 Sessa B. Can psychedelics have a role in psychiatry once again? *Br J Psychiatry*. 2005;186(6):457–8.

116 Coppola M, Mondola R. Is the 5-iodo-2-aminoindan (5-IAI) the new MDMA? *J Addict Res Ther*. 2012;3:134.

117 Nichols DE, Oberlender R. Structure-activity relationships of MDMA and related compounds: a new class of psychoactive drugs?" *Ann NY Acad Sci*. 1990;600(1):613–23.

118 Al-Samarraie MS, Vevelstad M, Nygaard IL, Bachs L, Mørland J. [Intoxation with paramethoxymethamphetamine.] [Article in Norwegian.] *Tidsskr Nor Laegeforen*. 2013 May 7;133(9):966–9. doi: 10.4045/tidsskr.12.0417.

119 Raznahan M, Hassanzadeh E, Houshmand A, Kashani L, Tabrizi M, Akhondzadeh S. Change in frequency of acute and subacute effects of ecstasy in a group of novice users after 6 months of regular use. *Psychiatr Danub*. 2013 Jun;25(2):175–8.

120 Parrott AC. Recreational ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. *Pharmacology Biochemistry Behavior*. 2002;71(4):837–44.

121 Young SN, Regoli M, Leyton M, Pihl RO, Benkelfat C. The effect of acute tryptophan depletion on mood and impulsivity in polydrug ecstasy users. *Psychopharmacology (Berl)*. 2014 Feb;231(4):707–16. doi: 10.1007/s00213-013-3287-2.

122 Travers KR, Lyvers M. Mood and impulsivity of recreational ecstasy users in the week following a 'rave'. *Addiction Research Theory*. 2005;13(1): 43-52.

123 Shulgin AT, Shulgin A. 4-MA; PMA; 4-methoxyamphetamine. In: *PIHKAL: A Chemical Love Story* (Monograph 97), pp. 707–9. Transform Press, 1991.

124 Shulgin AT, Shulgin A. Methyl-MA. In: *PIHKAL: A Chemical Love Story* (Monograph 97), pp. 707–9. Transform Press, 1991.

125 Office for National Statistics. *Deaths Related to Drug Poisoning in England and Wales, 2013*. 2014. http://www.ons.gov.uk/ons/dcp171778_375498.pdf (accessed February 2015).

126 Drugscope. *Business as Usual? A Status Report on New Psychoactive Substances (NPS) and Club Drugs in the UK*. 2014.

127 Cimbura G. PMA deaths in Ontario. *Can Med Association J*. 1974;110(11):1263.

128 BBC News. Seven deaths are linked to fake ecstasy tablets, police say. 10 July 2013. http://www.bbc.co.uk/news/uk-scotland-glasgow-west-23258117.

129 Rosenson J, Smollin C, Sporer KA, Blanc P, Olson KR. Patterns of ecstasy-associated hyponatremia in California. *Ann Emerg Med*. 2007 Feb;49(2):164–71, 171.e1.

130 Williams H, Dratcu L, Taylor R, Roberts M, Oyefeso A. 'Saturday night fever': ecstasy related problems in a London accident and emergency department. *J Accid Emerg Med.* 1998 Sep;15(5):322–6.

131 Luke LC, Dewar C, Bailey M, McGreevy D, Morris H, Burdett-Smith P. A little nightclub medicine: the healthcare implications of clubbing. *Emergency Med J.* 2002;19(6):542–5.

132 Milroy CM. 'Ecstasy' associated deaths: what is a fatal concentration?Analysis of a case series. *Forensic Sci Med Pathol.* 2011;7(3):248–52.

133 Gouzoulis-Mayfrank E. The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview. *J Psychopharmacology.* 2006;20(2):188–93.

134 Liechti ME. Gamma A, Vollenweider FX. Gender differences in the subjective effects of MDMA. *Psychopharmacology.* 2001;154(2):161–8.

135 Fineschi V, Masti A. Fatal poisoning by MDMA (ecstasy) and MDEA: a case report. *Int J Legal Med.* 1996;108(5):272–5.

136 Vecellio M, Schopper C, Modestin J. Neuropsychiatric consequences (atypical psychosis and complex-partial seizures) of ecstasy use: possible evidence for toxicity-vulnerability predictors and implications for preventative and clinical care. *J Psychopharmacol.* 2003 Sep;17(3):342–5.

137 Lin DL, Liu HC, Yin HL Recent paramethoxymethamphetamine (PMMA) deaths in Taiwan. *J Anal Toxicol.* 2007 Mar;31(2):109–13.

138 Gimeno Clemente C, Chiappini S, Claridge H, Corkery J, Goodair C, Loi B, Schifano F. The unregulated psychoactive compound: 'benzo fury'. *Current Drug Abuse Reviews.* 2013 Dec;6(4):285.

139 Chan WL, Wood DM, Hudson S, Dargan PI. Acute psychosis associated with recreational use of benzofuran 6-(2-aminopropyl) benzofuran (6-APB) and cannabis. *J Med Toxicol. 2013* Sep;9(3):278–81. doi: 10.1007/s13181-013-0306-y.

140 Weinmann W, Bohnert M. Lethal monointoxication by overdosage of MDEA. *Forensic Sci Int.* 1998 Jan 30;91(2):91–101.

141 Chen WH, Chui C, Yin HL. The antemortem neurobehavior in fatal paramethoxymethamphetamine usage. *Subst Abus.* 2012;33(4):366–72.

142 Spatt J, Glawar B, Mamoli B. A pure amnestic syndrome after MDMA ('ecstasy') ingestion. *J Neurol Neurosurg Psychiatry* 1997;62(4):418.

143 Meehan TJ, Bryant SM, Aks SE. Drugs of abuse: the highs and lows of altered mental states in the emergency department. *Emerg Med Clin North Am*. 2010 Aug;28(3):663-82. doi: 10.1*016/j.emc.2010.03.012*.

144 TOXBASE®. MDMA. http://www.toxbase.org/Poisons-Index-A-Z/M-Products/MDMA2/ (accessed 3 September 2014).

145 Drake WM, Broadhurst PA. QT-interval prolongation with ecstasy. *South African Med J. 1996;86*(2):180–1.

146 Hartung TK, Schofield E, Short AI, Parr MJA, Henry JA. Hyponatraemic states following 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') ingestion. *Q J Med. 20*02;95:431–7.

147 Dowling GP, McDonough ET, Bost RO. 'Eve' and 'ecstasy': a report of five deaths associated with the use of MDEA and MDMA. *JAMA*. 1987;257(12):1615–17.

148 Madhok A, Boxer R, Chowdhury D. Atrial fibrillation in an adolescent – the agony of ecstasy. *Pediatric Emergency Care.* 2003;19(5):348-9.

149 Qasim A, Townend J, Davies MK. Ecstasy induced acute myocardial infarction. *Heart*. 2001;85(6):e10.

150 Verhaert LLW. Methaemoglobinemia induced by MDMA? *Case Rep Pulmonology* 2011;2011:494328. doi: 10.1155/2011/494328. Epub 2011 Oct 19.

151 Mutlu H, Silit E, Pekkafali Z, Incedayi M, Basekim C, Kizilkaya E. 'Ecstasy' (MDMA)-induced pneumomediastinum and epidural pneumatosis. *Diagn Interv Radiol.* 2005;11(3):150–1.

152 Gungadeen A, Moor J. Extensive subcutaneous emphysema and pneumomediastinum after ecstasy ingestion. *Case Rep Otolaryngol.* 2013;2013:795867. doi: 10.1155/2013/795867.

153 Clause AL, Coche E, Hantson P, Jacquet LM. Spontaneous pneumomediastinum and epidural pneumatosis after oral ecstasy consumption. *Acta Clinica Belgica.* 2014;69(2):146–8.

154 James RA, Dinan A. Hyperpyrexia associated with fatal paramethoxyamphetamine (PMA) abuse. *Med Sci Law.* 1998;38(1):83–8.

155 Els A, Coopman VAE, Cordonnier JACM, Piette MHA, Chemiphar NV. One fatal and seven nonfatal

cases of 4-methylthioamphetamine (4-MTA) intoxication: clinico-pathological findings. In: Els A. Investigation of Fatalities Related to *the Use of 3,4-Methylenedioxymethamphetamine (MDMA, 'Ecstasy') and Analogues: Anatomo-Pathological and Thanato-Toxicological Approach*. PhD thesis, University of Ghent, 2002. http://lib.ugent.be/fulltxt/RUG01/000/745/574/RUG01-000745574_2010_0001_AC.pdf.

156 Pearson JM, Hargraves TL, Hair LS, Massucci CJ, Frazee CC 3rd, Garg U, Pietak BR. Three fatal intoxications due to methylone. *J Anal Toxicol.* 2012 Jul;36(6):444–51. doi: 10.1093/jat/bks043.

157 Campbell GA, Rosner MH. The agony of ecstasy: MDMA (3,4-methylenedioxymethamphetamine) and the kidney. *Clin J Am Soc Nephrol.* 2008 Nov;3(6):1852–60. doi: 10.2215/CJN.02080508.

158 National Poisons Information Service. *Annual Report 2012/13*. Public Health England, 2013.

159 Degenhardt L, Hall W. *The Health and Psychological Effects of 'Ecstasy' (MDMA) Use*. National Drug and Alcohol Research Centre, University of New South Wales, 2010.

160 Refstad S. Paramethoxyamphetamine (PMA) poisoning; a 'party drug' with lethal effects. *Acta Anaesthesiologica Scand*. 2003;47:1298–9. doi: 10.1046/j.1399-6576.2003.00245.x.

161 Giannikopoulos G, Stamoulis I, Panagi G, Karamouzos E, Georgopoulos I, Hatzidakis A, Tripodaki E, Tsouni P, Zorzou M-P. P0494 severe hypoglycaemia, acute renal failure and rhabdomyolysis associated with the use of 3, 4-methylenedioxymethamphetamine ('ecstasy'). *Eur J Intern Med.* 2009;20:S164.

162 Raviña P, Quiroga JM, Raviña T. Hyperkalemia in fatal MDMA ('ecstasy') toxicity. *Int J Cardiol.* 2004;93(2):307–8.

163 Greene SL, Dargan PI, O'Connor N, Jones AL, Kerins M. Multiple toxicity from 3,4-methylenedioxymethamphetamine ('ecstasy'). *American J Emerg Med.* 2003;21(2):121–4.

164 Watson JD. Exertional heat stroke induced by amphetamine analogues. *Anaesthesia.* 1993;48(12):1057–60.

165 Parrott AC. MDMA (3,4-methylenedioxymethamphetamine) or ecstasy: the neuropsychobiological implications of taking it at dances and raves. *Neuropsychobiology.* 2004;50(4):329–35.

166 Kiyatkin EA. Critical role of peripheral vasoconstriction in fatal brain hyperthermia induced by MDMA (ecstasy) under conditions that mimic human drug use. *J Neuroscience.* 2014;34(23):7754–62.

167 Green AR. A review of the mechanisms involved in the acute MDMA (ecstasy)-induced hyperthermic response. *Eur J Pharmacol.* 2004;500(1):3–13.

168 Hunt PA. Heat illness. *J Royal Army Medical Corps*. 2005;151(4):234–42.

169 Schütte JK, Schäfer U, Becker S, Oldewurtel C, Starosse A, Singler P, Richard A, Wappler F, Gerbershagen MU. 3,4-methylenedioxymethamphetamine induces a hyperthermic and hypermetabolic crisis in pigs with and without a genetic disposition for malignant hyperthermia. *Eur J Anaesthesiol.* 2013 Jan;30(1):29–37. doi: 10.1097/EJA.0b013e32835a1127.

170 Swan MC, Lam D, Giele HP. Intravascular ecstasy: an unusual cause of thigh compartment syndrome. *J Trauma*. 2006;60(5):1129–31.

171 Ferrie R, Loveland R. Bilateral gluteal compartment syndrome after 'ecstasy' hyperpyrexia. *J R Soc Med.* 2000;93(5):260.

172 Pilgrim JL. Deaths involving MDMA and the concomitant use of pharmaceutical drugs. *J Analytic Toxicol.* 2011;35(4):219–26.

173 Copeland JP. Ecstasy and the concomitant use of pharmaceuticals. *Addictive Behaviors.* 2006;31(2):367–70.

174 Pilgrim JL. Serotonin toxicity involving MDMA (ecstasy) and moclobemide. *Forensic Sci Int.* 2012;215(1):184–8.

175 Kraner JC, McCoy DJ, Evans MA, Evans LE, Sweeney BJ. Fatalities caused by the MDMA-related drug paramethoxyamphetamine (PMA). *J Anal Toxicol.* 2001 Oct;25(7):645–8.

176 Simmler LD, Hysek CM, Liechti ME. Sex differences in the effects of MDMA (ecstasy) on plasma copeptin in healthy subjects. *J Clin Endocrinol Metab*. 2011 Sep;96(9):2844–50. doi: 10.1210/jc.2011-1143.

177 Finch EL. Cerebral oedema after MDMA ('ecstasy') and unrestricted water intake. Drug workers emphasise that water is not an antidote to drug. *BMJ.* 1996;313(7058):690.

178 Chang JCYC. Late diagnosis of MDMA-related severe hyponatremia. *Case Rep Intern Med.* 2014;1(2):153.

179 Van Kampen J. Persistent psychosis after a single ingestion of 'ecstasy'. *Psychosomatics*. 2001; 42(6):525–7.

180 Bramness JGM. Amphetamine-induced psychosis – a separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry.* 2012;12(1):221.

181 Vaiva GV. An 'accidental' acute psychosis with ecstasy use. *J Psychoactive Drugs.* 2001;33(1):95–8.

182 Rugani FS. Symptomatological features of patients with and without ecstasy use during their first psychotic episode. *Int J Environmental Research Public Health*. 2012;9(7):2283–92.

183 Kim J, Fan B, Liu X, Kerner N, Wu P. Ecstasy use and suicidal behavior among adolescents: findings from a national survey. *Suicide Life-Threat Behav.* 2011;41:435–44.

184 Hinkelbein J, Gabel A, Volz M, Ellinger K. [Suicide attempt with high-dose ecstasy.] [Article in German.] *Der Anaesthesist.* 2003;52(1):51–4.

185 Karlovšek MZ, Alibegovic A, Balažic J. Our experiences with fatal ecstasy abuse (two case reports). *Forensic Sci Int*. 2005;147:S77–80.

186 Fernando T, Gilbert JD, Carroll CM, Byard RW. Ecstasy and Suicide. *J Forensic Sci.* 2012;57:1137–9.

187 Rojek S, Małgorzata K, Strona M, Maciów M, Kula K. 'Legal highs' – toxicity in the clinical and medico-legal aspect as exemplified by suicide with bk-MBDB administration. *Forensic Sci Int.* 2012;222(1):e1–e6.

188 Hoggett KD. Ecstasy-induced acute coronary syndrome: something to rave about. *Emerg Med Australasia.* 2012;24(3):339–42.

189 Mizia-Stec K, Gasior Z, Wojnicz R, Haberka M, Mielczarek M, Wierzbicki A, Pstras K, Hartleb M. Severe dilated cardiomyopathy as a consequence of ecstasy intake. *Cardiovasc Pathol.* 2008 Jul–Aug;17(4):250–3. doi: 10.1016/j.carpath.2007.07.006.

190 Stull BW. Spontaneous pneumomediastinum following ecstasy ingestion and sexual intercourse. *Emerg Med J.* 2008;25(2):113–14.

191 Marasco SF. Ecstasy-associated pneumomediastinum. *Ann R Coll Surg Engl.* 2007;89(4):389.

192 Kahn DE. 3 cases of primary intracranial hemorrhage associated with 'Molly', a purified form of 3,4-methylenedioxymethamphetamine (MDMA). *J Neurol Sci.* 2012;323(1):257–60.

193 Garbino JJ. Ecstasy ingestion and fulminant hepatic failure: liver transplantation to be considered as a last therapeutic option. *Veterinary Human Toxicol.* 2001;43(2):99–102.

194 Seymour HG. Severe ketoacidosis complicated by 'ecstasy' ingestion and prolonged exercise. *Diabet Med.* 1996;13:908–9.

195 Gama MP. Diabetic ketoacidosis complicated by the use of ecstasy: a case report. *J Medical Case Rep.* 2010;4(1):240.

196 Johnson MP, Nichols DE. Combined administration of a non-neurotoxic 3,4-methylenedioxymethamphetamine analogue with amphetamine produces serotonin neurotoxicity in rats. *Neuropharmacol.* 1991;30(7):819–22.

197 Vanattou-Saïfoudine NR. Caffeine promotes dopamine D1 receptor-mediated body temperature, heart rate and behavioural responses to MDMA ('ecstasy'). *Psychopharmacol.* 2010;211(1):15–25.

198 Papaseit E, Vázquez A, Pérez-Mañá C, Pujadas M, de la Torre R, Farré M, Nolla J. Surviving life-threatening MDMA (3,4-methylenedioxymethamphetamine, ecstasy) toxicity caused by ritonavir (RTV). *Intensive Care Med.* 2012 Jul;38(7):1239–40. doi: 10.1007/s00134-012-2537-9.

199 Antolino-Lobo I, Meulenbelt J, Nijmeijer SM, Maas-Bakker RF, Meijerman I, van den Berg M, van Duursen MB. 3,4-methylenedioxymethamphetamine (MDMA) interacts with therapeutic drugs on CYP3A by inhibition of pregnane X receptor (PXR) activation and catalytic enzyme inhibition. *Toxicol Lett.* 2011 May 30;203(1):82–91. doi: 10.1016/j.toxlet.2011.03.007.

200 Steele TD, McCann UD, Ricaurte GA. 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): pharmacology and toxicology in animals and humans. *Addiction.* 1994;89:539–51.

201 Kreth K, Kovar K, Schwab M, Zanger UM. Identification of the human cytochromes P450 involved in the oxidative metabolism of 'ecstasy'-related designer drugs. *Biochem Pharmacol.* 2000;59:1563–71.

202 Grunau BE, Wiens MO, Brubacher JR. Dantrolene in the treatment of MDMA-related hyperpyrexia: a systematic review. *CJEM*. 2010 Sep;12(5):435–42.

203 Banks ML, Sprague JE. From bench to bedside: understanding the science behind the pharmacologic management of MDMA and other sympathomimetic-mediated hyperthermia. *J Pharmacy Technology.* 2011;27(3):123–31.

204 Parrott AC. Residual neurocognitive features of ecstasy use: a re-interpretation of Halpern et al. (2011) consistent with serotonergic neurotoxicity. *Addiction.* 2011;106(7):1365–8.

205 Green D, Barry P, Green HD. Central cyanosis on a psychiatric unit treated at the Salford Royal Hospital. *Thorax*. 2014 Dec;69(12):1157–8. doi: 10.1136/thoraxjnl-2014-205769.

206 Di Iorio CR, Watkins TJ, Dietrich MS, Cao A, Blackford JU, Rogers B, Ansari MS, Baldwin RM, Li R, Kessler RM, Salomon RM, Benningfield M, Cowan RL. Evidence for chronically altered serotonin function in the cerebral cortex of female 3,4-methylenedioxymethamphetamine polydrug users. *Arch Gen Psychiatry*. 2012 Apr;69(4):399–409. doi: 10.1001/archgenpsychiatry.2011.156.

207 Benningfield MM, Cowan RL. Brain serotonin function in MDMA (ecstasy) users: evidence for persisting neurotoxicity. *Neuropsychopharmacology.* 2013;38(1):253–5.

208 Kish SJ, Lerch J, Furukawa Y, Tong J, McCluskey T, Wilkins D, Houle S, Meyer J, Mundo E, Wilson AA, Rusjan PM, Saint-Cyr JA, Guttman M, Collins DL, Shapiro C, Warsh JJ, Boileau I. Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[(11)C] DASB and structural brain imaging study. *Brain*. 2010 Jun;133(Pt 6):1779–97. doi: 10.1093/brain/awq103.

209 Bauernfeind AL, Dietrich MS, Blackford JU, Charboneau EJ, Lillevig JG, Cannistraci CJ, Woodward ND, Cao A, Watkins T, Di Iorio CR, Cascio C, Salomon RM, Cowan RL. Human ecstasy use is associated with increased cortical excitability: an fMRI study. *Neuropsychopharmacology*. 2011 May;36(6):1127–41. doi: 10.1038/npp.2010.244.

210 Urban NB, Girgis RR, Talbot PS, Kegeles LS, Xu X, Frankle WG, Hart CL, Slifstein M, Abi-Dargham A, Laruelle M. Sustained recreational use of ecstasy is associated with altered pre and postsynaptic markers of serotonin transmission in neocortical areas: a PET study with [^{11}C]DASB and [^{11}C]MDL 100907. *Neuropsychopharmacology*. 2012 May;37(6):1465–73. doi: 10.1038/npp.2011.332. Epub 2012 Feb 22.

211 Booij L, Soucy JP, Young SN, Regoli M, Gravel P, Diksic M, Leyton M, Pihl RO, Benkelfat C. Brain serotonin synthesis in MDMA (ecstasy) polydrug users: an alpha-[11C] methyl-tryptophan study. *J Neurochem.* 2014 Dec;131(5):634-44. doi: 10.1111/jnc.12826.

212 McCann UD, Szabo Z, Vranesic M, Palermo M, Mathews WB, Ravert HT, Dannals RF, Ricaurte GA. Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (±) 3, 4-methylenedioxymethamphetamine ('ecstasy') users: relationship to cognitive performance. *Psychopharmacology (Berl).* 2008 Oct;200(3):439–50. doi: 10.1007/s00213-008-1218-4.

213 Bosch OG, Wagner M, Jessen F, Kühn KU, Joe A, Seifritz E, Maier W, Biersack HJ, Quednow BB. Verbal memory deficits are correlated with prefrontal hypometabolism in 18FDG PET of recreational MDMA users. *PLoS One*. 2013 Apr 9;8(4):e61234. doi: 10.1371/journal.pone.0061234.

214 Gouzoulis-Mayfrank E, Daumann J. Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: how strong is the evidence for persistent brain damage? *Addiction*. 2006 Mar;101(3):348–61.

215 Clemens KJ, McGregor IS, Hunt GE, Cornish JL. MDMA, methamphetamine and their combination: possible lessons for party drug users from recent preclinical research. *Drug Alcohol Rev*. 2007 Jan;26(1):9–15.

216 Biezonski DK, Meyer JS. The nature of 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonergic dysfunction: evidence for and against the neurodegeneration hypothesis. *Current Neuropharmacol.* 2011;9(1):84.

217 Krebs TS, Pål-Ørjan J. Methodological weaknesses in non-randomized studies of ecstasy (MDMA) use: a cautionary note to readers and reviewers. *Neuropsychopharmacol.* 2012;37(4):1070.

218 Erritzoe D, Frokjaer VG, Holst KK, Christoffersen M, Johansen SS, Svarer C, Madsen J, Rasmussen PM, Ramsøy T, Jernigan TL, Knudsen GM. In vivo imaging of cerebral serotonin transporter and serotonin2a receptor binding in 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') and hallucinogen users. *Arch Gen Psychiatry.* 2011 Jun;68(6):562–76. doi: 10.1001/archgenpsychiatry.2011.56.

219 Adamaszek M, Khaw AV, Buck U, Andresen B, Thomasius R. Evidence of neurotoxicity of ecstasy: sustained effects on electroencephalographic activity in polydrug users. *PLoS One*. 2010 Nov 23;5(11):e14097. doi: 10.1371/journal.pone.0014097.

220 Thomasius R, Zapletalova P, Petersen K, Buchert R, Andresen B, Wartberg L, Nebeling B, Schmoldt A. Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective. *J Psychopharmacol.* 2006 Mar;20(2):211–25.

221 Parrott AC. MDMA and 5-HT neurotoxicity: the empirical evidence for its adverse effects in humans – no need for translation. *Br J Pharmacol.* 2012 Jul;166(5):1518–20; discussion 1521–2. doi: 10.1111/j.1476-5381.2012.01941.x.

222 Peraile I, Granado N, Torres E, Gutiérrez-López MD, Moratalla R, Colado MI, O'Shea E. Cocaine potentiates MDMA-induced oxidative stress but not dopaminergic neurotoxicity in mice: implications for the pathogenesis of free radical-induced neurodegenerative disorders. *Psychopharmacology (Berl).* 2013 Nov;230(1):125–35. doi: 10.1007/s00213-013-3142-5.

223 Angoa-Pérez M, Kane MJ, Briggs DI, Francescutti DM, Sykes CE, Shah MM, Thomas DM, Kuhn DM. Mephedrone does not damage dopamine nerve endings of the striatum, but enhances the neurotoxicity of methamphetamine, amphetamine, and MDMA. *J Neurochem*. 2013 Apr;125(1):102–10. doi: 10.1111/jnc.12114.

224 Parrott AC. MDMA in humans: factors which affect the neuropsychobiological profiles of recreational ecstasy users, the integrative role of bioenergetic stress. *J Psychopharmacol.* 2006;20(2):147–63.

225 Klomp A, den Hollander B, de Bruin K, Booij J, Reneman L. The effects of ecstasy (MDMA) on brain serotonin transporters are dependent on age-of-first exposure in recreational users and animals. *PLoS ONE*. 2012;7(10): e47524. doi:10.1371/journal.pone.0047524.

226 Huang X, Marona-Lewicka D, Nichols DE. p-Methylthioamphetamine is a potent new non-neurotoxic serotonin-releasing agent. *Eur J Pharmacol.* 1992 Dec 8;229(1):31–8.

227 Nichols DE, Johnson MP, Oberlender R. 5-iodo-2-aminoindan, a nonneurotoxic analogue of p-iodoamphetamine. *Pharmacol Biochem Behav*. 1991 Jan;38(1):135–9.

228 Nichols DE, Marona-Lewicka D, Huang X, Johnson MP. Novel serotonergic agents. *Drug Des Discov*. 1993;9(3–4):299–312.

229 Wagner D, Becker B, Koester P, Gouzoulis-Mayfrank E, Daumann J. A prospective study of learning, memory, and executive function in new MDMA users. *Addiction.* 2013;108(1):136–45.

230 Schilt T, de Win MM, Koeter M, Jager G, Korf DJ, van den Brink W, Schmand B. Cognition in novice ecstasy users with minimal exposure to other drugs: a prospective cohort study. *Arch Gen Psychiatry.* 2007 Jun;64(6):728–36.

231 Halpern JH, Sherwood AR, Hudson JI, Gruber S, Kozin D, Pope Jr HG. Residual neurocognitive features of long-term ecstasy users with minimal exposure to other drugs. *Addiction*. 2011;106:777–86.

232 Taurah L, Chandler C, Sanders G. Depression, impulsiveness, sleep, and memory in past and present polydrug users of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). *Psychopharmacol.* 2014;231(4):737-51.

233 Gerra G, Zaimovic A, Ampollini R, Giusti F, Delsignore R, Raggi MA, Laviola G, Macchia T, Brambilla F. Experimentally induced aggressive behavior in subjects with 3,4-methylenedioxy-methamphetamine ('Ecstasy') use history: psychobiological correlates. *J Subst Abuse.* 2001;13(4):471–91.

234 Wetherell MA, Montgomery C. Basal functioning of the hypothalamic-pituitary-adrenal (HPA) axis and psychological distress in recreational ecstasy polydrug users. *Psychopharmacol*. 2014;231(7):1365-75.

235 Parrott AC, Montgomery C, Wetherell MA, Downey LA, Stough C, Scholey AB. MDMA, cortisol, and heightened stress in recreational ecstasy users. *Behav Pharmacol.* 2014 Sep;25(5-6):458-72. doi: 10.1097/FBP.0000000000000060.

236 Sumnall HR, Cole JC. Self-reported depressive symptomatology in community samples of polysubstance misusers who report ecstasy use: a meta-analysis. *J Psychopharmacol.* 2005;19(1): 84–92.

237 Brière FN, Fallu JS, Janosz M, Pagani LS. Prospective associations between meth/amphetamine (speed) and MDMA (ecstasy) use and depressive symptoms in secondary school students. *J Epidemiol Community Health.* 2012 Nov;66(11):990–4. doi: 10.1136/jech-2011-200706.

238 McCann M, Higgins K, Perra O, McCartan C, McLaughlin A. Adolescent ecstasy use and depression: cause and effect, or two outcomes of home environment? *Eur J Public Health*. 2014 Oct;24(5):845–50. doi: 10.1093/eurpub/cku062.

239 Scott RM, Hides L, Allen JS, Burke R, Lubman DI. Depressive and anxiety symptomatology in ecstasy users: the relative contribution of genes, trauma, life stress and drug use. *Psychopharmacology (Berl).* 2010 Mar;209(1):25–36. doi: 10.1007/s00213-009-1763-5.

240 Soar K, Turner JJD, Parrott AC. Psychiatric disorders in ecstasy (MDMA) users: a literature review focusing on personal predisposition and drug history. *Human Psychopharmacology: Clinical Experimental*. 2001;16(8):641–5.

241 Bedi G, Van Dam NT, Redman J. Ecstasy (MDMA) and high prevalence psychiatric symptomatology: somatic anxiety symptoms are associated with polydrug, not ecstasy, use. *J Psychopharmacol.* 2010 Feb;24(2):233–40. doi: 10.1177/0269881108097631.

242 Daumann J, Hensen G, Thimm B, Rezk M, Till B, Gouzoulis-Mayfrank E. Self-reported psychopathological symptoms in recreational ecstasy (MDMA) users are mainly associated with regular cannabis use: further evidence from a combined cross-sectional/longitudinal investigation. *Psychopharmacology*. 2004;173(3-4):398–404.

243 Thomasius R, Petersen KU, Zapletalova P, Wartberg L, Zeichner D, Schmoldt A. Mental disorders in current and former heavy ecstasy (MDMA) users. *Addiction*. 2005;100:1310–19.

244 Marchesi C, Tonna M, Maggini C. Obsessive-compulsive disorder followed by psychotic episode in long-term ecstasy misuse. *World J Biol Psychiatry.* 2009;10(4-2):599–602.

245 Degenhardt L, Bruno R, Topp L. Is ecstasy a drug of dependence? *Drug Alcohol Depend.* 2010;107:1–10.

246 Uosukainen H, Tacke U, Winstock AR. Self-reported prevalence of dependence of MDMA compared to cocaine, mephedrone and ketamine among a sample of recreational poly-drug users. *Int J Drug Policy.* 2015 Jan;26(1):78–83. doi: 10.1016/j.drugpo.2014.07.004.

247 Bruno R, Matthews AJ, Topp L, Degenhardt L, Gomez R, Dunn M. Can the severity of dependence scale be usefully applied to 'ecstasy'? *Neuropsychobiology*. 2009;60(3–4):137–47. doi: 10.1159/000253550.

248 Cottler LB, Womack SB, Compton WM, Ben-Abdallah A. Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria. *Hum Psychopharmacol Clin Exp*. 2001;16:599–606.

249 Yen C, Hsu S. Symptoms of ecstasy dependence and correlation with psychopathology in Taiwanese adolescents. *J Nerv Ment Dis*. 2007;195:866–9.

250 Scheier L, Abdullah A, Inciardi J, Copeland J, Cottler L. Tri-city study of ecstasy use problems: a latent class analysis. *Drug Alcohol Depend.* 2008;98:249–63.

251 Abdallah A, Scheier L, Inciardi J, Copeland J, Cottler L. A psycho-economic model of ecstasy consumption and related consequences: a multi-site study with community samples. *Subst Use Misuse.* 2007;42:1651–84.

252 Milani RM, Turner J, Parrott AC. The contribution of ecstasy dependence and stress to ecstasy/MDMA-related psychiatric symptoms. *Open Addiction J.* 2011;4:28–9.

253 Topp L, Hall W, Hando J. *Is There a Dependence Syndrome for Ecstasy?* (National Drug and Alcohol Research Centre Technical Report No. 51). NDARC, 1997.

254 Parrott AC. Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or ecstasy. *J Psychopharmacol.* 2005;19:71–83.

255 McKetin R, Copeland J, Norberg MM, Bruno R, Hides L, Khawar L. The effect of the ecstasy 'come-down'on the diagnosis of ecstasy dependence. *Drug Alcohol Depend.* 2014 Jun 1;139:26–32. doi: 10.1016/j.drugalcdep.2014.02.697.

256 Schenk S. MDMA self-administration in laboratory animals: a summary of the literature and proposal for future research. *Neuropsychobiology*. 2009;60(3–4):130.

257 Laura WMD. MDMA doesn't effect (sic) me anymore. Blog entry, 2012. http://www.bluelight.org/vb/threads/640420-MDMA-doesn-t-effect-me-anymore (accessed 31 August 2014).

258 Wu LT, Parrott AC, Ringwalt CL, Patkar AA, Mannelli P, Blazer DG. The high prevalence of substance use disorders among recent MDMA users compared with other drug users: Implications for intervention. *Addict Behav.* 2009 Aug;34(8):654–61. doi: 10.1016/j.addbeh.2009.03.029.

259 Carhart-Harris RL, Nutt DJ, Munafo MR, Christmas DM, Wilson SJ. Equivalent effects of acute tryptophan depletion on REM sleep in ecstasy users and controls. *Psychopharmacology.* 2009;206(2):187–96.

260 McCann UD. Effects of (±)3,4-methylenedioxymethamphetamine (MDMA) on sleep and circadian rhythms. *Scientific World J.* 2007;*7*:231–8.

261 Smithies V, Broadbear J, Verdejo-Garcia A, Conduit R. Dysfunctional overnight memory consolidation in ecstasy users. *J Psychopharmacol.* 2014 Mar 4;28(8):751–62.

262 Gledhill JA. Subarachnoid haemorrhage associated with MDMA abuse. *J Neurol Neurosurg Psychiatry*. 1993;56(9):1036.

263 Karch SB. A historical review of MDMA. *Open Forensic Sci J*. 2011;4:20–4.

264 Droogmans SB. Possible association between 3,4-methylenedioxymethamphetamine abuse and valvular heart disease. *Am J Cardiol.* (2007);100(9):1442–5.

265 Bhattacharyya SA. Drug-induced fibrotic valvular heart disease. *Lancet*. 2009;374(9689):577–85.

266 Montastruc F, Montastruc G, Vigreux P, Bruneval P, Guilbeau-Frugier C, Cron C, Bagheri H, Delisle B, Lapeyre-Mestre M, Pathak A, Montastruc JL. Valvular heart disease in a patient taking 3, 4-methylenedioxymethamphetamine (MDMA,'ecstasy'). *Br J Clin Pharmacol*. 2012 Sep;74(3):547-8. doi: 10.1111/j.1365-2125.2012.04252.x.

267 Patel MM, Belson MG, Wright D, Lu H, Heninger M, Miller MA. Methylenedioxymethamphetamine (ecstasy)-related myocardial hypertrophy: an autopsy study. *Resuscitation*. 2005 Aug;66(2):197–202.

268 Marsden J, Stillwell G, Barlow H, Boys A, Taylor C, Hunt N, Farrell M. An evaluation of a brief motivational intervention among young ecstasy and cocaine users: no effect on substance and alcohol use outcomes. *Addiction*. 2006 Jul;101(7):1014–26.

269 Norberg MM, Hides L, Olivier J, Khawar L, McKetin R, Copeland J. Brief interventions to reduce ecstasy use: a multi-site randomized controlled trial. *Behav Ther.* 2014 Nov;45(6):745–59. doi: 10.1016/j.beth.2014.05.006.

270 Martin G, Copeland J. Brief intervention for regular ecstasy (MDMA) users: pilot randomized trial of a check-up model. *J Substance Use.* 2010;15(2):131–42.

271 Fox HC. Ecstasy use: cognitive deficits related to dosage rather than self-reported problematic use of the drug. *J Psychopharmacol.* 2001;15(4):273–81.

272 Larkin M. Dangerous sports and recreational drug use: rationalizing and contextualizing risk. *J Community Applied Social Psychol.* 2004;14(4):215–32.

273 Gamma AL. Is ecstasy perceived to be safe? A critical survey. *Drug Alcohol Depend.* 2005;77(2):185–93.

274 Baggott MJ. Preventing problems in ecstasy users: reduce use to reduce harm. *J Psychoactive Drugs*. 2002;34(2):145–62.

275 Liechti ME. Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') are attenuated by the serotonin uptake inhibitor citalopram. *Neuropsychopharmacology.* 2000;22(5):513–21.

276 Piper BJ. Dissociation of the neurochemical and behavioral toxicology of MDMA ('ecstasy') by citalopram. *Neuropsychopharmacology*. 2007;33(5):1192–205.

277 Fisk JE, Murphy PN, Montgomery C, Hadjiefthyvoulou F. Modelling the adverse effects associated with ecstasy use. *Addiction*. 2011 Apr;106(4):798–805. doi: 10.1111/j.1360-0443.2010.03272.x.

278 Vanden Eede H, Montenij LJ, Touw DJ, Norris EM. Rhabdomyolysis in MDMA intoxication: a rapid and underestimated killer. 'Clean' ecstasy, a safe party drug? *J Emerg Med.* 2012 Jun;42(6):655–8. doi: 10.1016/j.jemermed.2009.04.057.

279 Sainsbury PD, Kicman AT, Archer RP, King LA, Braithwaite RA. Aminoindanes – the next wave of 'legal highs'? Drug Test Anal. 2011 Jul-Aug;3(7-8):479-82. doi: 10.1002/dta.318.

280 Jebadurai J, Schifano F, Deluca P. Recreational use of 1-(2-naphthyl)-2-(1-pyrrolidinyl)-1-pentanone hydrochloride (NRG-1), 6-(2-aminopropyl) benzofuran (Benzofury/6-APB) and NRG-2 with review of available evidence-based literature. *Human Psychopharmacology: Clinical and Experimental*. 2013;28(4):356–64.

281 Iversen L, Gibbons S, Treble R, Setola V, Huang XP, Roth BL. Neurochemical profiles of some novel psychoactive substances. *Eur J Pharmacol.* 2013 Jan 30;700(1-3):147–51. doi: 10.1016/j.ejphar.2012.12.006.

282 Dawson P, Opacka-Juffry J, Moffatt JD, Daniju Y, Dutta N, Ramsey J, Davidson C. The effects of benzofury (5-APB) on the dopamine transporter and 5-HT2-dependent vasoconstriction in the rat. *Prog Neuro-Psychopharmacology Biological Psychiatry.* 2014;48:57–63.

283 Wood DM, Archer JRH, Measham F, Hudson S, Dargan PI. Detection of use of novel psychoactive substances by attendees at a music festival in the north west of England. *Clin Toxicol (Phila).* 2013;51:340–1.

284 Archer JRH, Dargan PI, Chan WL, Hudson S, Wood DM. Variability in recreational drugs and novel psychoactive substances detected in anonymous pooled urine samples from street pissoirs (street urinals) over time: a technique to monitor trends in drugs use. *Clin Toxicol (Phila).* 2013;51:343–4.

285 Baron M, Elie M, Elie L. An analysis of legal highs – do they contain what it says on the tin? *Drug Testing Analysis.* 2011;3(9):576–81.

286 Greene SL. Benzofurans and benzodifurans. In: Dargan PI, Wood DM, eds. *Novel Psychoactive Substances: Classification, Pharmacology and Toxicology*. Elsevier, 2013.

287 Bartoszyk G, et al. Benzofuran compounds and their use as antidepressants and anxiolytics. US Patent No. 7,262,216 (28 August 2007).

288 Clemente CG, Chiappini S, Claridge H, Goodair C, Barbara L. *Death Involving Benzo-Fury, United Kingdon 2011*. St George's University of London, 2012.

289 Liechti M. Novel psychoactive substances (designer drugs): overview and pharmacology of modulators of monoamine signalling. *Swiss Med Wkly*. 2015;45:w14043.

290 Rothman RB, Baumann MH, Savage JE, et al. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac vulvulopathy associated with fenfluramine and other serotonergic medications. *Circulation*. 2000;102:2836–41.

291 Dawson PO, Moffott JD. Cardiovascular toxicity of novel psychoactive drugs: lessons from the past. *Prog. Neuro-Psychopharm Biol Pschiatr.* 2012;39:244–52.