HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2013; **28:** 345–355.
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.2298

SPECIAL ISSUE ON NOVEL PSYCHOACTIVE SUBSTANCES

MDAI (5,6-methylenedioxy-2-aminoindane; 6,7-dihydro-5H-cyclopenta[f][1,3]benzodioxol-6-amine; 'sparkle'; 'mindy') toxicity: a brief overview and update

John M Corkery[1,3]*, Simon Elliott[2], Fabrizio Schifano[1,3], Ornella Corazza[3] and A Hamid Ghodse[1,†]

[1]*National Programme for Substance Abuse Deaths (np-SAD), International Centre for Drug Policy, St George's, University of London, London, UK*
[2]*ROAR Forensics Ltd, Malvern, Worcestershire, UK*
[3]*School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Hertfordshire, UK*

Objectives MDAI (5,6-methylenedioxy-2-aminoindane; 6,7-dihydro-5H-cyclopenta[f][1,3]benzodioxol-6-amine; 'sparkle'; 'mindy') is a psychoactive substance, sold primarily over the Internet and in 'head' shops as a 'legal high'. Synthesised and used as a research chemical in the 1990s, MDAI has structural similarities to MDMA (3,4-methylenedioxy-*N*-methylamphetamine) and shares its behavioural properties. Recreational use of MDAI appears to have started in Europe around 2007, with a noticeable increase after 2009 in the UK and other countries. Calls to National Poisons Information Services started in 2010, although there were few presentations to emergency departments by patients complaining of undesirable physical and psychiatric effects after taking MDAI. Recreational use of this drug has been reported only occasionally by online user fora. There is little scientifically based literature on the pharmacological, physiological, psychopharmacological, toxicological and epidemiological characteristics of this drug.
Methods Recent literature (including 'grey') was searched to update what is known about MDAI, especially on its toxicity.
Results The resultant information is presented, including on the first three UK deaths involving MDAI use in 2011 and 2012. 'Serotonin syndrome' appears to be a possible factor in these fatalities.
Conclusion It is vital that any other cases, including non-fatal overdoses, are documented so that a scientific evidence base can be established for them. Copyright

KEY WORDS—MDAI; 5,6-methylenedioxy-2-aminoindane; death; toxicity; poisoning; UK

LIST OF ABBREVIATIONS—2-DPMP, Desoxypipradrol, 2-benzhydrylpiperidine, 2-phenylmethylpiperidine; ACMD, Advisory Council on the Misuse of Drugs; AM 694, Synthetic cannabinoid; AM 1248, Synthetic cannabinoid; AM 2201, Synthetic cannabinoid; APB, (2-Aminopropyl)benzofuran; BZP, Benzylpiperazine; D2PM, Diphenyl-2-pyrrolidin-2-yl-methanol, diphenylprolinol; DAD, Diode array detector; ED, Emergency department; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; FSS, Forensic Science Service; HPLC, High performance liquid chromatography; HSGC-FID, Headspace sampling coupled with GCMS, Gas chromatography mass spectrometry using flame ionisation detector; LCMS, Liquid chromatography with mass spectrometry; LC-MS-MS, Liquid chromatography with tandem mass spectrometry; LD50, Median lethal dose; LSD, Lysergic acid diethylamide; MAO, Monoamine oxidase; MDA, 3,4-Methylenedioxyamphetamine; MDMA, 3,4-Methylenedioxy-N-methylamphetamine; MDPV, Methylenedioxypyrovalerone; MPA, Methiopropramine (sulphur-containing compound); NPS, Novel psychoactive substance; QTOF-MS, Quadrupole time of flight with mass spectrometry; ReDNet, Recreational Drugs European Network; 3-TFMPP, 1-(3-Trifluoromethylphenyl)piperazine; U/HPLC, Ultra high pressure liquid chromatography; UK, United Kingdom; USA, United States of America

INTRODUCTION

The last few years have seen increasingly rapid changes in the production, supply and consumption of novel psychoactive substances (NPSs). Typically, very little is known about the pharmacology, metabolism, toxicity and psychoactive effects of NPS. The only scientific inquiry that is conducted by manufacturers typically concerns their chemical structure. Suppliers and consumers are, therefore, unaware of the potential dangers presented by these chemicals.

The aim of this paper was to improve the knowledge base in respect of an NPS that recently appeared on the market, MDAI (5,6-methylenedioxy-2-aminoindane),

*Correspondence to: J. M. Corkery, School of Life and Medical Sciences, Department of Pharmacy, University of Hertfordshire, Hatfield, Hertfordshire AL10 9AB, UK. Phone: +44 (0)1707 281053 E-mail: j.corkery@herts.ac.uk
†Died 27 December 2012

Received 21 December 2012
Accepted 21 January 2013

by updating what has previously been published about it (Gallagher *et al*., 2012), especially its toxicology. The regular surveillance and monitoring of drug-related deaths assists in identifying both the epidemiological characteristics of NPS users and the nature of fatalities associated with their consumption. This paper reports on three fatalities caused or contributed to by MDAI.

CHEMISTRY

The chemical MDAI is known by several designations: 5,6-methylenedioxy-2-aminoindane; 6,7-dihydro-5H-cyclopenta[f][1,3]benzodioxol-6-amine; 'Sparkle'; and 'Mindy'. It is a psychoactive substance belonging to the aminoindane class of chemicals (Figure 1).

USE OF MDAI

During the 1990s, MDAI was synthesised and used as a research chemical by a group in the USA studying the structure–activity relationships around MDMA (Nichols *et al*., 1990; Monte *et al*., 1993). Research on rodents suggested that MDAI is structurally related to MDMA and shares its behavioural properties (Johnson *et al*., 1991a). It was developed due to its antidepressant properties. It has been reported previously to be a non-neurotoxic serotonin-releasing agent with mild empathogenic properties (Nichols *et al*., 1990; Kovar, 1998).

Recreational use of MDAI appears to have started in the European Union (EU) around 2007, with a noticeable increase after 2009. Discussions of the chemical in online drug user fora became more frequent from May 2010, following the UK ban on methcathinones and synthetic cannabinoids the previous month (Townsend, 2010). It then started being advertised as a legal alternative to mephedrone and similar chemicals (Leach, 2010). Use of MDAI is also reported from the USA (Mixmag, 2012).

In the context of the European Early Warning System on New Psychoactive Substances, the first report of MDAI to the EMCDDA was made by Sweden in December 2009 (EMCDDA and Europol, 2010). Further reports of its detection were received throughout 2011 and 2012 from several other EU Member States and countries forming part of the REITOX network.

MDAI was first identified in the UK in April 2010 in samples of brown powder bought online and analysed by TICTAC Communications based at St George's, University of London (Personal communication, John Ramsey, 21 November 2012). The first reports by UK law enforcement agencies were made to the FSS in the third quarter of 2010, involving two seizures of capsules ($n = 17$) and two powder seizures (157.5 g) (FSS, 2010). (No later information was published by the FSS because of its closure in 2012.) LGC Forensics had no submissions of MDAI during 2010, but received 12 in 2011 involving a total of 19.9 g. During 2012, they examined 10 cases, which contained a total of 27 samples of MDAI (c. 25 g), the majority most occurring in the first quarter. In some of these samples, only MDAI was detected; in others, methoxetamine, BZP, trifluoromethyphenyllpiperazine (TFMPP), 1-(3,4-methylenedioxyphenyl)-2-pyrrolidinyl-butan-1-one (MDPBP), methiopropamine, APB and MDMA were also detected (Personal communication, LGC Forensics Drugs Intelligence team, 21 December 2012).

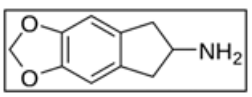

Figure 1. Chemical structure of MDAI

MDAI did not feature in the 2010 Mixmag survey, but in the 2010/11 sweep, lifetime use was reported at 6.7% and last year use at 4.7% ($n = 2500$) (Mixmag, 2011). The 2011/12 sweep, conducted by Global Drug Survey in conjunction with the Guardian newspaper, included responses from 7700 UK respondents. This showed that lifetime use of MDAI had fallen to 4.1%, last year use was 2.2% and last month use was <0.5%. Rates for regular clubbers were higher, at 3.0% and 0.5%, respectively (Mixmag, 2012). It is too early to say if the drop in lifetime use is just a dip or an indication that interest in MDAI may have peaked; the results of the current survey (now in the field) will help in this respect. Measham *et al*. (2011) conducted four surveys in Lancashire nightclubs during November 2010; the total number of respondents was 207. Lifetime use amongst these groups of night club attendees was 2%; last year, last month and current day use was 1%. A survey of 313 individuals attending 'gay' clubs in South London conducted in July 2011 revealed that MDAI use in this population was higher (as for other recreational drugs), with lifetime use at 7.7% and last month use at 1.3% (Wood *et al*., 2012).

This substance seems to have been hardly known about generally or encountered by law enforcement and forensic science agencies or emergency rooms. For these reasons, there is very little scientific information about the drug, its pharmacology, metabolism, effects, toxicity and epidemiology; these were first reviewed by Gallagher *et al*. (2012).

AVAILABILITY

MDAI is typically marketed as a 'research chemical', 'plant food' and so on, and is widely marketed as 'the research equivalent of Methylone (beta keto-MDMA)'.

DOI: 10.1002/hup

A survey of online shops selling to the EU found that the number of outlets selling MDAI had increased from 45/314 in January 2011 to 65/693 by January 2012, and was the fifth most common product offered (EMCDDA, 2012:91). Product descriptions often feature the following aspects: emphasis on white colouration suggesting high purity (up to 99%); advice against human consumption; the source is 'trusted', 'renowned' or 'exclusive'; discounted prices/offers; free delivery on quantities as small as 1 g; and credit/debit card payment is easily accessible (ReDNet, 2011). These ploys are similar to those employed by vendors prior to its control in the UK (Corkery *et al*., 2012a) and for products such as 2-DPMP and D2PM (Corkery *et al*., 2012b).

MDAI is often described on Internet sites as 'super spun sparkling crystals, low in odours and easily soluble in water or other liquid. At least 4 times as strong as our previous product and a must for research in this area.' Some anecdotal reports state that commercial samples vary in texture and colour rather than being a standard white crystalline powder (Bluelight, 2010a, 2010b; ReDNet, 2011). This suggests the possible (deliberate) mislabelling of supposed MDAI products that contain other psychoactive substances. Some commercial products, such as 'Blow' have been found to contain MDAI along with other psychoactive products (case study 3).

LEGAL STATUS

There are no international controls imposed on MDAI, although it is possible that it might be caught by 'analogue' legislation in countries such as the USA, Australia and New Zealand. The substance is now controlled in Finland (as a medicinal product), the Czech Republic (as an addictive substance) and Belarus, and is possibly caught by generic legislation in Poland (Sejm, 2010).

In the UK, MDAI falls outside the definition of a medicinal product under the Medicines Act 1968. At present, there are no controls on the substance in the UK, although the independent UK ACMD is keeping a 'watching brief' on the information on it. Following the completion of the inquest into the death described here (case study 1), the Isle of Man Government made it a class C drug under their Misuse of Drugs Act 1976 from 1 January 2012 (IOM, 2011). This period has been extended by another 12 months (BBC, 2012).

ROUTE OF ADMINISTRATION AND DOSAGE

There are several known routes of MDAI administration: insufflation (snorting, sniffing), oral (wrapped in a cigarette paper 'bomb', or swallowed in the form of a capsule/pellet/pill) and rectal (plugging, or dissolving the substance in alcohol and applying it as an enema). The latter route leads to rapid onset of psychoactive effects. Smoking and injecting do not appear to have been discussed as modes of use, but these cannot be excluded as possible routes. Doses range from 70–300 mg; typical doses appear to be 150–200 mg of active ingredient (equivalent to half of a 300 mg capsule or a whole 200 mg capsule). A 'low' dose of 70–80 mg produces subtle but noticeable effects; a strong dose is considered to be 250–300 mg. Redosing often occurs; typically a 'booster' of 100–150 mg is administered after the initial positive effects have worn off (Drugs-Forum, 2009a; Bluelight, 2010a; Herbalhighs, 2012a; Partyvibe, 2012). Tolerance may develop with heavy or extended use (Drugs-Forum, 2009a; Bluelight, 2010a).

PHARMACOLOGY

There is little information on the pharmacodynamics and pharmacokinetics of MDAI. The substance has structural similarities with MDMA and MDA, and appears to be a serotonin-releasing agent producing empathogenic effects and acting as a sedative, rather than generating stimulant action. Its precise mechanism (s) of action are still unclear (Nichols and Oberlender, 1991). The alpha-methyl group of the alkylamine amphetamine side chain is bound-connected back to the benzene nucleus to form an indane ring system, thereby changing its pharmacological properties (Monte *et al*., 1993). Studies suggest that the chemical substitutes for MDMA in rats with greater selectivity for serotonin. Its ability to release serotonin is similar to that of MDA but less than that of MDMA. It also inhibits the uptake of serotonin, dopamine and norepinephrine (Johnson *et al*., 1991c). There have been no human clinical studies looking at the pharmacological and toxicological effects of MDAI. Hard data are needed before any robust conclusions can be suggested.

EFFECTS

Most of the information published on the effects of MDAI is derived from first-hand personal accounts presented in discussion fora. User reports suggest that the onset of its positive effects is felt within 10–12 min of being taken orally, but the duration of such effects appears to vary considerably between users. The range for peak effects varies from 30–45 min up to 3 h (Drugs Forum, 2009a; ReDNeT, 2011). This variability may be due, in part, to products containing other substances (Brandt *et al*., 2010b). The desired psychoactive effects expected by MDAI users may include the following:

DOI: 10.1002/hup

mild euphoria, empathy, increased mental clarity, sexual arousal and intensification of sensory experience stimulation, music appreciation, visual distortions, mood enhancement, sociability and loquacity (Drugs-Forum, 2009a; Bluelight, 2010a; Herbalhighs, 2012a; Partyvibe, 2012; Bangingtunes, 2009; these are very similar to those described for Desoxypipradrol (Corkery *et al*., 2012b). Reported acute physical effects of MDAI may include the following: insomnia, nausea/vomiting, confusion and fatigue (Drugs-Forum, 2009a; Bluelight, 2010a; Herbalhighs, 2012a; Partyvibe, 2012).

HOSPITAL PRESENTATIONS

There have been few reported presentations of MDAI consumers to hospital EDs. However, after the banning of mephedrone in April 2010, the Wales Drug and Alcohol Helpline issued a warning about the emerging popularity of MDAI (BBC, 2010). Information from the National Poisons Information Service indicates that the first enquiries about MDAI were received in 2010/11 and continued into 2011/12 (NPIS, 2011, 2012). A 21-year-old man reported to an English ED (date not given) that he had taken 5 g of MDAI (George *et al*., 2011). Soon after consumption, he got confused, with evidence of psychosis and self-harm. On presentation, he was hyperpyrexial and tachycardic. The patient was intubated and sedated. Rapidly progressing multi-organ failure developed, including liver and renal failure, rhabdomyolysis and disseminated intravascular coagulation (DIC). Venous–venous haemofiltration was started to manage anuria, and he was treated with blood and blood products for DIC. In the liver intensive treatment unit, the patient was treated on a fulminant care pathway. After 6 days, liver function results had improved, and the patient showed signs of waking. He gradually improved and transferred to a psychiatric hospital where he remained for 3 months.

TOXICITY

When seeking to develop non-neurotoxic analogues of MDMA, Nichols *et al*. (1990) found that markers of MDMA-like serotonergic neurotoxic effects in rats revealed no evidence of a decrease in the density of 5-HT neuronal terminals 1 week after a 40 mg/kg dose of MDAI hydrochloride. They further found using MDAI that selective 5-HT nerve terminal degenerative effects are not necessary for MDMA-like behavioural activity in rats and that the complete substitution of MDAI for (+)MBDB suggests that the similarity of MDAI and MDMA involves the (+)MBDB-like actions of the MDMA behavioural profile. Whilst these single dose experiments showed a lack of serotonergic toxicity, multiple doses produce slight long-term deficits in serotonin markers (Johnson, 1991, cited in Prague *et al*., 1996).

There is no information on MDAI's long-term effects. Studies on rats suggest that the substance does not cause neurotoxicity (Nichols *et al*., 1990; Nichols and Oberlender, 1991). However, when used with dopamine-releasing agents, it contributes to toxicity in rats (Johnson *et al*., 1991c). Attempts by Sprague *et al*. (1996) to potentiate the selective serotonergic neurotoxicity of MDAI with either a non-specific dose of the MAO-B inhibitor L-deprenyl (10 mg/kg) or the MAO-A inhibitor chlorgyline (2 mg/kg) were unsuccessful. This contrasts with the findings of L-deprenyl potentiating non-neurotoxic doses of PCA (*p*-chloroamphetamine) (Benmansour and Brunswick, 1994). The findings of Sprague *et al*. (1996) suggest that MDAI is a safe substance in this regard. However, these assumptions about the apparently benign activity of MDAI at recreational levels are based on animal experiments and *in vitro* cell culture work. Thus, it remains unclear whether recreational doses in man would lead to neurotoxicity (Sainsbury *et al*., 2011).

By substituting for MDMA, aminoindanes such as MDAI are likely to elicit the empathogenic and entactogenic effects of serotonin-releasing drugs (Sainsbury *et al*., 2011). Whilst MDAI does appear to affect the 5-HT system but not dopamine or noradrenaline receptors, its purely serotonergic action is unlikely to elicit the range of desired effects expected by consumers, thus possibly leading to larger doses being consumed, with possible unpredictable outcomes (Sainsbury *et al*., 2011). Furthermore, if used in a similar fashion to other 'legal highs', aminoindanes such as MDAI are likely to be consumed as part of a cocktail of stimulant substances including cocaine, amphetamine and MDMA (Corkery *et al*., 2012a). This could result in unexpected toxicity as serotonin-releasing agents generally potentiate the effects of indirectly acting dopaminergic substances; dopamine contributes to both neurotoxicity and cardiotoxicity (Johnson *et al*., 1991a, 1991b; Monte *et al*., 1993). Sainsbury *et al*. (2011) suggest that combining analogues of 2-aminoindane with dopamine-releasing agents and/or re-uptake inhibitors could possibly alter substantially the toxicity profile of such drugs after acute or chronic consumption, especially by naïve users.

Second-generation 'legal highs' including MDAI and 5-IAI emerged after the controls placed on the first generation of these substances (synthetic cathinones such as mephedrone and other substances) in 2009 and 2010, and which were still available throughout 2011 and into 2012. Substances labelled as a particular

DOI: 10.1002/hup

product may be structural isomers of the expected active ingredient that have not been covered in the published literature and thus are 'unknown quantities' (Brandt *et al*., 2010a). An example of this type is reported by Baron *et al*. (2011) who purchased three 'legal high' samples offered online as MDAI in August and October 2010. Following analysis using Fourier-transform infrared spectroscopy, it was found that only one of these contained MDAI as advertised (0.723). The other 'MDAI' samples contained the following: (i) caffeine (0.677) with BZP and 3-TFMPP and (ii) caffeine (0.617) also with BZP and 3-TFMPP. A sample of MDAI purchased from the Internet after the UK ban on mephedrone (April 2010) was found to contain no MDAI but methylone (Ramsey *et al*., 2010). Two further samples purchased in June 2010 from the Internet were also found to be lacking MDAI as an ingredient: one contained mephedrone, and the other contained a mix of inorganic substances (Brandt *et al*., 2010b).

There have been no previously reported deaths from MDAI, although there has been at least one admission to hospital as mentioned earlier. Its safety profile is unknown. No definitive concentrations of MDAI have been established previously for toxic effects or death in animals or humans.

FATALITY CASE REPORTS

The National Programme on Substance Abuse Deaths (np-SAD) receives information on a voluntary basis from Coroners in the UK on relating to inquests completed on involving drug-related deaths (Ghodse *et al*., 2012). Here, we present a brief report on three deaths that occurred in 2011 and 2012 in which MDAI was implicated. These cases were notified to the programme between November 2011 and May 2012 as part of routine data submission. Additional information was provided by Coroners in the form of autopsy and toxicology reports.

Case 1

A 17-year-old employed white woman died in April 2011 on the Isle of Man. She was not known to the police or drug and alcohol services. She had arrived at her boyfriend's home about 18:30, where they had eaten and drunk alcohol. The boyfriend took some MDAI and went to take a shower. He believes the decedent consumed some of the drug whilst he was doing this as she was livelier when he returned. She then calmed down, acting as if she was sleepy, became overheated, sweated and fainted before slumping on the sofa and stopped breathing. Emergency services, called at 21:36, found her not to be breathing, without a pulse or cardiac activity. Intubation was unsuccessful as she had a clenched jaw. Resuscitation was unsuccessful, and she suffered a cardiac arrest in the ambulance en route to hospital.

A small amount of cannabis resin was found at the scene, together with white powder. This was confirmed as being MDAI, which the decedent's boyfriend had purchased on the Internet, together with '5-Ai' (likely to be 5-IAI or 5-iodo-2-aminoindan). Qualitative screening of femoral blood for a wide range of compounds taken 2 days after death by U/HPLC-DAD and LCMS detected MDAI. Subsequent measurement by HPLC-DAD found MDAI at a concentration of 26.3 mg/L. Quantitative screening by HSGC-FID found an ethanol concentration of 14 mg/dL. No other drugs or metabolites, including 5-iodo-2-aminoindan (5-IAI), were found. The low concentration of ethanol could have been due all or in part to microbial fermentation and does not necessarily indicate alcohol consumption prior to death. The pathologist in the case considered that even if the ethanol present derived from alcohol consumption, 'the concentration is such that it is very unlikely either to have been associated with significant clinical symptoms or to have contributed significantly to death.'

The animal studies mentioned earlier involving MDAI indicate that the substance can produce an increase in serotonin. A significant increase in serotonin can produce 'serotonin syndrome', symptoms of which may include the following: tachycardia (increased heart rate), hypertension (increased blood pressure), hyperthermia (increased body temperature), clenched jaw and seizures (Boyer and Shannon, 2005; Rasimas, 2012). Some of these symptoms are indicated to have occurred in respect of the deceased, suggesting therefore that an increase in serotonin had occurred especially as there were no other drugs detected that could have caused such an effect. As there were no reported or published non-fatal or fatal cases involving MDAI, it was not possible to determine whether the blood level of 26.3 mg/L corresponded to 'recreational' or excessive use prior to death.

The pathologist identified three 'clinical' observations and autopsy findings, all of which could be associated with MDMA toxicity, that support a diagnosis of MDAI toxicity as the cause of death in this case: (i) the boyfriend referred to her 'sweating' and 'overheating' before collapsing; (ii) one of the paramedics was unable to insert an airway into the deceased's mouth because her jaw was tightly clenched; and (iii) the external surfaces of the heart, lungs and the spleen showed multiple haemorrhages of various sizes, some almost petechial (less than 3 mm) and some considerably

DOI: 10.1002/hup

larger. This suggests DIC, a consequence reported in a number of deaths involving MDMA (White, 2002; Liechti *et al*., 2005; Strobbe *et al*., 2007; Dahl *et al*., 2008; Nadkarni *et al*., 2012). Furthermore, there was no natural disease present to cause or contribute to the death. In November 2011, the Coroner endorsed the pathologist's cause of death as 'toxicity of 5,6-methylenedioxy-2-aminoindane (MDAI)', recording a verdict of 'misadventure—toxicity of 5,6-methylenedioxy-2-aminoindane (MDAI) which was self-ingested'.

Opening the inquest, the Coroner said that the death of a young person so close to her 18th birthday should be a warning to anyone considering taking such substances (Manx Radio, 2011a). When concluding the inquest, he stressed the danger of MDAI's availability (Manx Radio, 2011b), recommending that it be added to the Island's list of controlled substances (IOMtoday.co.im, 2011). Following consultations with the Isle of Man's ACMD, Tynwald (the Island's parliament) designated MDAI as a class C drug under their Misuse of Drugs Act 1976, for an initial period of 12 months from 1 January 2012. After this, a further order will be made, subject to approval (three.fm, 2011).

Case 2

A single unemployed white man aged 35 years, living with his parents in Derbyshire (England), was found dead in bed in July 2011. He had a history of depression and anxiety but was not prescribed medications. Bags of powder labelled 'Benzo Fury', 'MDA-I' and '5-APB' were found at the scene, along with empty beer bottles and instructions for the manufacture of LSD.

Toxicological analysis using Gas Chromatography-Mass Spectrometry (GC-MS) of post-mortem samples, taken 2 days after death, was conducted. [It was not possible using this technique to distinguish between 5-APB and 6-APB, both of which were found at the scene (Personal communication, Dr Stephanie Barber, 26 November 2012).] A urine drug screen was positive for MDAI, MDMA, MDA, d-amphetamine (trace), BZP, TFMPP and caffeine. The alcohol levels detected were as follows: urine 81 mg/dL and blood 46 mg/dL. The blood levels of other substances were as follows: MDAI—3.3 mg/L; APB—0.34 mg/L [the authors have assumed that this concentration relates to 5-APB as one of the products found was labelled as such]; BZP—0.19 mg/L, d-amphetamine < 0.1 mg/L, MDMA 0.1 mg/L, MDA (interference) and caffeine 19.2 mg/L]. Intake of these compounds individually cannot be excluded. The levels of d-amphetamine, BZP and MDMA do not suggest toxicity. The level of caffeine is slightly higher than usually seen in caffeine consumption but is not at the level usually associated with significant toxicity. The results for MDAI and APB could not be interpreted at the time as there were no data on their toxicity. The ethanol level is consistent with moderate alcohol consumption and is unlikely to have contributed to the cause of death.

The aforementioned toxicological findings suggest that, apart from MDAI and APB, none of the substances found were at levels usually associated with toxicity alone. The possibility of combined or idiosyncratic effects cannot be excluded. All the drugs detected are stimulants, which, as a class, are associated with the potential to cause fatal idiosyncratic cardiac or cerebrovascular toxicity. All of the substances present in this case, except caffeine, are considered to cause serotonin release, with BZP and d-amphetamine also thought to reduce serotonin re-uptake at synapses. BZP is also considered to have serotonin receptor agonist properties (Antia *et al*., 2009). Therefore, it is possible that this combination of compounds could cause significantly raised levels of serotonin in the brain, possibly inducing 'serotonin syndrome' (or serotonin toxicity). This is a potentially fatal disorder resulting from high levels of serotonin in the brain (Mueller and Korey, 1998; Vuori *et al*., 2003; Pilgrim *et al*., 2009, 2012; Warrick *et al*., 2012). User fora suggests that the use of MDAI with other stimulants may have caused this syndrome in some individuals (Drugs Forum, 2009b; Bluelight, 2010b; Dmt-Nexus, 2010). The Coroner gave the cause of death as 'combined drug toxicity' and recorded a verdict of 'misadventure' in April 2012.

Case 3

A single white man aged 28 years died in Bedfordshire (England) in January 2012, having been found unresponsive on his bed at home. He was known to purchase drugs over the Internet. He was prescribed a number of medications, including the following: citalopram, clomipramine, doxylamine, ibuprofen, olanzapine and paroxetine. It was thought the decedent may have consumed 'legal highs' and cocaine. Numerous branded substances were seized and submitted for toxicological analysis. Mass spectrometry (QTOF-MS) of these products found the following: 'Blow'—MDAI, lignocaine, caffeine, MPA; 'Atomic Bomb'—AM 2201 (synthetic cannabinoid); 'Bombay Blue'—AM 2201; 'Ex-Ses Platinum'—AM 2201; 'Spike 99 Ultra'—AM 2201; 'Superchillem'—possibly AM 2201, unidentified compound (possible synthetic cannabinoids); 'Ice Bud'—AM 1248 (synthetic cannabinoid); 'Super Solar'—AM 1248, AM694 (synthetic cannabinoids); 'Tribal Warrior'—AM 1248, AM 694. A glass snort pipe containing white powder was found to contain

DOI: 10.1002/hup

MDAI, lignocaine, caffeine and MPA, thereby suggesting the 'Blow' product may have been used.

Preliminary immunoassay screening of post-mortem urine was positive for amphetamines (possibly because of the presence of MDAI); qualitative screening for a wide range of compounds by HPLC-DAD, QTOF-MS and LC-MS detected—MDAI, olanzapine (+ metabolite), lignocaine (+ metabolite), clomipramine (+ metabolites), caffeine and MPA. Analysis for possible drug glucuronide metabolites (e.g. synthetic cannabinoids) by LC-MS-MS and QTOF-MS detected no compounds. The ethanol concentrations were as follows: urine 30 mg/dL and blood 59 mg/dL. Corresponding qualitative screening of post-mortem femoral blood by U/HPLC-DAD and LC-MS detected: MDAI, clomipramine (+ metabolites), caffeine, lignocaine and MPA. The concentrations of MPA detected were 6.71 mg/L (unpreserved blood) and 5.47 mg/L (fluoride-preserved blood) in the blood samples. There was no evidence of recent use of cocaine or other class A drugs.

The concentrations of ethanol indicate the consumption of alcohol probably recently before death. The presence of olanzapine in the post-mortem urine but absence in the blood is consistent with previous rather than therapeutic use; alternatively, the olanzapine may have degraded as it is an unstable drug and must be assayed very quickly after death. The low concentration of clomipramine in the blood is consistent with therapeutic use. Lignocaine and caffeine were found both in the post-mortem blood and the 'Blow' product, along with MDAI and MPA. The presence of putrefactants in the blood prevented the accurate measurement of MDAI.

MPA is a sulphur-containing compound structurally similar to methylamphetamine and has been marketed on the Internet as a 'research chemical' or 'legal high'. It is not controlled in the UK and is available as a white powder, which is normally 'snorted'. The reported desired effects are mild euphoria and increased energy. There is very little information available regarding drug levels, effects and toxicity for this substance. Anecdotal reports include adverse effects such as increased heart rate, sweating, vasoconstriction and cold extremities, chest pain and nausea. It is not possible to relate the measured levels of MPA (6.7 and 5.5 mg/L) to 'normal' recreational or 'overdose' levels. In another fatal case involving MPA, investigated by the second author's laboratory, a preserved post-mortem femoral blood concentration of 3.2 mg/L was found; this should not be taken as indicating a fatal level for this drug.

The adverse effects of MDAI and MPA appear to be consistent with other stimulants and related drugs (e.g. MDMA and other amphetamine type substances) and therefore may result in cardiac effects. Recent drug user fora reports the combined use of both these substances (Herbalhighs, 2012b). The Coroner gave the cause of death in this case as 'drug toxicity' and recorded a verdict of 'He died from illicit and non-prescription drugs' in May 2012.

DISCUSSION

It is difficult to keep abreast of the new products being created by 'research chemists' involved in illicit markets/activities. It is important that both consumers of recreational drugs and health professionals treating them appreciate that the psychoactive ingredients of substances sold under brand names change rapidly over time, and thus, the effects experienced by users may vary, as may the potential for toxicity (Corkery *et al.*, 2012b).

At the time of writing, no poisonings, other than the case reported by George *et al.* (2011), or fatalities involving MDAI had been reported in the scientific literature. Indeed, this paper is believed to be the first such article to describe fatalities in which the presence of MDAI was recorded, let alone implicated. There is no relevant pharmacological information on this drug in terms of lethal dosage, LD_{50}, half-life, volume of distribution and so on. for either animal or human subjects. It is not possible to determine from a single blood sample when a substance was consumed or the exact amount taken. Because of the lack of comparative data, it was not possible to relate the MDAI concentrations reported here to 'recreational' or excessive use, nor comment as to the toxicological significance of the concentrations.

Fatalities involving MDAI appear to be very rare events, and thus, there was practically nothing in terms of hard evidence that could be used to inform cases such as the ones described here (Table 1). This paper now provides some insights into the potential fatal toxicity of MDAI. The experiences and effects of MDAI are similar to those reported by users of other products that have been controlled recently under UK drugs legislation, for example, piperazines, mephedrone, MDPV and other methcathinone analogues. 'Serotonin syndrome' appears to be a possible factor in these MDAI-related deaths. It is important that forensic toxicologists and ED staff do not overlook the possibility of the ingestion of recreational aminoindanes. Whenever possible, full details should be obtained of the circumstances leading to hospitalisation or death so that the appropriate toxicological investigations and, if necessary, medical interventions can be conducted.

DOI: 10.1002/hup

Table 1. Summary of fatal cases

Attribute/feature	Case 1	Case 2	Case 3
Age at death (years)	17	35	28
Gender	Female	Male	Male
Ethnicity	White	White	White
Drug use history	None	None	Purchased drugs over Internet
Employment status	Employed (non-manual)	Unemployed	Unemployed
Date of death	April 2011	July 2011	January 2012
Place of drug consumption	Boyfriend's home	At home	At home
Place of death	Cardiac arrest in ambulance en route to hospital	At home	At home
Post-mortem toxicological findings	MDAI 26.3 mg/L; ethanol 14 mg/dL	Urine drug screen positive for MDAI, MDMA, MDA, d-amphetamine (trace), BZP, TFMPP and caffeine. Alcohol levels: urine 81 mg/dL, blood 46 mg/dL. Blood levels of other substances were: MDAI—3.3 mg/L; APB—0.34 mg/L; BZP—0.19 mg/L; d-amphetamine < 0.1 mg/L; MDMA <0.1 mg/L; MDA (interference); and caffeine 19.2 mg/L.	Immunoassay urine screen positive for amphetamines (possibly due to the presence of MDAI); qualitative screening detected—MDAI, olanzapine (+ metabolite), lignocaine (+ metabolite), clomipramine (+ metabolites), caffeine, MPA. Ethanol levels: urine 30 mg/dL, blood 59 mg/dL. Qualitative screening of femoral blood: MDAI, clomipramine (+ metabolites), caffeine, lignocaine and MPA. MPA concentrations: 6.71 mg/L (unpreserved blood), and 5.47 mg/L (fluoride-preserved blood).
Key pathological findings	(a) sweating and overheating before collapsing; (b) paramedic was unable to insert an airway into the deceased's mouth because her jaw was tightly clenched; (c) the external surfaces of the heart, lungs and the spleen showed multiple haemorrhages of various sizes, some almost petechial (less than 3 mm) and some considerably larger. This suggests disseminated intravascular coagulation (DIC).	This combination of compounds could cause significantly raised levels of serotonin in the brain, possibly inducing 'serotonin syndrome'.	The adverse effects of MDAI and MPA appear to be consistent with other stimulants and related drugs (e.g. MDMA and other amphetamine type substances), and therefore may result in cardiac effects.
Cause of death	Toxicity of 5,6-methylenedioxy-2-aminoindane (MDAI)	Combined drug toxicity	Drug toxicity
Coroner's verdict	Misadventure—Toxicity of 5,6-methylene-dioxy-2-aminoindane (MDAI) which was self-ingested	Misadventure	Died from illicit and non-prescription drugs
Coroner's area	Isle of Man	North Derbyshire	Bedfordshire and Luton

DOI: 10.1002/hup

CONCLUSIONS

There is a significant lack of information for MDAI in terms of its pharmacology, pharmacokinetics, dose, acute toxicity and the harms caused by long-term use. This paper has updated what is currently known about the toxicity and lethality of this chemical. There is evidence now emerging of serious clinical issues arising from its use; we have described what we believe to be the first deaths in the UK, and possibly worldwide, involving MDAI. On the basis of the limited reliable evidence currently available, management of patients presenting with acute toxic effects from MDAI should remain pragmatic and be in line with treatments employed for stimulants such as amphetamine, cocaine and MDMA.

Because of the relatively recent emergence of this chemical on the recreational drug use scene, its lack of widespread use, unknown toxicity and lack of detection through routine toxicological screens in many forensic toxicology laboratories, use of this substance could be missed by clinicians. Similarly, fatalities caused by its consumption may be overlooked by those investigating sudden deaths with no apparent cause(s). Determination of the significance and role in death, if any, has to be provisional and delivered with caution, qualifications and reservations. Even if its use may no longer be increasing (evidence of which is still awaited), MDAI should not be ignored—least of all because of its potential to cause (fatal) toxicity.

CONFLICTS OF INTEREST

No conflicts of interest are declared here that may have influenced the interpretation of present data. Please note the following: F. S. is a full member of the UK ACMD; F. S. and J. C. are members of the ACMD's NPS working group; S. E. is a member of the Independent Scientific Committee on Drugs (ISCD); and A. H. G. was the immediate Past President of the United Nations International Narcotics Control Board (INCB). The views expressed here reflect only the authors' views and not necessarily those of the Home Office, the ACMD, ISCD or the INCB.

ACKNOWLEDGEMENTS

This paper is dedicated to the memory of Professor Abdol Hamid Ghodse who passed away unexpectedly on 27 December 2012. His inspiration and encouragement guided the careers of many who came into contact with him or had the privilege of working with him, including J. C. and F. S. Professor Ghodse played a key role in setting up the np-SAD in 1997 and guiding it over the past 15 years. Its success and impact are a testimony to his leadership. He will be sorely missed in the field of addiction research and evidence-based policy formulation.

The authors wish to thank Her Majesty's Coroners in England and Wales, Northern Ireland, and the Islands; procurators fiscal in Scotland; and the Scottish Crime and Drug Enforcement Agency for their assistance in providing data to the np-SAD. In particular, we would like to thank Her Majesty's Coroners for The Hundred of Scarsdale and High Peak (Derbyshire) and Bedfordshire and Luton, and the Coroner of Inquests for the Isle of Man, and their staff, for providing access to the coronial documents for these specific cases. Thanks are also due to John Ramsey, Director of TICTAC Communications Ltd, St George's, University of London; the Drugs Intelligence team at LGC Forensics, Teddington, UK; Dr Stephanie Barber, Consultant Clinical Biochemist, Nottingham University Hospitals NHS Trust.

This study received no funding. This study was conducted as part of an ongoing data collection by the np-SAD.

ETHICAL APPROVAL

The Central Office for Research Ethics Committees (COREC), National Patient Safety Agency confirmed in writing (February 2006) that the np-SAD programme does not require NHS REC review as the subjects of the research are deceased.

CONTRIBUTORS

John Corkery undertook data collection and preparation. Simon Elliott supervised and interpreted the toxicological analysis for two of the case reports. Fabrizio Schifano contributed information on pharmacology and market availability. Ornella Corazza provided information on epidemiological data from online websites. All authors contributed to the writing of the paper.

REFERENCES

Antia U, Tingle MD, Russell BR. 2009. 'Party pill' drugs—BZP and TFMPP. *N Z Med J* **122**(1307): 55–68.

Bangingtunes. 2009. MDAI. Retrieved 21 October, 2012 from http://www.bangingtunes.com/forum/topic/t124659/.

Baron M, Elie M, Elie L. 2011. An analysis of legal highs: do they contain what it says on the tin?. *Drug Test Anal* **3**(9): 576–581.

BBC. 2010. Drugs workers in Wales warn over new 'legal highs' Eye on Wales, 1830 BST on Monday 24 May on BBC Radio Wales. Retrieved 21 October, 2012 from http://www.bbc.co.uk/news/10144368.

BBC. 2012. Isle of Man government MDAI 'legal high' ban extended, 17 December. Retrieved 18 December, 2012 from http://www.bbc.co.uk/news/world-europe-isle-of-man-20754659.

Benmansour S, Brunswick DJ. 1994. The MAO-B inhibitor deprenyl, but not the MAO-A inhibitor clorgyline, potentiates the neurotoxicity of *p*-chloroamphetamine. *Brain Res* **650**(2): 305–312.

Bluelight. 2010a. MDAI New Experience. Retrieved 21 October, 2012 from http://www.bluelight.ru/vb/threads/511387-%28MDAI%29-New-Experience.

Bluelight. 2010b. The Big amp Dandy MDAI Thread. Retrieved 28 November, 2012 from http://www.bluelight.ru/vb/threads/434331-The-Big-amp-Dandy-MDAI-Thread/page21.

Boyer EW, Shannon M. 2005. The serotonin syndrome. *N Engl J Med* **352**(11): 1112–1120.

Brandt SD, Wootton RC, De Paoli G, Freeman S. 2010a. The naphyrone story: the alpha or beta-naphthyl isomer?. *Drug Test Anal* **2**(10): 496–502.

Brandt SD, Sumnall HR, Measham F, Cole J. 2010b. Analyses of second-generation 'legal highs' in the UK: initial findings. *Drug Test Anal* **2**(8): 377–382.

Corkery JM, Elliott S, Schifano F, Corazza O, Ghodse AH. 2012a. 2-DPMP (desoxypipradrol, 2-benzhydrylpiperidine, 2-phenylmethylpiperidine) and d2pm (diphenyl-2-pyrrolidin-2-yl-methanol, diphenylprolinol): a preliminary review. *Prog Neuropsychopharmacol Biol Psychiatry* **39**(2): 253–258.

Corkery JM, Schifano F, Ghodse AH. 2012b. Mephedrone-related fatalities in the United Kingdom: contextual, clinical and practical issues. In *Pharmacology*, Gallelli L (ed). InTech—Open Access Publisher: Rijeka, Croatia; 355–380. ISBN 979-953-307-482-4. Available at: http://www.intechopen.com/books/pharmacology/mephedrone-related-fatalities-in-the-united-kingdom-contextual-clinical-and-practical-issues.

Dahl MK, Johansen SS, Ramlau J, Jensen KA. 2008. Overlevelse efter svaer ecstasyforgiftning. [Survival after severe ecstasy intoxication] [Article in Danish]. *Ugeskr Laeger* **170**(45): 3678.

Dmt-Nexus. 2010. MDAI + aco-dipt = serotonin syndrome crisis. Retrieved 28 November, 2012 from https://www.dmt-nexus.me/forum/default.aspx?g=posts&t=17509.

Drugs Forum. 2009a. MDAI (5,6-methylenedioxy-2-aminoindane) Experiences. Retrieved 21 October, 2012 from http://www.drugs-forum.com/forum/showthread.php?t=98431.

Drugs Forum. 2009b. MDAI (5,6-methylenedioxy-2-aminoindane) Drug Info. Retrieved 28 November, 2012 from http://www.drugs-forum.com/forum/showthread.php?t=97712

EMCDDA. 2012. The state of the drugs problem in the EU. Annual Report 2012. European Monitoring Centre for Drugs and Drug Addiction: Lisbon. 15 November. Retrieved 19 November, 2012 from http://www.emcdda.europa.eu/publications/annual-report/2012.

EMCDDA, Europol. 2010. EMCDDA–Europol 2010 Annual Report on the implementation of Council Decision 2005/387/JHA. European Monitoring Centre for Drugs and Drug Addiction: Lisbon. Available at: http://www.emcdda.europa.eu/publications/implementation-reports/2010.

FSS. 2010. Drugs update Issue 52: July–September 2010. Drugs Intelligence Unit, Forensic Science Service: Birmingham, UK.

Gallagher CT, Assi S, Stair JL, *et al*.. 2012. 5,6-Methylenedioxy-2-aminoindane: from laboratory curiosity to 'legal high'. *Hum Psychopharmacol Clin Exp* **27**(2): 106–112.

George NC, James DA, Thomas SHL. 2011. Exposure to MDAI: a case report. abstract 71. [abstracts of the 2011 international congress of the European association of poisons centres and clinical toxicologists, 24–27 May 2011, Dubrovnik, Croatia]. *Clin Toxicol (Phila)* **49**(3): 197–269.

Ghodse H, Corkery J, Schifano F, Piolanti A, Trincas G, Di Melchiorre G. 2012. Drug-related deaths in the UK: annual report 2011. Drug-related deaths reported by Coroners in England, Wales, Northern Ireland, Guernsey, Jersey and the Isle of Man; Police forces in Scotland; and the Northern Ireland Statistics and Research Agency—Annual Report January–December 2010. International Centre for Drug Policy, St George's University of London: London, 7 November 2012. Retrieved 8 November, 2012 from http://www.sgul.ac.uk/research/projects/icdp/our-work-programmes/pdfs/np-SAD%2012th%20annual%20report%202011.pdf.

Herbalhighs. 2012a. MDAI. Retrieved 21 October, 2012 from http://forum.herbalhighs.com/showthread.php?tid=6715.

Herbalhighs. 2012b. MDAI + MPA Combo. Retrieved 21 October, 2012 from http://forum.herbalhighs.com/showthread.php?tid=6853.

IOM. 2011. Isle of Man bans so called 'legal high' MDAI, 14 December. Isle of Man Government. Retrieved 30 May, 2012 from http://www.gov.im/lib/news/dhss/isleofmanbanssoc.xml.

IOMtoday.co.im. 2011. Legal high is banned after death of teen, 15 December 2011. Retrieved 21 October, 2012 from http://www.iomtoday.co.im/news/isle-of-man-news/legal_high_is_banned_after_death_of_teen_1_4059791.

Johnson MP. 1991. Pharmacological characterization of 3,4-methylenedioxymethamphetamine analogues. Corollaries to mechanisms of behavioral and neurotoxic activity. Ph.D. thesis. Purdue University, West Lafayette, IN.

Johnson MP, Conarty PF, Nichols DE. 1991a. [3H] monoamine releasing and uptake inhibition properties of 3,4-methylenedioxyamphetamine (MDMA) and *p*-chloroamphetamine (PCA) analogues. *Eur J Pharmacol* **200**(1): 9–16.

Johnson MP, Frescas SP, Oberlender R, Nichols DE. 1991b. Synthesis and pharmacological examination of 1-(3-methoxy-4-methylphenyl)-2-aminopropane and 5-methoxy-6-methyl-2-aminoindan: similarities to 3,4-(methylenedioxy)methamphetamine (MDMA). *J Med Chem* **34**(5): 1662–1668.

Johnson MP, Huang XM, Nichols DE. 1991c. Serotonin neurotoxicity in rats after combined treatment with a dopaminergic agent followed by a non-neurotoxic 3,4-methylenedioxyamphetamine (MDMA) analogue. *Pharmacol Biochem Behav* **40**(4): 915–922.

Kovar KA. 1998. Chemistry and pharmacology of hallucinogens, entactogens and stimulants. *Pharmacopsychiatry* **31**(Suppl. 2): 69–72.

Leach B. 2010. 'Woof woof' is new 'miaow miaow'. The Telegraph, 28 June 2010. Retrieved 21 October, 2012 from http://www.telegraph.co.uk/news/uknews/crime/7858157/Woof-woof-is-new-miaow-miaow.html.

Liechti ME, Kunz I, Kupferschmidt H. 2005. Acute medical problems due to Ecstasy use. Case-series of emergency department visits. *Swiss Med Wkly* **135**(43–44): 652–657.

Manx Radio. 2011a. Teenager dies after taking legal high, 25 May 2011. Retrieved 21 October, 2012 from http://www.manxradio.com/newsread.aspx?id=52309.

Manx Radio. 2011b. 'Ban legal high drug' call from coroner, 9 November 2011. Retrieved 21 October, 2012 from http://www.manxradio.com/newsread.aspx?id=55985.

Measham F, Moore K, Østergaard J. 2011. Emerging drug trends in Lancashire: night time economy surveys—phase one report. Lancaster University, UK. Retrieved 12 July, 2012 from http://www.ldaat.org/files/emerging_trends_report.pdf

Mixmag. 2011. The 2011 Mixmag Drugs Survey. *Mixmag* (238): 49–59.

Mixmag. 2012. Mixmag/guardian drugs survey. *Mixmag* (251): 68–73.

Monte AP, Narona-Lewicka D, Cozzi NV, Nichols DE. 1993. Synthesis and pharmacological examination of benzofuran, indan, and tetralin analogues of 3,4-(methylenedioxy)amphetamine. *J Med Chem* **36**(23): 3700–3706.

Mueller PD, Korey WS. 1998. Death by "ecstasy": the serotonin syndrome? *Ann Emerg Med* **32**(3 Pt 1): 377–380.

Nadkarni GN, Hoskote SS, Piotrkowski J, Annapureddy N. 2012. Serotonin syndrome, disseminated intravascular coagulation, and hepatitis after a single ingestion of MDMA in an Asian woman. *Am J Ther* [Epub ahead of print].

Nichols DE, Brewster WK, Johnson MP, Oberlender R, Riggs RM. 1990. Non-neurotoxic tetralin and indan analogues of 3,4-(methyledioxy)-amphetamine (MDA). *J Med Chem* **33**(2): 703–710.

Nichols DE, Oberlender R. 1991. Structural–activity relationship of MDMA-like substances. *NIDA Res Monogr* **9**: 1–29.

NPIS. 2011. *National Poisons Information Service Annual Report 2010/2011*. Health Protection Agency: London.

NPIS. 2012. *National Poisons Information Service Annual Report 2011/2012*. Health Protection Agency: London.

Partyvibe. 2012. MDAI warning Read. Retrieved 21 October, 2012 from http://www.partyvibe.com/forums/legal-herbal-highs/50942-mdai-warning-read.html.

Pilgrim JL, Gerostamoulos D, Drummer OH, Bollmann M. 2009. Involvement of amphetamines in sudden and unexpected death. *J Forensic Sci* **54**(2): 478–485.

Pilgrim JL, Gerostamoulos D, Woodford N, Drummer OH. 2012. Serotonin toxicity involving MDMA (ecstasy) and moclobemide. *Forensic Sci Int* **215**(1–3): 184–188.

Ramsey J, Dargan PI, Smyllie M, *et al*.. 2010. Buying 'legal' recreational drugs does not mean that you are not breaking the law. *QJM* **103**(10): 777–783.

Rasimas JJ. 2012. "Bath salts" and the return of serotonin syndrome. *J Clin Psychiatry* **73**(8): 1126–1127.

ReDNet. 2011. MDAI technical paper. Recreational Drugs European Network. School of Pharmacy, University of Hertfordshire, UK, Unpublished report.

Sainsbury PD, Kicman AT, Archer RP, King LA, Braithwaite RA. 2011. Aminoindanes—the next wave of 'legal highs'? *Drug Test Anal* **3**(7–8): 479–482.

Sejm. 2010. O zmianie ustawy o przeciwdzialaniu narkomanii oraz ustawy o Państwowej Inspekcjii Sanitarnej [The Act on Counteracting Drug Addiction and the Act on State sanitary inspection]. Dziennik ustaw N. 213, Poz.1396. 8 October. Sejm: Warsaw.

Sprague JE, Johnson MP, Schmidt CJ, Nichols DE. 1996. Studies on the mechanism of *p*-chloroamphetamine neurotoxicity. *Biochem Pharmacol* **52**(8): 1271–1277.

Strobbe L, de Jaer CP, Louwerse ES, Rozendaal FW. 2007. Ecstasy-intoxicatie met fatale afloop bij een 22-jarige man. [Fatal ecstasy intoxication in a 22-year-old man]. [Article in Dutch]. *Ned Tijdschr Geneeskd* **151**(30): 1690–1694.

Three.fm. 2011. Legal high MDAI to be outlawed from January 1st, 14 December 2011. Retrieved 16 February, 2012 from http://www.three.fm/news/isle-of-man-news/legal-high-mdai-to-be-outlawed-from-january-1st-4643/.

Townsend M. 2010. New drug set to replace mephedrone as a legal high. The Guardian, 18 April. Retrieved 21 October, 2012 from http://www.guardian.co.uk/society/2010/apr/18/drug-replace-ban-mephedrone.

Vuori E, Henry JA, Ojanperä I, *et al*. 2003. Death following ingestion of MDMA (ecstasy) and moclobemide. *Addiction* **98**(3): 365–368.

Warrick BJ, Wilson J, Hedge M, Freeman S, Leonard K, Aaron C. 2012. Lethal serotonin syndrome after methylone and butylone ingestion. *J Med Toxicol* **8**(1): 65–68.

White SR. 2002. Amphetamine toxicity. *Semin Respir Crit Care Med* **23**(1): 27–36.

Wood DM, Hunter L, Measham F, Dargan PI. 2012. Limited use of novel psychoactive substances in South London nightclubs. *QJM* **105**(10): 959–964.

DOI: 10.1002/hup