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Abstract: 2-DPMP (Desoxypipradrol, 2-Benzhydrylpiperidine, 2-Phenylmethylpiperidine) and D2PM (Diphenyl-2-pyrrolidin-2-yl-methanol, Diphenylprolinol) are psychoactive substances, sold primarily over the Internet and in 'head' shops as 'legal highs', 'research chemicals' or 'plant food'. Originally developed in the 1950s for the treatment of narcolepsy and ADHD, 2-DPMP's use soon became very limited. Recreational use of 2-DPMP and D2PM appears to have started in March 2007, but only developed slowly. However, in the UK their popularity grew in 2009, increasing rapidly during summer 2010. At this time, there were many presentations to UK Emergency Department by, patients complaining of undesirable physical and psychiatric effects after taking 2-DPMP. In spring 2011 there were similar presentations for D2PM. Recreational use of these drugs has been reported only occasionally in on-line user fora. There is little scientifically-based literature on the pharmacological, physiological, psychopharmacological, toxicological and epidemiological characteristics of these drugs. Here we describe what is known about them, especially on their toxicity, including what we believe to be the first three deaths involving the use of 2-DPMP in August 2010. There are no international controls imposed on 2-DPMP or D2PM. However, a ban on their UK importation was imposed in November 2011. It is critical that any other cases, including non-fatal overdoses, are documented so that a scientific evidence-base can be established for them.

Ethical Statement

No ethical approval was required as the subjects were deceased.

Highlights

- 2-DPMP and D2PM are psychoactive and sold mainly on the Internet and in ‘head’ shops
- Recreational use of both drugs began slowly in March 2007, increasing rapidly during summer 2010, and into 2011 for D2PM
- Patients presented to UK EDs with undesirable physical & psychiatric effects
- Three UK deaths involving use of 2-DPMP occurred in August 2010
- Little is known about 2-DPMP and D2PM so a scientific evidence-base needs to be established for both drugs

2-DPMP (Desoxypipradrol, 2-Benzhydrylpiperidine, 2-Phenylmethylpiperidine) and D2PM (Diphenyl-2-pyrrolidin-2-yl-methanol, Diphenylprolinol): a preliminary review

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List of abbreviations:

2-DPMP = Desoxypipradrol, 2-Benzhydrylpiperidine, 2-Phenylmethylpiperidine
ACMD = Advisory Council on the Misuse of Drugs
CAT = Computed axial tomography
D2PM = Diphenyl-2-pyrrolidin-2-yl-methanol, Diphenylprolinol
DA = Dopaminergic
DAT = Dopamine transporter
ED = Emergency Department
EDND = European Database on New Drugs
EWS = Early Warning System
LD_{50} = Median lethal dose
MDA = 3,4-Methylenedioxyamphetamine
MDMA = 3,4-Methylenedioxy-N-methylamphetamine
MDPV = Methylenedioxypyrovalerone
NA = Noradrenergic
NPS = Novel Psychoactive Substance
ReDNet = Recreational Drugs European Network
UK = United Kingdom
USA = United States of America
UV = Ultra Violet

2-DPMP (Desoxypipradrol, 2-Benzhydrylpiperidine, 2-Phenylmethylpiperidine) and D2PM (Diphenyl-2-pyrrolidin-2-yl-methanol, Diphenylprolinol): a preliminary review

1 Introduction

1.1 The last few years have seen increasingly rapid changes in the production, supply, and consumption of novel psychoactive substances (NPS). 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.

1.2 The aim of this paper is to improve the knowledge-base in respect of two NPS that recently appeared on the market, 2-DPMP and D2PM, by reviewing what is known about them, especially their 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 contributed to by 2-DPMP.

2 Chemistry

2.1 The chemical 2-DPMP is known by several designations: Desoxypipradrol, 2-Benzhydrylpiperidine, 2-Phenylmethylpiperidine, and ‘Pippy’. It is very closely related chemically to the compounds pipradrol (diphenyl-2-piperidenemethanol), being its desoxy form, and methylphenidate (Ritalin, Concerta, Equasym XL, Metadate, or Methylin).

2.2 D2PM (Diphenyl-2-pyrrolidin-2-yl-methanol, Diphenylprolinol) is a pyrrolidine analogue of pipradrol. The size of the nitrogen containing ring distinguishes these two chemicals (Figure 1). Similar to pipradrols, 2-DPMP has a piperidines ring containing 6 members; D2PM has only 5 members (Wood et al., 2011b).

< Insert Figure 1 about here>

3 Use of 2-DPMP and D2PM

3.1 2-DPMP was developed by CIBA-Geigy (now Novartis) in the 1950s for the treatment of narcolepsy and Attention Deficit Hyperactivity Disorder (ADHD) (Tripod et al., 1954). However it was found that its elimination half-life was longer than the other related compounds (Ferris and Tang, 1979). Desoxypipradrol was reserved for other applications, including the facilitation of rapid recovery from anaesthesia (Bellucci, 1955).

3.2 From online drug user fora it appears that recreational use of 2-DPMP started being discussed about March 2007, appearing more widespread on the Internet during 2008 (Psychonaut, 2009), and gaining popularity as a replacement for methylphenidate. Since then, it has been increasingly available for purchase in the UK. According to the European Database on New Drugs (EDND), it was first seen as a white powder in a Customs seizure of a postal package at Helsinki airport, Finland, in February 2009. In its 2009 Annual Report to the EDND, the Finnish Focal Point gave information on 6 further seizures of powder. In the UK during 2009, 2-DPMP was found in a clear plastic sachet of white powder labelled ‘Desoxypipradol’ (sic) ‘20mg’ by TICTAC Communications Ltd, and in a collected sample (20mg) of “Ivory Wave” submitted to the Forensic Science Service in Scotland. Another case analysed in Liverpool also contained 2-DPMP. “Ivory Wave” seized in Cumbria contained in foil re-sealable packets was found to contain the substance, as was a seizure made by Lincolnshire police in December 2009 (EWS, 2010; EDND, 2012a). In December 2010 the Hungarian police made a seizure of the drug (EDND, 2012a).

3.3 D2PM was first identified in March 2007 in tablets bought online and analysed by the toxicology services at St George's, University of London. The recreational use of D2PM was first reported the following year by a patient presenting to a London Emergency Department (ED) with increased blood pressure, agitation, and a sinus tachycardia. He had taken tablets which were later found to contain D2PM and Glaucine (Lidder et al., 2008; Wood et al., 2008). In 2007 and 2008 there were 3 seizures of D2PM powder in Sweden and Finland. From July 2010 the number of seizures and countries reporting them has increased; reports have been made by Belgium, Czech Republic, Germany, Norway, Slovakia, and the UK (EDND, 2012b).

3.4 These substance seem to have been hardly used, known about generally, or encountered by law enforcement and forensic science agencies or Emergency Rooms. This is even true in the UK where most of their European use appears to be concentrated. For these reasons, there is very little scientific information about the drugs, their pharmacology, metabolism, effects, toxicity, and epidemiology.

4 Availability

4.1 2-DPMP was originally advertised under the brand name of "Ivory Wave", as a 'plant fertiliser' or 'plant food'. However, more recently it has been sold as a 'research chemical'. It comes as a hydrochloride salt or in free-base form. Retail websites describe it as "a white crystal powder with not much smell" or "a white coloured fine powder", with a purity of up to 99.9%. Manufacturers and wholesale suppliers appear to be based in countries associated with other 'legal highs' and 'research chemicals', e.g. China, North America, Australia, and Europe. A brief opportunistic Internet search in March 2012 revealed that supplies of 2-DPMP could be ordered in amounts ranging from 100mg to 10kg. Websites advertising 2-DPMP usually display a disclaimer to the effect that it is "not for human consumption", "chemicals are only to be used by laboratories, scientific institutions and some science enthusiasts for private testing", or they are for "technical use only". Some sites carry 'hazard' and 'precautionary' statements.

4.2 D2PM is marketed in similar fashion, usually as D2PM or "Head Candy", described as loose crystalline or fine powder in form, with very high purity levels (e.g. ≥ 98%). Users report that it is odourless and can easily be dissolved in liquids (Drugs Forum, 2007; Bluelight, 2012). Some marketing sites warn of toxic effects in users, and state the product is intended for "forensic purposes" or "chemical research". The amount that could be purchased online in March 2012 ranged from 5mg to 10kg,

5 Legal status

5.1 There are no international controls imposed on 2-DPMP; 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 and Sweden (EDND, 2012a), the Republic of Ireland (Iris Oifigiúil, 2011), and possibly Poland (Sejm, 2010). However, methylphenidate is controlled in the UK under the Misuse of Drugs Act 1971 as a Class B drug, and pipradrol as a Class C substance. The Chair of the independent Advisory Council on the Misuse of Drugs (ACMD) wrote to the UK Home Secretary on 29 October 2010 recommending that an immediate ban be placed on the import of 2-DPMP under the Open General Import Licence. This advice was accepted and the ban came into effect on 4 November 2010 (ACMD, 2010; Home Office, 2010). Following collation of additional information, including data relating to the three fatalities described here, further advice was submitted on 13 September recommending that 2-DPMP be controlled as a Class B drug; an additional recommendation was that the related compounds diphenylprolinol (diphenyl-2-pyrrolidinyl-methanol, D2PM) and 2-dephenylmethylpiperidine are also banned to prevent the development of alternatives to circumvent the ban (ACMD, 2011). On 15 September 2011, the Home Office announced that legislation would be laid before Parliament during the

autumn (Home Office, 2011). At the time of writing, draft regulations (revised to include related substances) which would make them Class B drugs are being debated by Parliament, but are not expected to come into effect until summer 2012. The Finnish Medicines Agency has recommended that D2PM be considered as a medicine with no medicinal use (EDND, 2012b). The drug may be controlled by existing legislation in Poland (Sejm, 2010).

6 Route of administration

6.1 There are several known routes of 2-DPMP administration: insufflation (snorting, sniffing); intravenous injecting; oral (wrapped in a cigarette paper 'bomb', or dissolved in water); and rectal. Smoking and injecting have also been discussed as modes of use (Drugs Forum, 2007). Oral ingestion appears to be the usual route of administration. Doses range from 1-10mg according to mode of use; typical oral doses being 1-2mg, but the optimum dose being thought of as 5-10mg (Drugs Forum, 2007). There is no information as to whether the effects of 2-DPMP are mode or dose-dependent. There are infrequent reports of 2-DPMP being used with cannabis, LSD and ecstasy (Drugs Forum, 2007; Bluelight, 2007).

6.2 The typical human active dose of D2PM is 2-5mg (EDND, 2012b); however user reports suggest that rectal doses range from 10-30mg and oral doses from 35-50mg (ReDNeT, 2011b). According to user for a the usual mode of administration of the drug is rectally in the form of an enema following dissolving D2PM powder in water. The snorting and oral ingestion of this drug are also reported (ReDNeT, 2011b).

7 Pharmacology

7.1 There is little information on the pharmacodynamics and pharmacokinetics of 2-DPMP. The substance acts as a norpinephrine-dopamine reuptake inhibitor (NDRI), and has a similar pharmacological action to pipradrol and methylphenidate (Maxwell et al., 1970; Ferris and Tang, 1979). It is a highly lipophilic molecule lacking polar functional groups that are typically targeted by metabolic enzymes. Limited research suggests that its dopaminergic (DA) and noradrenergic (NA) effects are involved in producing psychoactive effects, although its precise mechanisms of action remain largely unknown. 2-DPMP may act as a potent DA and NA reuptake inhibitor and dopamine transporter (DAT) inhibitor (Ferris and Tang, 1979; Schmitt et al., 2008). In vitro experiments suggest that 2-DPMP potently stimulates dopamine release; furthermore, it is more effective and potent than cocaine in both stimulating release of dopamine and inhibiting its reuptake (Davidson and Ramsey, 2011). *R*-pipradrol appears to be the basis for the psychoactive effects of racemic pipradrol, and is twice as active as the racemate chemical (Kaizaki et al., 2010).

7.2 D2PM also appears to inhibit norephedrine-dopamine reuptake (Davies, 2008; Wood et al., 2008), and is associated with sympathomimetic toxidromal characteristics (Hill and Thomas, 2011).

8 Effects

8.1 Most of the information published on the effects of 2-DPMP is derived from first-hand personal accounts presented in discussion fora. User reports suggest that its effects are felt within 60 minutes of being taken orally, and its effects may last up to 24 or even 48 hours (Bluelight, 2007; Drugs Forum, 2007; ACMD, 2010; ReDNeT, 2011a). The desired psychoactive effects expected by 2-DPMP users may include: euphoria, increased energy and alertness, sociability, and loquacity, as may be encountered from other structurally related phenethylamine stimulants such as amphetamine (Bluelight, 2007; Drugs Forum, 2007).

8.2 Reported acute physical effects of 2-DPMP may include: vaso-constriction; increase in blood pressure; tachycardia; chest pains; headache; loss of appetite; loss of concentration;

sweating; and raised creatine kinase (Herbert et al., 2010; James et al., 2011). Other side-effects reported include: tension in the neck and jaw; teeth grinding (bruxism); movement abnormalities (dystonia, hemiballismus, akathisia); and tremors (James et al., 2011). Acute mental effects reported include: increased alertness and awareness; increased arousal (including libido); anxiety; agitation; hallucinations; insomnia; restlessness; aggression; psychosis; and parasitoic/dermatozoic delusions (Herbert et al., 2010; James et al., 2011). Many of these effects are similar to those described for methylphenidate (Inchem, 2011). These effects are also evident in comments made in online user fora, together with cravings and an increased need to re-dose associated with prolonged use (Bluelight, 2007; Drugs Forum, 2007).

8.3 The desired psychoactive effects of D2PM, similar to those of 2-DPMP, appear to occur after 15 mins and may last up to 10hrs. Reported adverse effects of D2PM include: hyperactivity, confusion, hypertension (Wood et al., 2011b), cardiovascular disturbances (Wood et al., 2011b), hyperthermia, convulsions, bruxism, insomnia, and paranoia (ReDNeT, 2011b; Wood et al., 2011b). As with desoxypipradrol, there are user reports that prolonged use of D2PM causing craving and increased need to re-dose (Bluelight, 2012; Drugs Forum, 2007). Again, it is often used with other substances, including alcohol, absinthe, 2-AI, 4-ACO-MiPT, and phenazepam (ReDNeT, 2011b).

9 Hospital presentations

9.1 In the Republic of Ireland between 30 May and 16 June 2010 the National Poisons Information Centre received 49 calls regarding patients who had suffered adverse effects after taking “Ivory Wave, which laboratory analysis tentatively identified as containing Desoxypipradrol and fluorotropacocaine (Herbert et al., 2010). In August 2010, initial analysis of a collected sample of “Ivory Wave” showed it contained 2-DPMP. Its use in the UK led to many visits to hospital EDs. All 19 patients who presented to an Edinburgh ED in August 2010 with undesirable psychiatric effects after using “Ivory Wave” gave biological samples which proved positive for 2-DPMP (James et al., 2011). Following these and other such incidents, Government Departments and Chief Medical Officers across the British Isles issued advice on how to handle users of “Ivory Wave” who presented to health services seeking assistance (DH England, 2010; CMO & PHD (Scotland), 2010). There were no Edinburgh cases in 2011, and information from the National Poisons Information Service (NPIS) indicated a significant reduction nationally at this time (ACMD, 2011), especially after September 2010 (NPIS, 2011).

9.2 Lidder et al. (2008) report the case of a 21-year old male who presented with acute onset agitation and chest pain after using D2PM. On 5 separate occasions, males aged 17 to 33 years presented to a London ED having used a range of different novel psychoactive substances. They all had ongoing prolonged neuro-psychiatric symptoms of agitation, anxiety and insomnia lasting 24-96 hr after ingestion (Wood et al., 2011b). Sympathomimetic toxicity was not present in any of the cases. Following reassurance and review, all were discharged. Post-discharge urine analysis indicated the presence of D2PM in all five cases, as sole drug in three; mephedrone had been also consumed by one case, and MDMA and amphetamine in the final case.

10 Toxicity

10.1 Despite the time-period during which 2-DPMP has been on the scene, there is no information on its long-term effects. There have been no previously reported deaths from 2-DPMP, although there has been at least one admission to hospital for observation following a particularly unpleasant ‘trip’ (Herbert et al., 2010), and many ED presentations. Its safety profile is unknown. No definitive concentrations of 2-DPMP have been established previously for toxic effects or death in humans. The LD_{50} for desoxypipradrol is lower for the mouse and rabbit than those for amphetamine and methylamphetamine, but higher for the rat in

comparison with these two substances (Novartis, 1955; ACMD, 2011). Fatalities from methylphenidate ingestion have occurred at dose levels as low as 1.3mg/kg in adults (Inchem, 2011). The LD_{50} for methylphenidate in adult monkeys is 15-20mg/kg but for young monkeys only 5mg/kg (Inchem, 2011). One posting on a user forum suggests that methylphenidate doses > 500mg are toxic (Drugs Forum, 2007). The researchers are unaware of any deaths involving pipradrol, although there are reported of methylphenidate causing heart problems and causing fatalities (Levine et al., 1986; Kuehn, 2009; Gould et al., 2009).

10.2 A number of cases of neuropsychiatric and cardiovascular toxicity have been recorded after recreational use of 2-DPMP's pyrrolidine analogue D2PM (Lidder et al., 2008; Wood et al., 2011a; Wood et al., 2011b). It appears that D2PM has more severe cytotoxic effects on nerve cells than MDMA and MDA. It produces inhibitory effects on nerve-growth factor-induced neurite outgrowth, thereby giving the possibility that it may cause impaired neuronal development (Kaizaki et al., 2010).

11 Fatality case reports

11.1 The National Programme on Substance Abuse Deaths (np-SAD) receives information on a voluntary basis from coroners in the United Kingdom on inquests completed on drug-related deaths (Ghodse et al., 2010). Here we present a brief report on three deaths that occurred in August 2010 in which 2-DPMP was implicated. These cases were notified in May and June 2011 as part of routine data submission. Additional information was provided by coroners in the form of autopsy and toxicology reports.

11.2 Case 1: A single white male aged 34 (height 1.83m; weight 86kg) was reported missing to the police by his parents concerned for his safety after not being seen for three days. A further three days later his partially decomposed naked body was found in the foetal position under a sail inside a locker on a yacht he had been repairing at his place of work. An autopsy was conducted but the pathologist could not establish a cause of death. He said, however, that the deceased could have suffocated due to his body being in such a cramped area, or suffered a heart-attack. An open packet of "Ivory Wave" and white powder were found at the scene. Post mortem toxicological tests found Desoxypipradrol at a level of 1.16mg/L in his blood, and a blood alcohol level of 40mg/dL. The Coroner gave the cause of death as "Unascertained" as it was not known if the amount of Desoxypipradrol found in his body could have killed the decedent. The Coroner returned an "Open" verdict, saying he believed the deceased had been experiencing paranoid delusions, causing him to hide in the small locker and attempting to block out light from the yacht; he added "This shows all the aspects of someone feeling they were being pursued". The deceased had moved back home after his long-term relationship ended and his business had collapsed; he had been depressed but was reportedly more "upbeat" recently (Heart South Coast, 2011; IOW County Press 2011a, 2011b).

11.3 Case 2: A single white male aged 24 (height 1.83m; weight 68kg) was seen by a witness running along the edge of a 100 metre-high cliff with his arms outstretched. The following day his body was found floating in the sea by a local fisherman. It is suspected from his injuries and earlier witness evidence that he fell from the cliff above. The cause of death was given as: 1(a) Brain injury; (b) Skull fractures; and 2 Multi-organ injury. Post mortem toxicological tests found desoxypipradrol at a level of 0.79mg/L in his blood, and a blood alcohol level of 14mg/dL. Returning an "Open" verdict, the Coroner said: "the ingestion of this legal high may have been a very strong contributory factor to the behaviour which was out of character". In the days before his death the deceased had exhibited "bizarre and paranoid" behaviour, having auditory and visual hallucinations. He had received mental health counselling voluntarily, and had been advised he had had a psychotic reaction to "Ivory Wave", as well as alcohol and mephedrone. He told doctors he had been taking drugs to cope with work-related stress and difficulties in his relationship with his girl-friend. He had

purchased the “Ivory Wave” from a local ‘head’ shop (Heart South Coast, 2011; IOW County Press, 2011a, 2011c).

11.4 Case 3: A married white female with Type I diabetes aged 35 (height 1.60m; weight 57kg) started snorting “Ivory Wave”, purchased over the Internet, 10 months before her death after reading on an online forum that it could help with weight loss. She had put on a lot of weight because of being on anti-depressants and insulin. Over 4 months she dropped in size from a UK size 16 to a 6 (European size 44 to 34), and became paranoid, aggressive agoraphobic, and insomniac. The deceased began to hear voices. She separated from her husband of 8 months and moved in with her parents because of the strain her behaviour put on the relationship. One night she lost consciousness, went into a coma, and was hospitalised. Two days later a CAT scan found severe swelling on her brain, unrelated to her diabetes. She was taken off life-support and died of heart failure two days later, after 12 days in intensive care. Post-mortem toxicological investigation found a blood concentration of desoxypipradrol 0.025mg/L; midazolam and haloperidol – probably used in her treatment – were also detected. The cause of death was recorded as “Desoxypipradrol (Ivory Wave) overdose”. The Coroner returned a verdict of “Accidental [death]” (Porter, 2010; McBride, 2011).

11.5 Toxicological investigations: Cases 1 and 2 were received and investigated at the same time. An initially unidentified compound was detected in both cases as part of a general (non-targeted) screening protocol, an initial toxicological investigation using high performance liquid chromatography with UV-diode array detection (HPLC-DAD). The compound had a UV spectrum very similar to diphenhydramine (but different retention parameter) and was found in the post-mortem femoral blood of Case 1 and in the post-mortem vitreous humour, liver and stomach contents of Case 2. In none of the biological samples were there any additional compounds present or any with similar UV characteristics, a feature of HPLC-DAD that can often be used to identify prospective drug metabolites. Following further analysis using liquid chromatography with mass spectrometry (LC-MS) with UV-diode array detection, the mass spectrum of the previously detected compound was obtained. A pseudo molecular ion [M+H] of 252.4 was observed which would be consistent with a corresponding molecular weight (MW) of ~251.4, the same as that of desoxypipradrol. This was confirmed following analysis of pure reference material which also allowed for the measurement of desoxypipradrol in the femoral blood of Case 1 (1.16 mg/L) and in the vitreous humour of Case 2 (0.79 mg/L). Due to the lack of comparative data, it was not possible to relate such concentrations to “recreational” or excessive use, nor comment as to the toxicological significance of the concentrations. Similar issues were faced for Case 3.

12 Discussion

12.1 It is difficult to keep abreast of the new products being created by ‘research chemists’. 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 such as “Ivory Wave” change over time, and thus the effects experienced by users may vary, as may the potential for toxicity. For example, “Ivory Wave” has been shown to contain MDPV, naphyrone, and then 2-DPMP (Ghodse et al., 2010; Herbert et al., 2010; James et al., 2011).

12.2 Wood et al. (2011b) report that the initial pattern of acute toxicity seen after use of D2PM is similar to that exhibited by other sympathomimetic drugs, with users describing a high or rush. What is different is the prolonged neuropsychiatric symptoms lasting for up to and longer than 24-72h after use. Prolonged psychiatric symptoms were a key feature of the 2-DPMP presentations reported by Murray et al. (2011).

12.3 At the time of writing, no poisonings or fatalities involving 2-DPMP 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 2-DPMP was recorded, let alone implicated. There is no

reliable relevant pharmacological information on 2-DPMP and D2PM in terms of lethal dosage, half-life, volume of distribution, etc. for human subjects. It is not possible to determine from a single blood sample when a substance was consumed or the exact amount taken. It is notable that although a relatively low level of desoxypipradrol was found in the post mortem blood sample of Case 3, the deceased had been in hospital for 15 days; the concentration is likely to have been much higher at the time of her admission.

12.4 Fatalities involving piperidines appear to be very rare events and thus there was practically nothing in terms of hard evidence which could be used to inform cases such as the ones described here. This paper now provides some insights into the potentially fatal toxicity of 2-DPMP. The experiences and effects of 2-DPMP and D2PM are similar to those reported by users of other 'legal highs' which have become controlled under UK drugs legislation, e.g. piperazines, mephedrone, methylenedioxypyrovalerone (MDPV), and other methcathinone analogues. The undesirable effects of 2-DPMP and D2PM, including those related to poisoning, are very similar to those described for methylphenidate (Inchem, 2011). It is important that forensic toxicologists and ED staff do not overlook the possibility of the ingestion of recreational piperidines. Reference standards are currently being produced for UK forensic toxicology laboratories; this should facilitate quicker identification. 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 conducted.

13 Conclusions

13.1 There is a significant lack of information for 2-DPMP and D2PM in terms of their pharmacology, pharmacokinetics, dose, acute toxicity and the harms caused by long-term use. This paper has outlined what is currently known about the toxicity of these two chemicals. There is evidence now emerging of serious clinical issues arising from their use; we have described what we believe to be the first deaths in the UK, and probably world-wide, involving 2-DPMP. On the basis of the limited reliable evidence currently available, management of patients presenting with acute toxic effects should remain pragmatic and be in line with treatments employed for stimulants such as amphetamine, cocaine and MDMA.

13.2 Due to the relatively recent emergence of these chemicals on the recreational drug use scene, their lack of widespread use, unknown toxicity and lack of detection through routine toxicological screens in many forensic toxicology laboratories, use of these substances could be missed by clinicians. Similarly, fatalities caused by their use 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.

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Conflicts of interest

No conflicts of interest are declared here which may have influenced the interpretation of present data. Please note the following: FS is a full member of the UK Advisory Council on the Misuse of Drugs (ACMD); FS and JC are members of the ACMD's Novel Psychoactive

Substances working group; SE is a member of the Independent Scientific Committee on Drugs (ISCD); and AHG is the current 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.

Declaration

This work has not been previously published and has not been submitted for publication elsewhere. Publication is approved by all authors and the responsible authorities where the research was undertaken. If accepted, the paper will not be published elsewhere in the same form, in English or in any other language, without the written consent of the copy-right holder.

Contributors

John Corkery undertook data collection and preparation. Simon Elliott supervised and interpreted the toxicological analysis for two of the case-reports, and Valerie Forbes Forsyth for the third case. 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.

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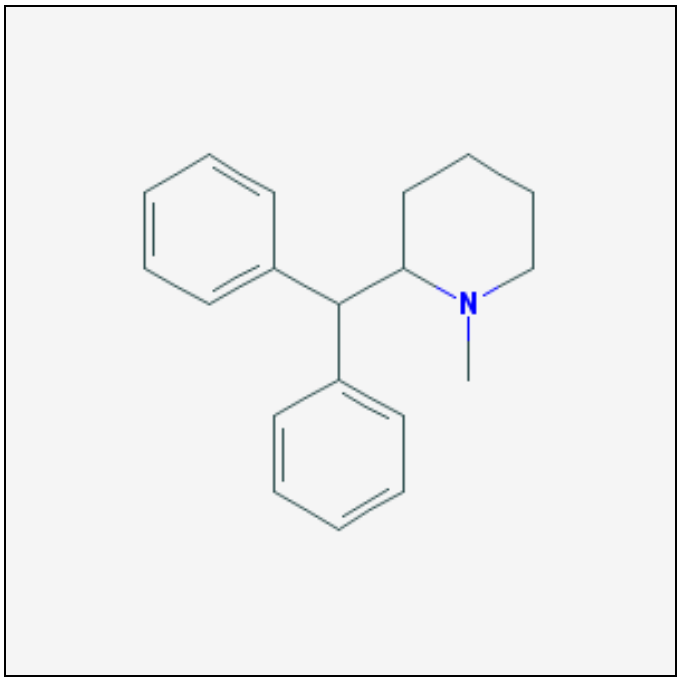
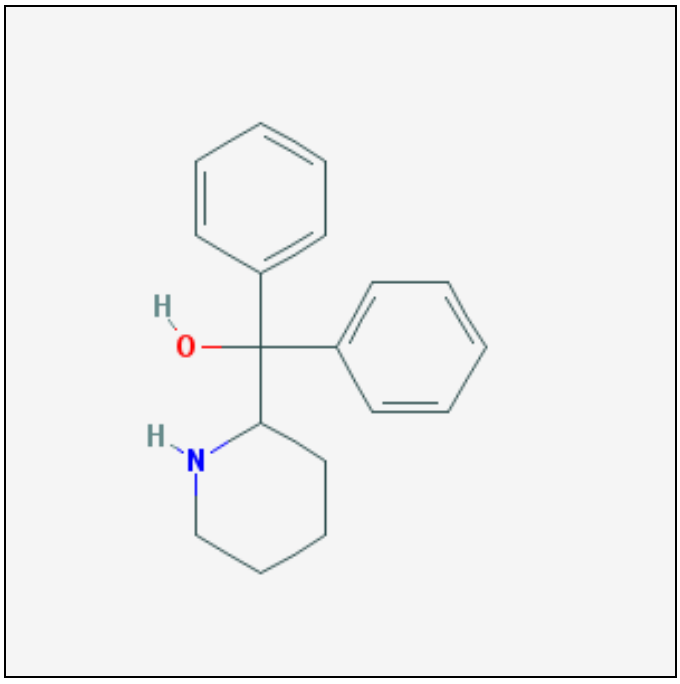
Figure 1: Chemical structure of desoxypipradrol, pipradrol, methylphenidate, and diphenylprolinol.

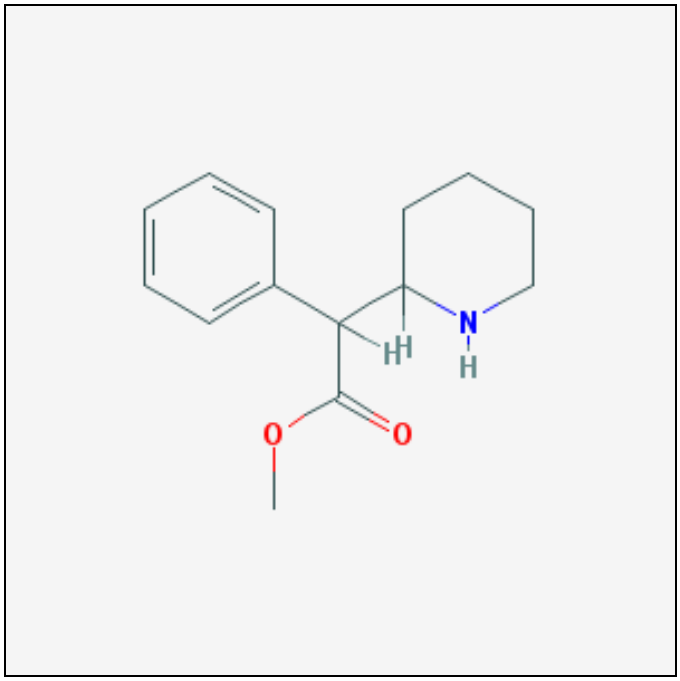
Desoxypipradrol



Pipradrol



Methylphenidate



Diphenylprolinol