

# Designer Drug (DD) abuse in Poland; a review of the psychoactive and toxic properties of substances found from seizures of illegal drug products and the legal consequences thereof. Part II – Piperazines/Piperidines, Phenylethylamines, Tryptamines and miscellaneous 'Others'

Przemysław Biliński<sup>1,2</sup>, Piotr Hołownia<sup>1</sup>, Lucyna Kapka-Skrzypczak<sup>3,4</sup>, Andrzej Wojtyła<sup>5,6</sup>

<sup>1</sup> Chief Sanitary Inspectorate, Warsaw, Poland

<sup>2</sup> Institute of Haematology and Transfusion Medicine, Warsaw, Poland

<sup>3</sup> Independent Laboratory of Molecular Biology, Institute of Rural Health, Lublin, Poland

<sup>4</sup> Department of Public Health, University of Information Technology and Management, Rzeszow, Poland

<sup>5</sup> Department of Mother and Child Health, University of Medical Sciences, Poznan, Poland

<sup>6</sup> Department of Higiene, Chair of Social Medicine, University of Medical Sciences, Poznan, Poland

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## Abstract

As the second and concluding part, this paper continues the summary review of the scientific evidence obtained from the literature and focuses on the remaining 4/6 groupings of DDs identified in illegal products found in the huge drug seizures made recently in Poland. They consist of piperazines/piperidines, phenylethylamines, tryptamines, (briefly mentioned), and a miscellaneous 'others' category; cannabinoids and cathinones derivatives having been reviewed in the first part. Also included in the introduction and discussion sections, in both reviews, are some legal aspects variously interwoven with the science. It is thus intended that these two articles may help suitable legislation to be rapidly devised to make the prohibition of DDs permanent whenever deemed necessary, as well as providing an up-to-date reference source for those engaged in the DD issue; whether scientists or regulatory bodies.

## Key words

designer drugs, legal highs, new psychoactive substances, drug abuse

## INTRODUCTION

In Poland, a novel anti-drug strategy was implemented during 2009-2010 in response to having the fastest growing EU market for new psychoactive substances with hundreds of hospitalisations arising; in October 2010 alone, 248 such DD-related cases occurred while in September two attributable deaths were recorded. Due to a legal loophole, the production and sale of DDs has flourished in Poland with over 1,500 'smart/head shops' vending DD containing products spread throughout both large cities and small towns [1]. Widespread reporting of such events in the press resulted in a strong public response at both local and national levels leading to many protests and campaigns. Draft legislation was first fast-tracked through parliament where the EU-wide mephedrone ban of 4 Dec 2010 was extended to initially over 50 other DDs confirmed to be psychoactive as a culmination of ongoing studies undertaken recently as part of a long term public health investment of 5 million Euros, as well as available scientific evidence from the literature and/or expert opinion.

At the beginning of October, 2010 the Polish Ministry of Health accordingly amended the Act on Counteracting Drug Addiction to embrace DDs now suitably defined as 'substitute substances'. Henceforth, substances and/or structural analogues determined by the aforementioned studies to be psychoactive were thus prohibited. The Act is constantly being updated as new results filter through, and a banned list is thus legally in force leading to the closure of 'head shops' selling such products. As well as a drug law, a further amendment was also made to the Food Safety regulations whereby if reasonable grounds of suspicion exist on the threat posed by a given product, then the Chief Sanitary Inspectorate may withdraw it for up to 18 months for study, or alternatively, businesses can be shut down for 3 months. Legal costs are refundable only if no health threat has been proved in the product. A certified database register of chemical substance information on the DDs is also being produced as a point of reference and will be available in the public domain shortly; already a list containing details of the 26 most frequently found DDs in Poland has been compiled and will be added to. At the time of writing, all legal challenges have been upheld resulting from the direct action taken by the Polish authorities on October 2nd 2010 where the Chief Sanitary Inspectorate (CSI), together with law enforcement officers checked over 3,500 wholesale/

Address for correspondence: Lucyna Kapka-Skrzypczak Independent Laboratory of Molecular Biology, Institute of Rural Health, Jaczewskiego 2, 20-090 Lublin, Poland  
E-mail: lucynakapka@gmail.com

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retail premises of which around 40% were immediately shut down and samples collected that were found to confirm transgressions.

As mentioned before, the DDs identified from the described seizures are arranged by 6 chemical groupings, (Tab. 1, 2. Part I), where their biological actions are individually outlined, including interactions with particular neurotransmitter receptor systems. Part II of the presented review deals with piperazines/piperidines, phenylethylamines, tryptamines and a miscellaneous 'others group'. In addition to the DDs found in the Polish drug seizures, other upcoming novel DDs are also considered as they are very likely to become problems in the future. Alternative classification based on effects was deemed inappropriate in this instance as individual drugs have multiple effects, not to mention those found in drug cocktails.

### SUBSTITUTED BENZYL OR PHENYL PIPERAZINE AND PIPERIDINE DERIVATIVES

**Principally:** BZP, MeOPP, pFPP, TFMPP, D2PM, and 2-DPMP.

**Mentioned:** MDBZP, mCPP and DBZP.

**MDBZP**, piperazine, BZP and its associated impurity DBZP belong to the benzyl piperazines, while MeOPP, TFMPP and mCPP belong to the phenyl types. Piperazine DDs are marketed as being safe, however, many studies indicate quite the opposite [2]. mCPP and MDBZP are not considered further as the former is avoided by drug users due to the presence of some very unpleasant effects coupled with the absence of hardly any pleasant ones [3], and the latter being only a very mild stimulant. BZP and DBZP are synthetic aryl-substituted piperazine derivatives. Initially, piperazine derivatives were used in veterinary practice, amongst other things for antiparasitic treatment. Exploratory studies were also carried out to test their blood vessel dilation and anti-cancer action, as well as antidepressant properties -none of which were indicated [4]. Due to similar psychoactive properties to MDMA, piperazine derivatives were found on the addictive substance market as ingredients of many products termed 'DDs' [5, 6, 7, 8, 9].

**BZP.** The main representative of this group which, due to its stimulant action on the CNS, is the most frequent constituent of the so-called 'party pills'. This substance is controlled in many countries but in others it is legally available where criminal groups limit themselves to providing them in capsule or tablet form in order to satisfy users [9, 10, 11]. In Poland, the use of BZP is illegal [12]. Despite the EU decision made in 2008 to limit the availability of BZP some EU countries still notify large amounts of the confiscated substance. Unfortunately, BZP can be simply synthesised by cheap and easily available reactants: chlorobenzene and piperazine mono-hydrochloride [13]. In capsule/tablet form BZP is taken orally, occasionally it is nasally inhaled or injected [14]. Due to the similarity of action between BZP and its derivatives (including MeOPP & DBZP), they are frequently found on the illegal market as ecstasy tablets. Sometimes, modified piperazine compounds are used together with 4-hydroxybutyric acid (GHB), which can initially lead to a complicated and misleading clinical picture. Poisonings from piperazine

derivatives can also be misdiagnosed as being caused by amphetamines, especially as routinely used immunoassays do not test for the presence of piperazine or its metabolites. In order to confirm a diagnosis an appropriate toxicological analysis is required, e.g. GC/MS [15, 16, 17].

The centrally-acting stimulation of BZP is similar to amphetamine but 10 times weaker and is linked to an increased release of dopamine and noradrenaline, together with inhibiting reuptake of these neurotransmitters in the CNS [4, 18, 19, 20]. This substance has a high affinity for alpha-2 adrenoreceptors which results in an increased release of noradrenaline. As a non-selective agonist for serotonin receptors, BZP also influences this pathway of transmission. Binding to 5HT<sub>2A</sub> receptors may explain its moderate hallucinogenic action at high BZP doses. In addition, the partial agonist/antagonist action on 5HT<sub>2B</sub> receptors are probably responsible for some of the peripheral adverse effects of this substance. BZP releases serotonin in the amygdale nuclei, stimulating 5HT<sub>1</sub> receptors and increasing anxiety/stress levels in laboratory animals [21, 22]. In low doses, BZP has stimulatory action and in high doses it is hallucinogenic [4]. The dose range of 75-150mg gives improved mood, self-satisfaction, euphoria, heat flush, improved concentration, and sometimes mild optical hallucinations. Tactile and sound stimuli are also more acutely perceived [21]. A New Zealand study undertaken on the population in general, where piperazine is particularly popular, demonstrated that 20.3% of 2,002 respondents aged 13-45 had taken BZP tablets at least one in their lives, and 15.3% had done so in the last 12 months [23]. These BZP users reported several unpleasant psycho-emotional experiences related to BZP, such as sleep disorder (50.4%), general weakness (18.4%), 'dark thoughts' (15.6%), mood disorders (14.8%), being disorientated (12.1%) and muscle tremors and shivers (18.4%). The literature also describes other adverse effects of BZP, such as: nystagmus, lockjaw, dry throat, psychosis, difficulties in passing urine and feeling inebriated [11, 21, 24, 25]. Piperazine derivatives can also cause irritation to the skin as well as nasal, throat and trachea membranes in persons inhaling BZP in powder form. A recent review, however, has concluded that overall current evidence on BZP-party pills suggests limited social and health harm; nevertheless, long-term effects have still to be investigated [6]. A legal holding category for ambiguous drugs was thus proposed until such time when confirmative evidence becomes available, a solution already previously adopted by Poland, the UK and Eire.

Depending on genetic conditions and individual traits, piperazine analogues demonstrate rather a narrow range of safe use, thus the risk of adverse reactions is high, such as: dehydration, palpitations, tachycardia, hypertonia or convulsions, especially when combined with alcohol [26, 27, 28]. Taking 5 tablets of BZP has been shown to be neurotoxic and deaths have also occurred when taken in conjunction with MDMA, MDA and alcohol [29]. In Switzerland there was one fatality resulting from hyponatraemia and brain oedema after taking 2 tablets of BZP and one of MDMA, together with drinking a large amount of water (10 litres in 15 hours). However, in this case the role of BZP was unclear [30].

The typical dose of 100mg BZP elicits a biological effect lasting 6-8 hours [4, 31]. Observed differences in individual susceptibility to BZP is linked to genetic polymorphism in enzymatic systems dealing with its metabolism [4]. Plasma levels reach a peak ( $C_{max}=262\text{ng/ml}$ ) 75 minutes after taking



a single 200mg dose orally, and has a biological half-life of 5.5hrs and clearance rate of 99L/h [21]. As well as the native form, the urine contains metabolites, 3 and 5 hydroxy-BZP and glucuronide and sulphated forms of hydroxylated piperazine derivatives, N-benzyloethylendiamine, as well as benzylamine; phenolic metabolites often being excreted in forms conjugated with glucuronides and sulphates.

**MeOPP.** Belongs to the synthetic analogues of benzylpiperazine whose actions are similar but weaker than amphetamine [21, 32]. The MeOPP acronym covers all 3 isomers (i.e. para, meta and ortho forms). According to the opinions of MeOPP users, the effects last for 4-6 hrs and cause a lower level of anxiety compared with other piperazine analogues. When taken in typical 120-200mg doses there was no significant arousal but a feeling of relaxation. MeOPP acts as non-selective agonists to serotonin receptors. Their use leads to increased release and inhibited reuptake of monoamine, [33]. Amphetamine acts in a similar way; however, MeOPP gives weaker stimulation. The effect of a 200mg dose of MeOPP are: euphoria, empathy, relaxation, changes in how music is heard, a similar afterglow to LSD, but also headache, appetite loss, increased temperature and nausea. MeOPP is metabolised mainly by O-demethylation catalysed by cytochrome P450 2D6 [15, 34]. Because of the large genetic polymorphism of CYP2D6, there is an increased risk of interaction with drugs containing inhibitors or substrates of this enzyme (e.g. MDMA or cocaine), and an enhanced toxicity of MeOPP, especially for the so-called weak metabolisers. The main metabolite of MeOPP found in rat urine is 4-HO-PP 1-(4-hydroxyphenyl)piperazine [34].

**pFPP.** This is the main metabolite of Niazprazine, a sedative and hypnotic drug used for treating insomnia, especially in children due to its safety record, and in not having any potential for abuse [35]. Unlike its parent, pFPP does not bind to the 5-HT<sub>2</sub> and  $\alpha$ 1-adrenergic receptors (as an antagonist), but instead binds and activates the 5HT<sub>1</sub> subclasses as an agonist shown in *in vitro* studies [36]. Animal behaviour studies have shown strong serotonergic stimulation by pFPP, as opposed to sedation by Niazprazine, [37], and it is suggested that p-FPP decreases turnover of 5HT and dopamine. It has been observed more recently that p-FPP significantly inhibits the cytochrome P450 enzymes that metabolize BZP and TFMPP [38], as indeed they inhibit each other, thus raising concerns about interactions in drug cocktails alluded to in the next section. The effects of pFPP are mildly euphoric and psychedelic, however, little else of consequence has been reported on pFPP.

**TFMPP.** Since the 1990s, this has been used for recreational purposes, usually in conjunction with BZP, where the net stimulant effect has been described as being somewhat similar to amphetamines such as ecstasy [38, 39 40]. It is thus marketed in this way for those countries where it is still legal. Extensive pharmacological studies on animal models (rats and mice) have shown that TFMPP is a serotonin agonist for most of the 5-HT receptor sub-types, whereas BZP also releases noradrenaline and dopamine [40, 41]. At higher doses the effect becomes synergistic. Major behavioural changes have also been demonstrated, e.g. appetite suppression [42], addiction [38], learning inhibition

[43], MDMA-like behavioural effects [44], and others. In humans, several recent clinical and toxicity studies have been performed – all showing negative findings. A hospital-based placebo-controlled trial on 64 volunteers (testing various combinations of BZP and TFMPP, 300mg, 74mg respectively +/-alcohol), had to be stopped early as severe adverse effects developed in 35 cases in all test combinations, with symptoms of agitation, anxiety, hallucinations, vomiting, insomnia, migraine and increased heart rate observed [45]. Another similar study performed at lower doses of 100mg and 30mg, respectively, showed increased blood pressure and heart rate, together with increased dysphoria and self-confidence similar to MDMA. In a case report of 3 patients presenting at an emergency department with MDMA-like symptoms of dis-association, nausea and sympathomimetic toxicity, both serum TFMPP and BZP were subsequently found (46-263 ng/ml); however, no other drug was detected [46]. A further clinical trial subjectively tested doses of BZP and TFMPP at 200mg and 60 mg alone or together 100/30mg, respectively, on participants who completed appropriate questionnaires. BZP alone or in combination produced MDMA-like stimulant effects (euphoria, sociability, drug liking), whereas TFMPP alone showed only minor effects together with anxiety symptoms [39]. Another study on TFMPP alone, testing for central information processing speed in humans, showed reduced inter-hemispheric transfer time in 15 healthy adult male volunteers [47]. Both substances can cross the BBB and the serum half-lives are short. A peak in plasma is reached after about 90mins, and within 44 hours they are primarily metabolised through cytochrome P450 and catechol-o-methyl transferase enzymes [48]. Seizures and multi-organ toxicity have also been reported where treatment is firstly with benzodiazepines and a symptom direct approach [29].

**D2PM and 2-DPMP.** These are currently the principal pyrrolidine and piperidine derivative DDs, respectively, that demonstrate stimulant properties. The former consists of a nitrogen containing 5-membered ring, while the latter is a 6-membered ring. D2PM (diphenyl-2-pyrrolidinyl-methanol or Diphenylprolinol) is a structural analogue of Pipradrol, a drug previously given to treat obesity, narcolepsy, and attention deficit hyperactivity disorder, which was withdrawn from the medical drugs list because it was considered to have sufficient potential for recreational abuse. It has been shown to be a psychomotor stimulant leading to disorders of movement coordination, ataxia, tremor, clonic seizures and psychotic episodes [49]. D2PM belongs to the inhibitors of noradrenaline and dopamine reuptake with moderate action. When used in 2-5mg doses it causes moderate arousal and euphoria. The most common adverse effect reported by users are chest pains and increased blood pressure which may suggest a cardiotoxicity of the psychoactive substance [50, 51]. Preclinical studies also indicate neurotoxicity of D2PM. This compound inhibits, *in vitro*, the growth and differentiation of the PC12 cell line and also limits the formation of neuronal appendages. Toxicity is greater than for MDMA and MDA [52, 53]. A case study of 5 patients admitted to an emergency department presented symptoms of agitation, anxiety and insomnia 24-96 hrs after ingestion [50] where D2PM was later confirmed by LC/MS/MS. None had sympathomimetic toxicity and all were subsequently discharged.

A closely-related substance, desoxy-D2PM or DPMP,



(2-(diphenylmethyl)pyrrolidine) has been identified very recently in new generation DDs which have a known history of being psychoactive but have been re-discovered by abusers [54]. 2-DPMP together with DPMP are likewise noradrenaline and dopamine reuptake inhibitors [55, 56] and are highly lipophilic, thus easily crossing the BBB. Both have long half-lives making them attractive candidates for new DDs as well as some of their derivatives which can have fairly simple substitutions or ring modifications that may confer psychoactive properties and/or find use as therapeutic agents [56]. This has been recognised since the 1960s [58, 59, 60]. A recent *in vitro* study [61] demonstrated that 2-DPMP derivatives have cocaine-like binding profiles which inhibit the various forms of the neuronal dopamine transporter, (DAT). Furthermore, recent animal studies have demonstrated that 2-DPMP has a two-fold greater ability to increase dopamine release than cocaine from the nucleus-accumbens region of the rat brain, and also a three-fold increase in the half-life of re-uptake compared to cocaine [62], this brain region being particularly sensitive to dopamine releasing drugs. A thorough analysis of Desoxypradol and its related substances has been made recently by the Advisory Council for the Misuse of Drugs (ACMD) in the UK [63] which included many instances of reported poisoning in emergency hospital departments (symptoms including hallucinations, paranoia and severe agitation). Animal studies had shown that Desoxypradol was more toxic than amphetamine or d-methylamphetamine in rats. This has been used to support an import ban now in place in the UK. As well as the documented health risks, analytical techniques now exist whereby these substances can be distinguished, with the appropriate reference standards in place, for forensic analysis [54].

## SUBSTITUTED PHENYLETHYLAMINES

**Principally:** MDOH, MMDPEA, PEA, 2-AT, 2C-E.

**Mentioned:** MDMA, 2C-I, 2C-C, 2C-N, 2C-B, 2C-D, and 2C-H.

**MDOH and MMDPEA.** In recent years, a large number of new and uncontrolled synthetic derivatives of amphetamine have appeared. They constitute a major challenge to the current strategy adopted in the monitoring and control of new addictive substances, of which MDOH and MMDPEA are good examples, and belong to psychoactive substance analogues of MDMA [64]. The substitution of a methyl group with a hydroxyl one on MDMA results in a significantly weaker stimulatory action and decreases the level of monoamine transport inhibition. Because of the structural similarity between MDOH and MDMA it is both a substrate and inhibitor of serotonin, noradrenaline and dopamine transporters [65, 66]. MMDPEA is an alpha-demethylated homologue of MDMA which has similar central action to mescaline, an alkaloid with psychotropic properties occurring in the cactus genus *Lophophora Williamsii*, the mescaline content in this plant being 0.5-1.5%. In typical doses, mescaline is a hallucinogen, about 2-3 times weaker than LSD. Mescaline produces colourful optical hallucinations, with loss of the sense of time and space lasting 20 hrs. An overdose can lead to death due to respiratory failure [67].

**PEA.** Also an amine, with powerful biological effects. It can be synthesised in the body from the exogenous amino acid phenylalanine through enzymatic decarboxylation. PEA is found in some foodstuffs, e.g. those containing cocoa (chocolate, among others), and in cheese and wine [68]. Even in the early 1970s it was discovered that PEA occurs in mammalian brains in trace amounts (about 2nM), and is quickly and intensively metabolised by monoamine oxidase type B [69, 70]. It can act as a stimulant of the CNS [70], and many studies have shown it to improve mood [71, 72]. The CNS has special places for binding of PEA and its derivatives (receptors for trace amines –TA1) [74] which are localised in the amygdale and mid-brain, thus explaining their roles in depression and anxiety disorders. It has been shown that PEA and tryptamines, as well as their synthetic analogues selegilina and BPAP (1-benzofuran-2-yl-propylamnopentane), increase the release of catecholamines and serotonin from the isolated brain stem of the rat.

*In vitro* studies have demonstrated that PEA inhibits uptake and facilitates the release of dopamine and noradrenaline to a lesser degree than serotonin. PEA changes the activity of these neurotransmitters in the CNS. The concentration of PEA which causes an increase in amine levels, however, is 100 times higher than the concentrations observed in the CNS. Such concentrations may only be achieved upon taking large exogenous PEA doses, or by inhibiting MAO-B enzyme activity. PEA action is comparable with the psychostimulation of the sympathomimetic d-amphetamine. It is found that giving PEA increases motor activity and stereotypic behaviour in rats, mice and monkeys. Its action may be enhanced during the administration of a single dose of a reversible inhibitor of MOA-B, e.g. selegiline, as in the treatment of Parkinson's disease [75].

When PEA is given with or without the MAO-B inhibitor it produces a syndrome of hyperactivity in animals. This action is linked to the influence of catecholamine in the CNS [76]. Other animal studies have also demonstrated an effect on the amount of food consumed by animals [77]. Studies on PEA performed at the turn of the last century demonstrate a similar effect to amphetamine. PEA, like amphetamine, increases the production of free oxygen radicals [68]. Many studies show the hazards of using amphetamines, both singly or continually. Adverse reactions to PEA on the CNS include disorders of mood, memory and psychosis, together with increased mortality due to complications arising from the cardio-vascular and respiratory systems or increased susceptibility to infection [78].

**2-AT.** This acts on the CNS; it is an amphetamine analogue and a substitute for d-amphetamine for discriminatory tests in rats. 2AT's action is 1/8th as strong as amphetamine, [79]. Parenteral administration of 2AT decreases the concentration of 5-hydroxyindole acetic acid and increases free serotonin levels in rat brain. In animals, 2AT inhibits the reuptake of serotonin and noradrenaline and induces the release of these neurotransmitters at synaptic endings. 2AT also inhibits dopamine beta hydroxylase [80]. Animal studies show that 2AT leads to changes in body temperature where both hypo- and hyperthermia are observed. The former being probably due to noradrenaline, whereas the latter is linked to the release of 5-HT (5-hydroxy-tryptamine) [81].

2AT is a selective and powerful agonist of the dopaminergic receptor D2, and it also shows affinity to the D type [82]. Like



amphetamine, 2AT has anorexic action (inhibiting hunger) in rats; however, this does not influence their motor activity [83]. Large doses [84] of 2AT derivatives increase motor activity in mice, whereas studies on dogs show that 2AT derivatives increase blood pressure, which is due to the antagonist nature of alpha-adrenolytic phetolamine [85].

2C-E is a recognised hallucinogenic drug which belongs to the 2C series of psychoactive 2,5-phenethylamines that are substituted with various alkyl or halide groups on the 4<sup>th</sup> position of the aromatic ring. They are considered to be 5HT<sub>2A/2C</sub> moderate agonists [86]. Due to its fairly recent emergence as a DD, 2C-E has been little studied compared to other 2C series members. Some – 2C, I, E and C – are known to inhibit serotonin and noradrenaline re-uptake (possibly also dopamine), as shown in rat brain synaptosomes [87] with IC<sub>50</sub>s in the 30–80 μM range. Release of these monoamine transmitters, however, was undetectable. Compared to other DD phenethylamines (e.g. MDMA, Methylone) or tryptamines and piperazines, inhibition was generally 10–100 times weaker. It has been suggested that binding to the 5HT receptors, and hence activity, is graded according to steric hindrance in the 2C series. Indeed, a study on functional selectivity in human cell lines showed a ranking of decreasing efficacy, 2CI, N, B, D, H for both 5HT<sub>2A</sub> and 2C receptors [86]. Structure-activity studies also indicate the possibilities of predicting the potency of untested 2C members [88]. Various other studies also demonstrate that the 2C series bind to serotonin receptors and can be agonists or antagonists, according to the receptor sub-type [89]. As the physiological effects of serotonin are regulated by G protein activation mediated by receptors (except 5HT<sub>3</sub>), an *in vitro* GTP binding assay has been developed [90] to determine the binding of a range of DDs, including 2C, I and E. A very high potency in eliciting G protein activation via 5HT<sub>1</sub> receptors was in fact observed, which is consistent with a much earlier study on related phenethylamines [91].

Metabolism of the 2C series, including 2C-E, is principally by O-demethylation and MAO A and B deamination in humans, confirming previous studies in rat models [92, 93, 94]. For this reason, taking MAO-inhibitor type drugs with 2C series drugs must be avoided. Subsequent reactions include various hydroxylation and oxidation steps followed by glucuronidation/sulfation and N-acetylation where these metabolites are present in the urine and can thereby serve as a non-invasive way of identifying these drugs [92, 93, 94], as opposed to validated methods for plasma [95].

Together with others of the 2C series, the effects of 2C-E have been extensively documented by their original discoverer [96]. 2C-E has profound and intense hallucinogenic effects starting about 1 hour after ingestion and lasting up to 24hrs. The potency varies according to dose – 5–20mg are normally taken, with higher doses producing more intense visual and sound distortion. Positive effects vary according to the individual and include feelings of well-being, heightened mental and physical stimulation, improved thinking processes, perception of time, sound, vision and touch are altered, heightened and distorted and spiritual/psychological awareness is raised. Adverse effects are reported as being increased body temperature, muscle tension and ache (particularly in the jaw), sweating, GI disturbances, nausea, vomiting, dizziness, confusion, paranoia, fear, oversensitivity to stimuli, unpleasant spiritual and social experiences [97].

In the last year there have been two reports of fatalities and mass poisonings apparently attributed to 2C-E in the USA. In March 2011 in the USA, 11 teenagers/young adults were hospitalised and one died following a massive drug overdose in Blaine, Minnesota [98], and in Konawa, Oklahoma [99] 8 young adults were hospitalised with one death ensuing. In the latter case, there is still some confusion about which drug was actually responsible for the death.

## TRYPAMINES

**Mentioned:** 4-HO-MET (4-hydroxy-N-methyl-N-ethyltryptamine), 5-MeO-DALT (N,N-diallyl-5-methoxytryptamine), 5-AcO-DMT (N,N-dimethyltryptamine DMT), 5-MeO-DET (5-N,N-diethyl-5-methoxytryptamine), 5-MeO-AMT (5-methoxy- $\alpha$ -methyltryptamine), 5-MeO-DIPT (5-Methoxy-N,N-diisopropyltryptamine)

There were in fact hardly any tryptamine-related DDs detected in the Polish seizures, (none in the 46 most commonly detected), but for the sake of completeness a list of the newer ones are included below, with a reference where further and very recent information can be obtained: 4-HO-MET [100], 5-MeO-DALT [90], 5-AcO-DMT [101, 102], 5-MeO-DET [103], 5-MeO-AMT [103] and 5-MeO-DIPT [104].

## OTHERS

**Principally;** Dimethocaine, p-FBT, Lidocaine, 3-(4-Hydroxymethylbenzoyl)-1-pentylindole, 2-AI, MMAI, DMAA, LSA -*Argyrea nervosa*, Salvinorin A and GBL.

**Mentioned;** 5-IAI, MDAI, and MDMAI

**Dimethocaine and pFBT.** Both have actions similar to cocaine [105, 106, 107]; Dimethocaine affects dopaminergic neurotransmission (like cocaine) [108, 109], whereas pFBT is very closely related to tropacocaine, a substance with parasympathomimetic/cholinergic action which blocks Na<sup>+</sup>-dependent choline uptake, as well as synthesis and release of acetylcholine [110]. The main effect of taking cocaine is a strongly heightened state of arousal where one of the basic mechanisms of its euphoric effect is the blocking of noradrenaline, dopamine and serotonin uptake in the CNS [111, 112, 113]. Through directly affecting structures in the brain, it causes a rapid and powerful psychological addiction, but when applied topically it acts as an anaesthetic. Taking cocaine, especially in combination with other addictive substances, creates many health problems mainly cardiovascular dysfunction and neurological and psychotic disorders [114]. People who regularly use cocaine become wasted, develop personality and identity disorders, psychosis and significantly show increases in physical activity [115, 116]. Large doses can cause muscular tremor and increased body temperature. Other complications are seen in the respiratory system, increased breathing, coughing, hoarseness, dyspnea and pulmonary bleeding [117]. Cocaine also causes changes to the capillary system bedding and can lead to heart muscle ischaemia, arrhythmia, increased blood pressure, elongation of the electrocardiogram QRS complex and increased ventricular contractile frequency [118].



The majority of deaths caused by cocaine are due to its toxicity leading to complications in the heart-circulatory and neurological systems. The p-FBT as a cocaine analogue causes central effects weaker than cocaine with reputed symptoms of anxiety, frequent spasms, increased arterial pressure and psychotic episodes [119]. The local anaesthetic action of p-FBT is of similar strength to cocaine and it was the first synthetic cocaine analogue to be placed illegally on the market, as first noted in Ireland 2008 under the name 'Whack and Stardust'. Since that time, 40 males have received medical treatment due to serious instances of mainly psychotic episodes which were untreatable with conventional therapy [120]. There are also some recent methods available for facilitating p-FBT's analysis [121, 122].

**Lidocaine.** Surprisingly, among the most common psychoactive substances detected in the drug seizures in Poland (9<sup>th</sup> in rank order) was lidocaine, a substance commonly used as a local anaesthetic and antiarrhythmic drug, and not usually considered as a drug of abuse. It acts by blocking sodium channels thereby blocking neuronal signal propagation. A possible explanation is that lidocaine is often added to low-grade cocaine where the feeling of numbness gives the perception of enhanced potency; this characteristic may now be being exploited for DDs. It has, in fact, been recently detected in an analysis of 2<sup>nd</sup> generation DDs from the UK [11]. Unlike cocaine, lidocaine is devoid of catecholnergic action [123]. Some evidence of abuse and harmful contraindications, however, does exist, bearing in mind that lidocaine is metabolised by the cytochrome 450 system, thus increasing the potential for drug interactions [124]. Adverse reactions include dizziness, drowsiness, coma, seizures, respiratory arrest, muscle twitching, paresthesia, dysarthria, numbness of the tongue, tinnitus, diplopia, and other visual disturbances. Feelings of euphoria, however, have been documented, as shown by a case report [124, 125] of two patients with no known history of drug abuse, admitted for routine surgery who developed very exaggerated states of happiness lasting up to 50 minutes. A similar case was seen in a cocaine addict [126].

In contrast, rare but unpleasant psychotic reactions (e.g. fear from death, doom anxiety and delirium) have also been previously reported [127, 128]. It is also recognised that caution should be exercised in treating cocaine abuse with lidocaine as it may lower the seizure threshold [129]. The ability of Lidocaine to increase free intracellular calcium in brain tissue, and thus protein kinase activity [130, 131, 132, 133], is thought responsible for its neurotoxicity, both in human tissue and animal models, and as cocaine produces the same effect [123] the combination of the two is another cause for concern for drug users, particularly at high doses.

**3-(4-Hydroxymethylbenzoyl)-1-pentylindole.** At the sitting of the EMCDDA on 15 November 2010, a list of substances withdrawn from the market was presented which had been added to the banned substances list. Among these was 3-(4-hydroxymethylbenzoyl)-1-pentylindole, which has been shown to have euphoric action and was withdrawn in the UK in 2010 [134]. A similar procedure was enacted in Norway where on 8 March 2011 this substance was placed on the list of substances withdrawn from the legal market [135].

**Aminoindanes including 2AI.** These are conformationally rigid analogues of amphetamines with a closed 5-membered ring system next to the parent 6-membered one which, due to minimal neurotoxicity [136, 137] and high serotonin releasing properties, are considered as perhaps becoming the 'new wave' of DDs [138] as they are available on Internet sites as 'research chemicals'. Common types include 2AI, 5-IAI, as well as others, such as MDAI, MDMAI and MMAI.

2-AI is a short-acting stimulant the effects of which resemble 1-benzylpiperazine and methamphetamine, and in combination with caffeine and cola-vera, an increased heart rate and insomnia have been observed [139]. Older studies have demonstrated the strong interaction of various substituted and native 2-AI isomers with the 3 dopamine receptor types [140, 141]. 2-AI has an action 1/6th that of amphetamine [79], with pain killer effects, and in contrast to morphine it does not depress the respiratory nerve centre and is unaffected by the antagonist nalorphine. In contrast to amphetamines, 2-AI does not increase motor action in test animals (rats & mice), but in similar fashion it decreases food consumption in rats [83]. It has been shown that 2-AI disrupts cholinergic transmission by its effect on calcium concentrations in nerve endings [142]. 2-AI decreases peristalsis in mice and increases their arterial blood pressure [143]. When given to animals it becomes distributed to various tissue and organs where it is found in lungs, kidney, liver, spleen, muscle, adipose tissue, heart and brain. Its biological half-life in the brain is 1-2 hours [144]. Studies performed on rats [145, 146] have shown also that MMAI is a potent releaser of serotonin similar to MDMA, but only slightly inhibits the uptake of dopamine [145] where MMAI, through its stimulation of serotonergic neurotransmission, can increase hormonal secretion, e.g. ACTH [146]. In addition, 5-IAI [136] is also a greater releaser of serotonin and dopamine than MDMA coupled to a smaller reuptake inhibition. Both are non-neurotoxic. The closely-related 1-Aminoindanes are regarded as promising candidates for the treatment of psychosis [147], and a substituted derivative – rasagiline, is used as a treatment for Parkinson's Disease [148].

**DMAA.** One of the results of making the derivative BZP illegal was the introduction of substitute substances onto the market. A new group appeared 'BZP-free part pills' which contained the synthetic stimulant DMAA [149]. This is a simple aliphatic amine which acts as a CNS stimulant, but is weaker than amphetamine or ephedrine, and causes an increase in alertness and aggression [150]. DMAA was patented in 1950 as a topically-administered nasal decongestant vasoconstrictor; however, to date, there is still little known about its pharmacology after oral administration. It is used to treat rhinitis and hyperplasia of oral tissue. Its toxicity is low. From rather dated studies [151], the LD50 in rodents is 39mg/kg body weight after administering an intravenous dose, and 185mg/kg body weight when given intraperitoneally, which is equivalent to giving an adult 65kg person 206mg intravenously or 978mg intraperitoneally.

The most commonly reported adverse effects in DMAA users are headache and nausea. A case has been reported of a 21-year-old male who suffered a cerebral haemorrhage after taking 2 capsules of DMAA [149]. A recent clinical study has demonstrated significant increases in systolic and diastolic pressure, as well as rate pressure product without any heart



rate increase in healthy men and women following acute ingestion of DMAA (50-75mg), with and without caffeine (250mg) [152].

DMAA is also used as a dietary supplement, e.g. Geranamine, and is present in low concentrations in geranium oil [139] and also in other plants related to *Pelargonium*. In accordance with regulations from the FDA and Dietary Supplement Health Education Act (DSHEA), DMAA is allowed as an ingredient of food and dietary supplements, although recently it has been implicated in a health scare at an USA military establishment [153]. In November 2009, the New Zealand Government, however, restricted its use; the Ministry of Health banned the wholesale purchase of this substance in powder form, but its sale as capsules and tablets are permitted [154]. In the same year, the World Anti-doping Agency placed DMAA on its list of prohibited substances. The use of DMAA by sportspersons carries the risk of disqualification when tested positive for other illegal substances that increase physical performance [155, 156, 157].

**LSA.** Around 2006, a new spice drug appeared based on seeds of the *Argyreia nervosa* plant (Hawaiian Baby Woodrose) containing, among the other 19 identified alkaloids [158], LSA and its stereoisomer, responsible for the psychoactive effects. It belongs to the ergoline group that includes the very well known psychedelic drug LSD. Ingestion of LSA containing seeds are known to cause alterations in seeing colours and textures, perceiving time, mood elevation and sedation [159]. However, negative side-effects such as nausea, vertigo, hypertension, tachycardia, tachypnea to mydriasis and psychosis are reported [160]. Indeed, a recent study on volunteers [161] was discontinued as alarming symptoms of cardiovascular dysregulation or psychosis were observed in some, from which it took 9 hours to recover. It was concluded that this legalised DD is far more dangerous than supposed due to the unpredictable nature and intensity of responses, the inherent variations in seed alkaloid content, and the potential for use in multi-drug cocktails. Although legally available, the lack of information on side-effects, contraindications, etc., poses a serious health risk to users, especially when considering, for example, that a survey has shown it to be the third most frequently available legal high in the UK [162].

**Salvinorin A.** This is another psychoactive substance of note found (0.18% dry leaf weight) in the commonly occurring *Salvia Divinorum* plant (Diviners Sage) which, due to its relatively low and little known risk profile, is legal in most countries with varying degrees of control. Australia is the most strict, while Spain is the most lenient.

Unlike most plant psychoactives which are alkaloids, this substance is a diterpenoid and is a kappa-opioid receptor and D2 receptor agonist [163, 164] producing potent hallucinogenic effects when smoked (as is customary), lasting around 10 minutes; some users reporting positive experiences while others categorically do not [165]. Symptoms are quite diverse and intense [166, 167, 168], ranging from improved mood, insight and confidence, light-headedness, floating feelings, calmness, mind racing, unreality, overlapping realities, weird thoughts, sweating, feeling hot or cold, uncontrollable laughter, difficulty in talking, visions, being artistically inspired, and in some cases, possible depression and psychosis. Generally speaking, there have been no

instances of any long-term ill effects, with addiction potential being small (around 2%), although it is cautioned against using strong doses.

Legalised products containing Salvinorin A, however, fail to provide any meaningful information to users thereby constituting serious risk [160]. Animal studies have previously shown no toxicity [169, 170]; more recent studies, however, have shown some disturbing results: in rats, impairment of learning and memory was observed [171]. Furthermore, a small clinical study (n=37 cases of intoxication), based at a poison centre of human exposures to *Salvia Divinorum* was conducted over 10 years [172] with the following observations: when used alone (49% cases), symptoms of anxiety, unpleasant hallucinations, dizziness, distortions in space/time perception, nystagmus, palpitations, hypertension, tachycardia, nausea and vomiting were seen. Moreover, much more serious problems are seen in combination with alcohol and other drugs, e.g. seizures, intubation. A case report [173] also demonstrated unpleasant and intense neurologic effects, and the serious dangers of drug interactions was highlighted by a large survey of drug users [174]. A controlled study in 4 mentally and physically healthy subjects demonstrated some of the more exotic hallucinogenic effects as mentioned above, but there were no increases in heart rate or blood pressure [168]. Other more loosely based surveys and anecdotal evidence obtained from *Salvia Divinorum* users on YouTube show few negative experiences, with effects being short-term and risks likened to those experienced with alcohol [175, 176].

Some therapeutic potential has also been advocated/suggested [163, 177] in treating, e.g. Alzheimer's, depression, schizophrenia, chronic pain, etc. Nevertheless, the widespread availability of this drug, coupled with both a dearth of scientific knowledge and its intense effects, must constitute a risk whether it be physical harm or resulting from errors of judgement [178].

**GBL.** Despite its promising therapeutic potential, the gamma-aminobutyric acid (GABA) neurotransmission system is still relatively poorly exploited as a target for treating depression following the successes achieved by benzodiazepines and tricyclic antidepressants. One of the reasons being serious health concerns over abuse and overdosing [179]. Nevertheless, it remains a candidate system in developing new treatments for disorders such as Parkinson's disease, fibromyalgia and narcolepsy, as well as possibly alcoholism [180]. GBL is a gamma-hydroxybutyrate (GHB) precursor and is also an industrial solvent which is fast becoming a popular legal DD, (termed as 'coma in a bottle'), causing at low doses euphoria, states of delirium, a hypnotic effect and in high doses severe sickness, irrational behaviour, coma and death [181]. It can be very dangerous when taken with alcohol. There have also been reports of a high dependency potential in humans despite there being no evidence of dependence or withdrawal from animal studies [181, 182]. A recent clinical study, [183] on GHB poisoning/overdose in subjects (n=505) admitted for emergency care, principally demonstrated unconsciousness/coma which in 26% cases required antidote treatment. Those who had taken other drugs and/or alcohol took much longer to recover. Due to its rapid metabolism in blood, detection is only possible before 3hrs after ingestion, [184] which has led to its possible use as a 'date rape drug' [185].



GBL is converted endogenously to GHB which is thus naturally the GHB receptor agonist through which the effect becomes manifest. In most countries it is a controlled substance, either classified under drugs or chemicals, but in some countries – including Poland – it can be legally purchased as a solvent for paint stripping, stain removing, superglue solvent, etc. Very recent press reports [186] indicate that GBL is fast overtaking other DDs in Poland as their use and availability is becoming restricted due to legislative and law enforcement actions taken in 2010. Evidently, it seems they are starting to bite.

## DISCUSSION

The intention of both these reviews is to help provide the scientific basis on which legislative bans on DDs can be made according to health risk. In addition, it is also worth considering the legal viewpoint arising from the science complicated by the different legal systems and legislation between countries, including those in the EU. Some countries do not have constitutions, e.g. the UK, where imposing a generic ban on whole groups of DD substances is relatively straightforward, whereas in others, such as Poland, such action may be contrary to its constitution, especially regarding criminal law. Accordingly, the option to amend an existing Act on counteracting drug addiction was taken by the Polish authorities to embrace DDs now suitably defined as 'substitute substances', as described in the introduction. This approach has been recently welcomed by the UK Advisory Council on the Misuse of Drugs (ACMD) where a similar system has been in place, requiring parliamentary approval for placing a temporary ban on each new DD whenever they appear, thus allowing time for an assessment of harm to be completed [187].

As a general point, by its very nature, scientific evidence deals with probabilities not certainties, this being especially true in the medical-biological sciences where theories stand and fall as new data becomes available. This is not the case when dealing with mathematical proofs/laws which are based on logic and not observation of natural phenomena. A problem thus arises when applying the law to scientific evidence. What is considered to be current scientific opinion on any given subject is quite often variable where data/evidence can sometimes be used to support different conclusions – a potential legal minefield. Such may be the case with DDs where extensive, expensive and time-consuming studies are required to conclusively demonstrate risk/threats to human health, frequently obtained by indirect means through, for example, having to resort to animal studies due to obvious ethical considerations. By extension, actually proving legal culpability that human health has been seriously harmed by taking DDs, or even if fatalities occur, is fraught with difficulty. Moreover it is frequently seen that DDs are completely new substances with as yet no documented effects although reasoned opinion can indicate major threats. As mentioned previously, despite belonging to the same chemical group, substances with only minor modifications may have drastically different biological effects. Various solutions are under discussion, for example, in creating a comprehensive drugs data library.

Another option could be to focus on the interaction of drugs with their receptors as many have already been cloned, e.g. the psychoactive CB1 cannabinoid receptor [188].

Assays have been developed along these lines in Japan [189] for measuring re-uptake and the release of monoamines (dopamine, serotonin and norepinephrine), and the activation of [(35)S]guanosine-5'-O-(3-thio)-triphosphate binding to guanine nucleotide-binding proteins (G proteins). On this basis, the Japanese authorities designated psychoactive drugs as prohibited substances. It is with this in mind that any laws and legal actions have to be very carefully and judiciously applied, together with scientifically developing an effective risk assessment.

## CONCLUSIONS

Confronted with the growing menace of DDs worldwide it is hoped that a more concerted legal action can be taken at the EU level, as well as in effectively assigning resources, some EU countries giving less priority to DDs than others [190]. This should help with the problem of Internet sales where differences in banned lists between countries can be exploited. It is vital to prevent DDs becoming a serious problem, as seen with 'conventional' illegal drugs, particularly among the younger generation who are more impressionable and thereby a vulnerable section of society who constitute the future. Thus it is hoped that the presented 2-part review may contribute towards these ends.

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