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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 1 – Cannabinoids and Cathinones

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Abstract

Faced with the rapidly growing increase of designer drug abuse, particularly amongst the younger generation, various legislative strategies are currently employed world-wide for tackling this problem – however with mixed results. The key issue is that the producers of DDs are able to either exploit existing legal substances intended for other uses, but which have been found to possess psychoactive properties, or to synthesise new psychoactive substances by introducing chemical modifications, often very minor ones, thereby avoiding the prohibited use of chemicals included on any banned lists. Some countries opt to ban new drugs as and when shown or considered to be harmful, while others introduce sweeping bans based on chemical structure. Nevertheless, an ever increasing diversity of new DDs are constantly appearing on domestic and Internet markets. Poland, together with the UK and Eire, has placed temporary bans on all DDs whenever they have been identified, thus enabling sufficient time for assessing their potential hazards to health. Part of this 'holding' strategy entails a thorough review of the scientific literature, including expert opinion when direct evidence is lacking, as well as information received from EU support organisations Europol and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). This paper, in two parts, therefore aims to provide an up-to-date summary review of available scientific evidence on the harm caused by the six main chemical groupings of DDs found in drug seizures of illegal products recently made in Poland. The first part is devoted to Cannabinoids and Cathinones derivatives. Ensuing legislation can therefore be rapidly formulated to make the bans permanent as appropriate.

Key words

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

INTRODUCTION

Since the 1980s it has become apparent that the long-standing problem of the abuse of new psychoactive drugs has recently increased, from around 2008, to become a global concern and especially affecting youth. This is now recognised by many national public healthcare and regulatory authorities, the scientific community, and world health bodies where the EU region has been identified as one of the fastest growth areas [1] although the proportion of users relative to established narcotics is estimated to be still relatively small but rapidly increasing. Tackling this problem is compounded by the ever-increasing diversity of these substances appearing on illicit/legal markets eliciting varied responses from national authorities worldwide already alluded to. However, the effects vary, with increases seen in drug trafficking and/or a re-branding strategy adopted by suppliers on substitute alternatives in attempts to circumvent laws. In fact the medical literature is frequently taken advantage of, for finding new prospective DDs.

According to the latest reports, an ever-increasing diversity of DDs (or legal highs), are becoming available at 'unprecedented rates' with record numbers [2] registered by the EU Early Warning System (EWS), which is reflected by the very many different ways of marketing and distribution. Each year, new products not under control are manufactured to supply an ever-increasing and diversified demand for psychoactive substances, thus keeping ahead of all efforts to control them. In 2009, 24 new drugs were notified compared to 40 in 2010, 48 in 2011 and 44 in 2012, up until 28 September. It has also been recently noted [3] that the gains made in tackling the global use of cocaine and heroin are being offset by the rising consumption of DDs. Clearly urgent action is required to establish the most effective course of action to prevent DDs replacing 'conventional drugs', especially in youth. This problem became particularly acute in Poland

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around 2009-2010, [4] and a novel response was launched by the authorities at about that time, as described in the second review article.

The current banned list has been drawn up from an exhaustive screening and analysis of approximately 6,000 DD samples taken from products that up till then had been available on the market, which included using liquid chromatography/mass spectroscopy (LC/MS), analysis together with nuclear magnetic resonance (NMR), analysis. The highest incidences were for Methylenedioxypyrovalerone (MDPV) – 23%, and 16% for 1-pentyl-3-(4-methoxynapthol – indole, JWH-081 and 1-pentyl-1H-indol-3-yl – methanone, RCS-4 (Tab. 1) from n=3,794 samples analysed at the National Medicines Institute in Warsaw.

Table 1. %-age incidences (n=3,794) of identified substances, including psychoactive, found in DD products from drug seizures in Poland

Rank order	Chemical name/ code	% Incidence	Rank order	Chemical name/code	% Incidence
1	MDPV	11.7	24	Pentedrone	1.0
2	JWH-081	9.0	25	FMC	0.9
3	RCS-4	9.0	26	JWH-210	0.9
4	Valine	9.0	27	JWH-203	0.9
5	Caffeine	9.0	28	Cathinone	0.8
6	Butylone	5.8	29	MBZP	0.8
7	4-MEC	4.0	30	Ephedrine	0.7
8	JWH-122	4.0	31	JWH-018	0.7
9	Lidocaine	3.7	32	Tyrosine	0.6
10	pFPP	2.7	33	JWH-007/019	0.6
11	Methylone	2.1	34	Metamphepramon	0.6
12	Buphedrone	2.1	35	BZP	0.5
13	Proline	2.1	36	Cellulose	0.5
14	TFMPP	2.1	37	D2PM	0.4
15	MMDP & MDOH	1.6	38	2C-E	9.4
16	MDOH	1.6	39	2-AI	0.4
17	Mephedrone	1.5	40	Kynurenic acid	0.4
18	DMAA	1.3	41	3-FMC	0.4
19	AM-694	1.2	42	Tadalafil	0.4
20	JWH-019	1.1	43	PEA	0.3
21	Phenylalanine	1.1	44	JWH-073	0.3
22	JWH-250	1.1	45	JWH 015	0.3
23	MDPBP	1.1	46	JWH-200	0.3

In fact, five main chemical groupings were identified and a miscellaneous 'others' group including pharmaceuticals (Tab. 2). Consistent with studies in other countries, the real composition of many of the products were also found in many cases to differ markedly from information given to the purchaser, thus posing a potentially serious health risk. They also frequently contained already banned substances [1, 2, 5, 6, 7]. Indeed, possession of legal DDs found to actually contain illegal drugs is a cause for prosecution and should be borne in mind by users [8].

Table 2. Chemical groupings of recent DDs, including those identified in Poland

Chemical Grouping	Psychoactive Substances
Substituted cathinones	Cathinone, mephedrone, ethcathione, buphedrone, pentedrone, pentylone, 4-MEC, 3-FMC, iso-3-TMC , MDPBP, MDPV, MPBP, MPPP, MOPPP, MDPPP, MPHP, dimethylcathinone, butylone, methylone, ethylone
Substituted phenethylamines	MDOH, MDMA, MMDPEA, 2-AT, PEA, amphetamine, fluoroamphetamine, ephedrine, 2C-E (& series),
Synthetic cannabinoids	JWH-081, RCS-4, JWH-098, JWH-251, JWH-307, JWH-015, JWH-018, JWH-073, JWH-203, JWH-250, JWH-019, AM-694
Substituted phenyl / benzyl piperazines or piperidines	BZP, MeOPP, MPZP, DBZP, pFPP, TFMPP, D2PM, 2-DPMP, MDBZP, m-CPP,
Tryptamines	5-HTP, 4-HO-MET, 5-AcO-DMT, 5-MeO-DALT, 5-MeO-DET, 5-MeOAMT
Others (incl. pharmaceuticals)	Diphenylprolinol, 2AI, MMAI, DMAA, tadalafil, lidocaine, benzocaine, procaine, Dimethocaine, p-FBT, GBL, Salvinorin A, LSA, 5-IAI, MDAI, MDMAI, 3-(4-Hydroxymethylbenzoyl)-1-pentylindole

The presented first article now reviews in turn the biological effects of cannabinoid and cathinone derivative DDs according to the evidence and expert opinion. The second is focused on piperazines/piperidines, phenylethylamines, tryptamines and a miscellaneous 'others' category. Several of the other substances found were not included in the review as they consist of universally consumed food product constituents, such as amino acids: phenylalanine (some commonly found in dietary supplements) and caffeine or medicinal drug substances, such as Tadalafil (for treating erectile dysfunction) or Kynurenic acid, an antagonist to the N-methyl d-aspartate receptor (NMDAR), tentatively proposed as a disease marker for diagnosing schizophrenia and other conditions. Ephedrine (in 29th place), is obviously extremely well known and therefore not considered further.

A list of compound structures is provided in a supplementary diagram file including the common and IUPAC names. For convenience, Table 3 also show the corresponding acronym and IUPAC names and, for the sake of brevity, acronyms or common names are chiefly used in the main text.

Table 3. Acronyms (in alphabetical order) and corresponding IUPAC names of reviewed DDs-Parts1 & 2

DD Acronym	IUPAC NAME
2-AI	2,3-Dihydro-1H-inden-2-amine
AM-694	1-[(5-Fluoropentyl)-1H-indol-3-yl]-(2-iodophenyl) methanone
2-AT	1,2,3,4-Tetrahydronaphthalen-2-amine
Bupehedrone	2-(Methylamino)-1-phenylbutan-1-one
Butylone	1-(1,3-Benzodioxol-5-yl)-2-(methylamino)-butan-1-one
BZP	1-Benzylpiperazine
Cathinone	(S)-2-Amino-1-phenyl-1-propanone
2-AT	1,2,3,4-Tetrahydronaphthalen-2-amine
2C-E	1-(2,5-Dimethoxy-4-ethylphenyl)-2-aminoethane
2C-I	2,5-Dimethoxy-4-iodophenethylamine

Table 3 (continuation**).** Acronyms (in alphabetical order) and corresponding IUPAC names of reviewed DDs-Parts1 & 2

DD Acronym	IUPAC NAME
2C-C	1-(4-Chloro-2,5-dimethoxyphenyl)-2-aminoethane 1-(4-Chloro-2,5-dimethoxyphenyl)-2-ethanamine
2C-N	2,5-Dimethoxy-4-nitrophenethylamine
2C-B	2-(4-Bromo-2,5-dimethoxyphenyl)ethanamine
2C-D	1-(2,5-Dimethoxy-4-methylphenyl)-2-aminoethane
2C-H	2-(2,5-Dimethoxyphenyl)ethanimine
DBZP	1,4-Dibenzylpiperazine
DMAA	4-Methylhexan-2-amine
Dimethocaine	3-Diethylamino-2,2-dimethylpropyl)-4-aminobenzoate
Dimethylcathinone	(RS)-2-Dimethylamino-1-phenylpropan-1-one
D2PM	Diphenyl(pyrrolidin-2-yl)methanol
2-DPMP	(RS)-2-Benzhydrylpiperidine
Ethcathinone	(RS)-2-Ethylamino-1-phenyl-propan-1-one
Ethylone	(RS)-1-(1,3-Benzodioxol-5-yl)-2-(ethylamino) propan-1-one
3-FMC	(RS)-1-(3-Fluorophenyl)-2-methylaminopropan-1-one
iso-3-FMC	1-(3-Fluorophenyl)-1-(methylamino)propan-2-one
GBL	Dihydrofuran-2(3H)-one
3-(4-Hydroxymethylbenzoyl)-1-pentylindole	[4-(Hydroxymethyl)phenyl] (1-pentyl-1H-indol-3-yl) methanone
5-IAI	5-Iodo-2,3-dihydro-1H-inden-2-amine
JWH-081	4-Methoxynaphthalen-1-yl-(1-pentyl-indol-3-yl) methanone
JWH-098	4-Methoxynaphthalen-1-yl-(1-pentyl-2-methylindol-3-yl)methanone
JWH-251	2-(2-Methylphenyl)-1-(1-pentyl-1H-indol-3-yl) ethanone
JWH-307	5-(2-Fluorophenyl)-1-pentylpyrrol-3-yl)-naphthalen-1-ylmethanone
JWH-015	2-Methyl-1-propyl-1H-indol-3-yl)-1-naphthalenylmethanone
JWH-018	Naphthalen-1-yl-(1-pentylindol-3-yl)methanone
JWH-073	Naphthalen-1-yl-(1-butylindol-3-yl)methanone
JWH-203	2-(2-Chlorophenyl)-1-(1-pentylindol-3-yl) methanone
JWH-250	2-(2-Methoxyphenyl)-1-(1-pentylindol-3-yl) ethanone
JWH-019	1-Hexyl-3-(naphthalen-1-oyl)indole
Lidocaine	2-(Diethylamino)-N-(2,6-dimethylphenyl) acetamide
LSA	(8β)-9,10-Didehydro-6-methyl-ergoline-8-carboxamide
mCPP	1-(3-Chlorophenyl)piperazine
MDMA	(RS)-1-(Benzo[d][1,3]dioxol-5-yl)-N-methylpropan-2-amine
MDAI	6,7-Dihydro-5H-cyclopenta[f][1,3]benzodioxol-6-amine
MDBZP	1-(Benzo[1,3]dioxol-5-ylmethyl)piperazine
MDMAI	N-Methyl-6,7-dihydro-5H-cyclopenta[f][1,3] benzodioxol-6-amine
MDOH	(±)-1-(Benzo[d][1,3]dioxol-5-yl)-N-hydroxylpropan-2-amine
MDPPP	(RS)-1-(3,4-Methylenedioxyphenyl)-2-(1-pyrrolidinyl)-1-propanone
MDPBP	(RS)-1-(3,4-Methylenedioxyphenyl)-2-(1-pyrrolidinyl)-1-butanone
MDPV	(RS)-1-(Benzo[d][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl) pentan-1-one
4-MEC	2-Ethylamino-1-(4-methylphenyl)propan-1-one
Mephedrone	1-(4-Methylphenyl)-2-methylaminopropan-1-one
Methylone	1-(1,3-Benzodioxol-5-yl)-2-(methylamino)-propan-1-one
MeOPP	1-(4-Methoxyphenyl)piperazine
MMAI	5-Methoxy-6-methyl-2,3-dihydro-1H-inden-2-amine
MMDPEA	2-(7-Methoxy-1,3-benzodioxol-5-yl)ethanamine
MOPPP	(RS)-1-(4-Methoxyphenyl)-2-(1-pyrrolidinyl)-1-propanone
MPBP	(RS)-1-(4-Methylphenyl)-2-(1-pyrrolidinyl)-1-butanone
MPHP	(RS)-1-(4-Methylphenyl)-2-(1-pyrrolidinyl)-1-hexanone
MPPP	(RS)-1-(4-Methylphenyl)-2-(1-pyrrolidinyl)-1-propanone
pFPP	1-(4-Fluorophenyl)piperazine
PEA	Phenylethan-2-amine
Pentedrone	(±)-1-Phenyl-2-(methylamino)pentan-1-one
Pentylone	(±)-1-(1,3-Benzodioxol-5-yl)-2-(methylamino) pentan-1-one
p-FBT	(1R,5S)-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-fluorobenzoate
RCS-4	2-(4-Methoxyphenyl)-1-(1-pentyl-indol-3-yl) methanone
Salvinorin A	Methyl (2S,4aR,6aR,7R,9S,10aS,10bR)-9-(acetyloxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-2H-benzo[f]isochromene-7-carboxylate
TFMPP	1-[3-(Trifluoromethyl)phenyl]piperazine

Cannabinoids. Principally, JWH-081, RCS-4, JWH-098, JWH-251, JWH-307, JWH-015, JWH-018, JWH-073, JWH-203, JWH-250, JWH-019 and AM-694. Synthetic cannabinoids have been extensively used for research over the last 30 years, particularly in studying cannabinoid receptors CB1 and CB2; however, they are not approved for drug treatment in most countries. On the illicit market they have appeared for many years in the guise of addictive replacements for marihuana/grass/gunga, etc. The production and development of new substances acting as cannabinoid receptor agonists is continually being observed [9]. These compounds can occur in products as individual substances or camouflaged in preparations of plant origin. Recently, such products have been widely advertised and are available on the illegal drugs market, for example, as 'spice' or 'herbal mixtures', not only in Europe and North America, but also in Asia [10, 11, 12] where, for example, 'spice' contains the synthetic cannabinoid CP-47,497, which has a fourfold stronger binding to cannabinoid receptors than the main psychoactive substance of the cannabis plant – delta 9-THC [13].

The dangers of chronic abuse of cannabinoids are seen mainly in youth, leading to long-lasting changes in the central

nervous system (CNS) function, [14, 15]. Prospective studies have also shown a twofold greater risk of schizophrenia occurring [16]. It is recognised that the use of cannabinoids during brain development in the formative years leads to an increased incidence of psychotic and memory disorders in later life [17, 18, 19, 20], which has been confirmed by a large number of pre-clinical studies [21, 22, 23]. Furthermore, cannabinoids increase the risk of acute psychotic symptoms and paranoid schizophrenia [24], especially in predisposed people [25]. Recently, it is becoming recognised that these effects are more serious in synthetic cannabinoids when compared to the naturally processed *Cannabis Indica*, [26]. Data obtained from the EMCDDA confirm that the population profiles of drug users are similar to the USA where cannabinoids are used once every month by about 30% of the population and by 5% daily [27]. In Europe, this problem mostly affects youngsters and young adults aged 15-34 years [1].

The pharmacological effects of cannabinoids depend on their binding to the complementary subclasses of CB1 & CB2 receptors [28]. The former occur throughout the CNS and their activation is responsible for most of the observed pharmacological effects [29, 30, 31, 32]. Both CB1 & CB2 receptors primed with Protein G decrease adenylocyclase activity and the stimulation of CB1 receptors also blocks some types of calcium channels while activating potassium channels [33, 34]. CB2 receptors are located chiefly in the peripheral nervous system (PNS) and in cells of the immunological system, e.g. spleen, and also in sperm [35, 36].

Cannabinoids also negatively affect reproduction in both females and males. Concentrations of testosterone are decreased as well as increased sperm damage, lowered sperm count and function [37]. Detrimental effects during pregnancy are seen as well on foetal development [38]. Nevertheless, cannabinoids are shown to have therapeutic benefits in the treatment of Alzheimer's disease [39], and modulating the activity of the endocannabinoid system holds promise in the treatment of a wide range of different diseases/conditions, including, among many others, mood and anxiety disorders, Parkinson's and Huntingdon's disease, neuropathic pain, multiple sclerosis and spinal cord injury, cancer, atherosclerosis, myocardial infarction, stroke, hypertension, glaucoma, obesity/metabolic syndrome and osteoporosis [40].

The use of selective CB2 receptor agonists without psychoactive properties also hold promise [41], especially in serving as novel anti-inflammatory/immunosuppressive agents. The negative effects on the CNS give rise to symptoms such as anxiety, increased physical activity, disorders of perception, time and space, depersonalisation, increased sensitivity to sound, hallucinations and psychotic episodes, and convulsions, whereas the effects on other systems/organs include nausea and vomiting, increased heart rate and arterial pressure. After sustained use, tolerance to these cannabinoids appears, but during withdrawal, symptoms of anxiety, sleeplessness, palpitations and convulsions occur [42, 43, 44, 45].

Taking cannabinoids additionally results in acute changes to the respiratory system causing inflammation of the naso-pharynx, coughing and chronic bronchitis, as well as circulatory disorders; it is especially dangerous for those with ishaemic heart disease. Synthetic cannabinoids have been found to affect the function of neurotransmitters in the CNS, particularly affecting the plasticity of neurones during CNS development in the young [46, 47, 48]. The cannabinoids listed below, which mainly appear on the Polish list, bind to the afore-mentioned receptors: JWH-098 [49, 50], JWH-251 [44, 50, 51, 52], JWH-307 [50, 51] JWH-015 [34, 39] JWH-018 and JWH-073 [53], JWH-203 [54] JWH-250 [50], JWH-081 [10], JWH-019 [55].

The two substances JWH-081 and RCS-4 that occupy 2nd and 3rd place of those most frequently detected in the afore-mentioned Polish drug seizures are structurally similar where the methoxynapthalene group in the former is replaced by the methoxyphenyl group in the latter. Both are cannabinoid indoles which have been only fairly recently identified in various 'herbal high' concoctions, and are marketed as alternatives to cannabis [56]. Another reason for the upsurge in their use was that until quite recently they remained undetectable by standard methods; however, within the last two years this has changed where, together with other occult napthyl/phenylacetyl indole-cannabinoids (e.g. JWH-203, JWH-250, JWH-073, JWH-015, JWH-018, JWH-019, JWH-122 which were seen less often in the Polish case), validated methods have now become fairly widespread [10, 57, 58, 59, 60]. This has also included sensitive detection in whole blood of some of these substances from persons taking 'herbal highs' [61] or using urinary metabolites as confirmation, e.g. JWH-250 [62]. RCS-4 is a JWH-018 analogue, [63], and banned in Scandinavia, but more is known about JWH-081, an analgesic, and although there is little clinical evidence of their effects *per se*, the known interactions of cannabinoid ligands with the CB1 and CB2 receptors, however, are generally well recognised, thus their effects can be predicted with a great degree of confidence. Previous studies on affinities to these receptors have demonstrated the effect of increasing N-1 alkyl side-chain length, as well as additional substitutions on the napthyl moiety where optimal configurations (such as 3-6 carbon alkyl chain length) were defined for maximal receptor affinities [55]. A later study continued this work [50] on 47 substituted indole derivatives where further optimal configurations in terms of CB2 receptor/agonist interactions were defined; these principally included JWH-120, 151, 267, with JWH-120 and JWH-267 being partial agonists.

High CB1 receptor affinities were seen, however, in three groups of naphthoyl indoles, (divided according to various substitutions on the naphthoyl ring), which in the case of JWH-081 showed a 10-fold higher affinity for the CB1 CNS receptor compared to CB2 of the PNS. JWH-018 is also an analgesic naphthoyl-indole with documented cases of serious physiological effects, withdrawal and potent effects on the CB1 receptor [53] and is widely banned throughout the world.

AM-694 (1-(5-fluoropentyl)-3-(2-iodobenzoyl) indole) is noticeable in the Polish seizure list (18th place) and is a very potent and selective agonist of the CB1 receptor [64]; however, very little else is known. Current UK generic legislation on synthetic cannabinoid receptor agonists [65] does not cover this substance and it seems new forms of legislation are therefore required.

SUBSTITUTED CATHINONES

Principally: Cathinone, Mephedrone, Buphedrone, Ethcathinone, 4-MEC, MDPBP, MDPV, MPBP, MPPP, Dimethylcathinone, Butylone, Methylone and Ethylone.
Mentioned: 3-FMC, iso-3-FMC, Pentylone, Pentedrone, MOPPP, MDPPP, and MPHP.

In 2009, the European early warning system alerted that 24 new psychoactive substances had appeared on the market, of which 4 synthetic cathinones were identified. Cathinones, in fact, were included on the list of psychotrophic substances in 1988 [66, 67]. Structurally similar analogues of cathinones, such as pentedrone, mephedrone or methylone, with euphoric action, are treated as substitutes of cocaine, ecstasy or amphetamine [6, 68, 69]. Taking into account the pharmacological action and molecular structure, cathinone derivatives related to amphetamines differ only at the substituted beta carbon position (they are therefore termed as being beta-keto-amphetamine analogues). Their molecular structure allows a series of several different compounds to be made through substitution at various positions in the aromatic ring, N-alkylation and substitutions at the alpha carbon position [67, 70]. Data obtained from the UK between January 2006 – February 2010 indicate that 95% of cathinone derivatives are in powder form, and only 4% are in tablet/capsule form [71].

Cathinone and its synthetic derivatives act as arousal/stimulants of the CNS, but this action is somewhat less than amphetamine, probably due to the presence of the beta-keto group which increases the polarity of the molecule and limits the ability of crossing the, blood brain barrier (BBB), [72]. Cathinone analogues affect monoamine neurotransmission and, among other things, increase the release of dopamine, serotonin and nor-adrenaline in the brain [73, 74, 75, 76]. As an inhibitor of the noradrenaline transporter NET, cathinone is a strong sympathomimetic and causes increased release of noradrenaline at the nerve endings to the heart and circulatory/capillary system [77]. Most of the effects, usage and hazards of cathinones have been documented by users themselves. Harmful effects of cathinone analogues are reported on the heart-circulatory system and the GI tract [78], where in the former, they recall those caused by amphetamine derivatives [73, 79, 80]. Cathinones like cathinone and methcathinone show stimulation of the CNS, similar to amphetamine, when given to animals where increased motor activity is also seen [67].

One of the very few clinical studies [81] confirmed the toxic, sympathomimetic action of one of the cathinone derivatives – mephedrone. Another recent review of available clinical and neurobiological data support this finding [82] which now more importantly includes data on the new synthetic cathinones. The most common symptoms clinically seen ascribed to the action of cathinone analogues are: chest pains, difficulty in breathing (dyspnoea), tachycardia, heart palpitation, increased blood pressure, capillary dilation, haemorrhage, headache, arousal, anxiety, pupil dilation, nausea, vomiting, confusion, hallucinations and convulsions [67, 73]. Only in the UK have several dozen deaths occurred related to cathinone derivatives abuse; however, their precise role and relationship to episodes causing death is still difficult to establish.

Recently, a major retrospective clinical study [83] was undertaken on 236 subjects intentionally abusing DDs (termed 'bath salts') from two USA poisons units that focused on exposure to synthetic cathinones, including comprehensive quantitative blood/urine analysis on 18 patients, as well as a detailed breakdown of symptoms, management and outcomes for all. 21% cases required critical care. For the first time MDPV levels were identified in both live and dead patients, (ranging 24-1400ng/ml). 37 different DD product names were found. Symptoms were mainly of a neurological and cardiovascular nature; the main ones being agitation and combative behaviour, sympathomimetic syndrome with psychotic episodes requiring sedation, movement disorders, tachycardia, hallucinations, paranoia, confusion, chest pain, myoclonus and hypertension. Legislation in many US states has now banned these emerging substances. As mentioned previously, the highest incidence of DDs was detected recently in Poland, following a major analysis of over 6,000 samples seized 23% were MDPV.

Cathinone. This is a sympathomimetic amine naturally occurring in the Khat shrub (*Catha edulis*), [63, 69, 84, 85]. The raw material contains from 36 up to even 343 mg of cathinones in 100g of fresh leaves. It is estimated that the daily world consumption is around 5 million portions (1990 data). The plant is used traditionally by around 10 million people mainly from the southwestern part of the Arabian peninsula and eastern Africa [86, 87, 88, 89]. Chewing 100-200g of the leaves produces an arousal effect 2-10 times weaker than amphetamine [90]. The plant causes arousal/stimulation, increased sensitivity, irritability and anxiety, but in low doses of 0.6g does not influence pupil width, light response nor delayed reaction [91, 92]. The addictive potential of the plant causes a moderate but enduring psychological addiction. The symptoms from an overdose due to prolonged consumption are usually mild (lethargy, mild depression, tremor and recurring nightmares are seen). Large overdoses of the plant can lead to psychological illness bringing about two types of psychological reactions: symptoms of delusional mania or paranoid psychosis [66, 93, 94, 95]. The euphoric effect starts an hour after consuming 60g of fresh leaves constituting 0.1-1mg cathinones/kg body weight. Themaximum concentration of cathinones in the blood plasma is reached after 127±30 minutes at levels of 127±53(SD) ng/ml. Cathinone is metabolised quickly by the first pass through the liver. Only 2% of the dose is excreted in the native form, 22-52% is recovered in the urine as aminoalcoholic norephedrine and norpseudoephedrine forms [66, 96, 97, 98, 99, 100].

In persons using Khat leaves, central and peripheral toxicity is seen in the presence of cathinones, the symptoms of which, among others, are generally bad mood, insomnia (in 65% cases), irritability, migraine, constipation, appetite loss, (about 51%), and decreased sexual performance. Preclinical studies have shown that cathinones cause several disorders of the cardiovascular system including constriction of the coronary arteries, increased blood pressure, tachycardia, arrhythmia and positive inotropic and chronotropic action [78, 89, 101, 102]. The risk of myocardial infarction is also increased [73, 103]. Regular use of the plant can worsen social interaction and lead to social, economic and health problems, as well as often being linked to becoming addicted to other substances [104, 105]. Long-term use may cause an increases in morbidity of Type 2 diabetes, cardiomyopathy, duodenal ulceration, liver inflammation and cerebrovascular ischaemia and clot embolism [78, 101, 106]. It has also been demonstrated that direct contact of the mucosa with the leaf components during chewing may increase the risk of gastro-intestinal, brain and thoracic cancer [66]. The leaf components may also influence reproductive function by decreasing sperm quality, (decreasing motility and abnormalities in production, as seen in 65% men who constantly use Khat) [107]. Using Khat

during pregnancy may cause disorders of blood flow between the mother and placenta, resulting in increased mortality and decreased body mass of the newborn [78, 108].

Mephedrone. In retrospect, this key psychoactive and now notorious substance is a classic example of how DDs come about, thereby meriting additional discussion even though some of its seriously adverse effects have since become well known, leading to its widespread banning worldwide. After being 'rediscovered' in the early 2000s as a legal and highly attractive substitute for illegal recreational drugs (those such as cocaine, ecstasy, amphetamines BZPs etc), mephedrone use, not surprisingly, has burgeoned forth to such an extent as to have made it the principle legal DD of abuse at the end of that decade. Due to the large and ever-increasing number of hospitalisations/fatalities arising from its use in the EU, (especially in the UK), as well as in many other countries, mephedrone was made illegal throughout the world. The EU issued a ban in 2010 followed by the USA in 2011, and subsequently many others following suite; a frequently adopted preventative strategy being to ban substances until proven not to be harmful.

Various historical stages can be discerned in this process: initial re-discovery of psychoactive/recreational properties, rising to public prominence as a favoured and legal DD (aided by increase of Internet use as well as media reporting), widespread abuse coupled with increasing health hazards/concerns, medical reporting of problems thus arising, official recognition, debate and statutory prohibition, relegation of mephedrone to black market use, and finally, the continuous and overlapping appearance of more and newer DDs as replacements, thus perpetuating the cycle. A good example is that of MDPV (as discussed later), which filled the gap left by mephedrone, only to itself become subsequently banned for similar reasons through a similar but quicker turn of events.

An increasing number of mephedrone toxicity cases and some deaths have been reported, mainly from various hospital departments (usually emergency departments), from on-line poisons databases, and surveys aimed at those considered most vulnerable, e.g. schoolchildren/students [109, 110]. These include severely adverse and moderate sympathomimetic effects [111, 112, 113], severe cardiovascular and psychoactive toxicity [114, 115], deaths attributed to mephedrone, sometimes in conjunction with other substances, [116, 117, 118], methaemoglobinaemia [119], psychosis [120, 121] and serotonin syndrome [122]. As well as a high risk to health, mephedrone dependency is also observed [109, 123] with some likely mechanisms for this proposed [76]. Experimental studies on the pharmacology and acute toxicity are starting to surface, both in humans and animal models [76, 124, 125, 126, 127, 128, 129], confirming what had really been a previously held opinion based actually on structural considerations alone, that the toxic effects of mephedrone are on the whole quite similar to MDMA, amphetamine, cocaine and others, thus justifying the aforementioned worldwide bans alluded to earlier. Essentially mephedrone's mechanism of action is by stimulating release of monoamine neurotransmitter (dopamine, serotonin), together with inhibiting their uptake; in the latter case, this also included non-adrenaline [126]. The greater hydrophilic nature of mephedrone results in decreased ability to cross the BBB, compared to other drugs like amphetamine and indeed MDPV, which may partly explain why the latter became an attractive replacement for mephedrone where the advantage of required smaller doses are effective.

Analytical GC/MS studies on human and rat urine revealed Phase 1 metabolism of mephedrone [130, 131], where the principal metabolites detected were nor-mephedrone, nor-dihydro mephedrone, hydroxytolyl mephedrone and norhydroxytolyl mephedrone, as well as the parent substance. A further *in vitro* study [132] using human liver microsomes, confirmed these results by NMR and UPLC-QTOF/MS9(E), as well as detecting several new metabolites. Mephedrone and some of these metabolites were also detected in blood by similar means. The basis for forensic drug testing is thus facilitated.

Buphedrone (MABP). Has sympathomimetic action similar to amphetamines and cathinones. Its central action, stronger than methylcathinone, persists after nasal application for about six hours. Its effects resemble cocaine, amphetamine or MDMA (ecstasy) [133, 136] and have been well known since it was synthesised in 1928 [133]. Together with pentedrone and pentylone it has been well characterised in recently seized DD shipments [135, 136].

4-MEC. Another cathinone derivative to feature high up on the Polish drug seizure list (7th place), and has only recently appeared in the so-called second generation legal high energy products called 'NRG-1 & NRG-2'[137]. It is a stimulant and entactogen belonging to the phenethylamine, amphetamine, and cathinone chemical groupings, and has been used to replace mephedrone. Recent methods for its detection have been developed together with other cathinone related DDs [138], as well as a fully validated one for analysing NRG-2 products [139].

Ethcathinone. is a synthetic analogue of cathinones being a pharmacologically-active alkaloid found also in Khat. Its pharmacological action is similar to cocaine, amphetamine, MDMA and mephedrone, and is a an active metabolite of diethylcathinone which itself has very weak pharmacological effects. On the illegal market it is sold as an MDMA (ecstasy) substitute and, through various complex analytical methods of identification, increasing examples of illicit sales are emerging [140]. The principle pharmacological effect is to release noradrenaline, and to a lesser extent, to inhibit dopamine reuptake by presynaptic structures of the CNS [141, 142]. A recent emergency case of ethcathione and methylone poisoning was reported [143] with seizures and hyponatraemia followed by Rhabdomyolysis, consistent with serotonin toxicity that required a six-day course of treatment.

3-FMC and iso-3-FMC. The former is another synthetic analogue of cathinone, being a pharmacologically-active alkaloid found in Khat. Its pharmacological action is likewise similar to amphetamine and another analogue of cathinones – mephedrone. It strongly stimulates the sympathetic nervous system where heart action is stimulated with a significant increase in arterial pressure [134, 144, 145, 146]. Iso-3-FMC is a side-product obtained during the synthesis of 3-FMC, but of as yet unknown activity.

In the UK, the cathinones methcathinone and lately also 3-FMC [145] are listed as controlled substances and there have been two cases documented of hospitalisations resulting from their derived consumption [144]. There have been only

a few reports on the action of these cathinones. They may be responsible for monoamineoxidase inhibition, and it is also recognised that they are structurally similar to the amphetamine 1-phenylpropan-2-amine and are analogues of beta-keto amphetamines [67, 145].

MDPBP. belongs to α-pyrrolidinophenones compound group closely related α-aminophenones, such as cathinone, methcathinone, MDVP and others [147]. This was first identified on the black market in Germany in 2009 and since then has been frequently identified in supposedly legal DD coctails such as in 'bath salts' products in the USA [148] and, following the mephedrone ban of April 2010, in NRG-1 and NRG-2 products in the UK [6]. It was placed on the EMCCDA list of new in psychoactive substances in 2010 originating from the UK [149]. Various complex spectroscopic methods, (IR, MS and NMR), have recently been developed to elucidate this substance and are necessary in order to keep pace with identifying newly emerging DDs [147].

MDPV. Since 2010 this substance, with the slang/street name of 'ivory wave/bath salts', has increasingly become a very popular DD throughout the EU, [137, 150], due to the then existing cathinone derivatives becoming illegal substances, principally the EU-wide ban on mephedrone resulting from its seriously adverse effects (psychoactive and cardiovascular toxicity) becoming recognised [114, 125]. However, together with others, (e.g. MPHP, MPBP, MPPP, MOPPP & MDPPP), MDVP's potential as a DD has been previously noted in the literature since 2005 [151, 152, 153]. MDPV is a pyrovalerone analogue [154], a substance previously used in the 60s and 70s to treat chronic fatigue, lethargy and obesity, but its use has since been limited [155, 156] because of recognised abuse and dependence risks, probably through stimulation of the dopaminergic reward system [157]. A recent study also showed that opioid-dependent patients mainly took MDPV as an amphetamine substitute [158]. In contrast to other cathinone derivatives, MDPV is more lipophilic and much more able to cross the BBB, thus significantly increasing its psychoactive potency. It acts as a powerful stimulant through being an inhibitor of nor-adrenaline and dopamine uptake by blocking their protein transport, thus increasing neurotransmission of these monoamines. Reports suggest that its stimulatory effects can be even greater than cocaine and amphetamine [159], typical doses ranging from 5-30mg; however, a marked tendency to re-dose has been observed leading to doses >200mg, [159, 160, 161]. Despite there being relatively little detailed pharmacology known about this substance, some inference can be made to other pyrovalerone derivatives, as previously mentioned [162], although care should be exercised as structurally similar compounds may have different effects, as in the case of MDMA structurally resembling MDPV. After ingestion, the psychoactive effects may last up to four hours while other more unpleasant physiological effects (e.g. tachycardia) can last eight hours.

MDPV has been shown to be metabolised to glucuronides and sulphated forms of catechol and methyl catechol pyrovalerone whose presence in the urine can be used for anti-doping analysis by sophisticated LC/MS techniques [163, 164]. The desired effects by users have been extensively reported on the Internet in which smaller doses increased concentration in work or study, aphrodisiac effects and mild euphoria. Others include increased sociability, energy, motivation, wakefulness, alertness, arousal, less need for food/drink and mild empathogenic effects [159, 161]. Untoward effects arise from overstimulation of the nervous system and cardiovascular complications [150, 160, 165, 166, 167] mainly consisting of fatigue, insomnia, nausea, GI problems, tremor, temperature, sweating, tachycardia, headache, renal pain, tinnitus, numbness, dizziness, overstimulation, problems breathing, panic attacks, altered vision, confusion, thoughts of suicide, anhedonia, depression and psychosis, as well as possible tolerance and dependence. Clinical incidents related to MDPV have been relatively few in the past but are now fast increasing, consistent with the gaining popularity of this DD. Acute kidney injury has been observed in a case of repeated bath salt intoxication [168], together with other serious cardiovascular and neurologic symptoms. A common practice amongst intravenous drug users is injection of bath salts which has been shown to lead to local tissue injury, e.g. extensive abscess formation [169].

Complementary to the above-described retrospective MDPV study [83], other cases in the USA that required emergency care have also been recently reported following 'bath salts' abuse [165]; frequently, other drugs also being identified. Recent serious cases of paranoid psychosis and agitation have also been reported [150, 170, 171, 172, 173] requiring specialist intensive care and/or psychiatric care, including detoxification treatment and benzodiazepine sedation and, if necessary, other antipsychotics – even general anaesthesia. A study from Finland [174] demonstrated 259 positive MDPV cases, (0.016-8mg/L in blood), from apprehended drivers suspected to be under the influence of drugs, by showing clear driving impairment and, interestingly, it was found that most of them had also taken benzodiazepines and/or amphetamine, as well as other drugs; however, these were mostly present in small amounts. Indeed the habit of taking other drugs to either enhance the pleasurable effects and/or counteract the unpleasant ones is a widespread practice adopted by users of many DDs, (including MDVP), usually resulting from information readily available on the Internet [159]. This is obviously a matter of concern for physicians/clinicians in diagnosis and treatment [82] which, in the absence of guidelines, should be symptomatic and supportive [160, 166, 173]. MDPV and baths salts are often labelled as 'plant food', 'not for human consumption' or 'for bathing' [167] as a means to bypass any legal obstacles as is the common practice with many other drugs. Due to the current wide abuse of this substance it has only been very recently placed as a controlled substance in many countries, including the USA [175], where a temporary one year ban is in place. It is now illegal in Australia as well as several EU countries – including the UK, Sweden, Ireland and Denmark. In Poland, it is covered by the temporary ban of 2010 described earlier.

MPBP and MPPP. These are closely similar pyrrolidinophenones where a pyrrolidinyl group replaces the amine group on the cathinone moiety, a methyl group has been added to the 4 position on the aromatic ring and the alpha carbon possesses either a methyl group, (MPPP) or ethyl group, (MPBP). Both have been identified many times recently as components of designer drugs (party pills, powder and bath salt forms) in both Europe and Asia [63, 67, 176, 177], and as constituents of NRG legal high energy products [6, 137].

The pharmacological effects have not been reported *per se* in the literature, although they share many structural features of known amphetamine-like stimulants and enactogens, as well as the closely-related α-pyrrolidinopropiophenone, (α-PPP), for which its stimulant effects on animals and *in vitro* studies have been documented [153, 178], through releasing dopamine and norepinephrine and inhibiting their reuptake. It is therefore arguably reasonable to suppose that the same side-effects resulting from other substituted cathinones will also be seen as described previously in the cathinone section. Indeed, this has been recently confirmed in a case of acute poisoning by 4'-Methyl-α-pyrrolidinohexiophenone (MPHP) in a 27-year-old man resulting in toxic liver damage and rhabdomyolysis [153].

MPHP is a closely-related substance belonging to this group where an extended chain on the alpha carbon, i.e. a butyl group, has replaced the ethyl group of MPBP. The metabolism of MPBP and MPPP is well-known from rat models [162, 179] and human studies [178, 180] from which methods have arisen for their detection in urine, from which the toxicity risk to humans can be assessed . Hydroxylation and demethylation of both occur in the liver by enzymes CYP2D6, CYP2C19 and to lesser extents by CYP1A2, CYPP2B6 and CYP2C9 [162, 179, 181, 182, 183]. MPBP has been shown to undergo intensive oxidation of its methyl groups to carboxyl ones and is excreted in this form in the urine [179]. Other metabolites appear in the urine in glucuronide and sulphated forms [162, 164, 182].

Dimethylcathinone. This substance is used to treat colds and hypotonic conditions as well being an anorectic; however, it is recognised to have potential as a stimulatory DD sufficient for anti-doping controls [69, 167, 184]. Although the psychoactive mechanism of action of this quite commonly found but recent DD is not really known, its properties can be reasonably expected to be deduced from the other afore-mentioned synthetic cathinones [167]. In this case, however, care should be exercised in that an animal study has shown dimethylcathinone to have a nine times more potent amphetamine-like stimulation in rats than could be predicted from structure activity relationships, [69] from among the other investigated cathinones. Dimethylcathinone is rapidly metabolised to methylpseudoephedrine and methcathinone, forming the basis of forensic testing of this substance [183].

Butylone, Methylone, Ethylone and Pentylone. These relatively new and emerging DDs are reviewed together, not just due to their structural similarities, but also because of their related effects, metabolism and methods of analysis. They are also closely akin to the phenylethylamine and amphetamine groupings.

Butylone, or bk-MBDB, as the name implies, is a beta ketone analogue of MBDB, a substance with mild euphoric MDMA-like effects widely recognised since the 1990s and showing moderate serotonin release in the brain and an inhibition of serotonin and noradrenaline re-uptake [185]. In most countries it is not controlled because its effects are perceived to be mild and non-toxic [186].

Methylone, or bk-MDMA, is also a beta ketone analogue of a structurally very similar substance, the notorious MDMA drug otherwise known as 'ecstasy' which, in contrast to MBDB, and as previously mentioned, has powerful stimulant, entactogenic and psychedelic effects, as well as being neurotoxic, the only difference between these molecules being a methyl group linked to the alpha carbon for MDMA in place of an ethyl group for MBDB. Reports identifying methylone among samples or seizures of street drugs surfaced in Holland [187], and together with butylone, have ever more frequently been reported, e.g. in Japan [188, 63], the UK [137], and Switzerland [189].

Case reports following butylone and methylone abuse are mainly limited to these DDs being taken together or with other DDs. A very recent and detailed report of a fatality due to serotonin syndrome arising from methylone and butylone poisoning has just been published [190]. In summary, a healthy 24-year-old patient had ingested two 'ecstasy-like' capsules containing in total 844 mg methylone and 106 g butylone, and became unconscious. Following various symptoms from presentation (i.e. 'comatose febrile, tachycardia, tachpnea, hypertensive and upon examination diaphoretic, tremulous, hyperreflexic with sustained clonus'), and after intensive care treatment, the patient died 48 hours later from multisystem-organ failure. The autopsy showed generalised coagulopathy, fatty liver and anoxic encephalopathy. Admittedly, the doses were high, but nevertheless this demonstrates how easily they can be taken. Another less serious case was seen in a 31-year-old man presenting with prolonged palpitations sweating and insomnia following mistaken ingestion of a 1 g mixture of butylone and MDPV [8]. A 16-year-old boy (with a history of infant cardiac malformation and asthma), after losing consciousness, died from sudden cardiac death two hours later in intensive care after taking an unknown amount of methylone. Levels in the blood and liver were 272ng/ml and 387ng/g, respectively, after autopsy [191]. Also seen were liver microvascular steatosis and damage to cardiac striated muscle. Another emergency methylone poisoning was reported, this time in conjunction with ethcathione, of serotonin toxicity [143], as previously described in the cathinones section. Substance intoxication was also observed in a hospitalised 27-year-old male [192] following ingestion of a combined dose of 120 mg methylone and 76 g 5-MeO-MIPT, labelled as pure methylone; thus, again highlighting the dangers in misleading/false information about DD ingredient.

The above-mentioned hepatotoxic effects of methylone (together with MDMA, MBDB and others), have been confirmed previously in a study on rat hepatocytes [193] where mitochondrial failure and DNA damage were identified as the cytotoxicity target areas. Methylone, however, has been known for some time to powerfully inhibit noradrenaline and dopamine transporters, as demonstrated by *in vitro* animal studies showing a similar potency to MDMA and methcathione [194]. More recently, further *in vitro* studies using CHO cells have demonstrated a ranked inhibition of noradrenaline>dopamine>serotonin transporter systems in those cells where these monoamine transporters are expressed, but none for GABA ones. A synergistic toxic effect with methamphetamine was also observed [195] and it was suggested that cell death may be caused by oxidative stress of these accumulating monoamines. Methylone, together with other phenethylamines derivatives, strongly inhibited dopamine, 5HT and noradrenaline reuptake in a developed assay for measuring monoamine reuptake, based on rat brain synaptosomes [196], thus supporting their role in effects on

the CNS. Further *in vitro* studies on rat synaptosomes [76] showed that, like MDMA, methylone (and mephedrone), are non-selective substrates for plasma membrane monoamine transporters while *in vivo* experiments showed dose-related increases of extracellular dopamine and 5HT in the rat nucleus accumbens following administration of methylone by i.v. (0.3-1.0mg/kg). Unlike methamphetamine, methylone was a weak motor stimulant and unlike MDMA, methylone caused only modest hyperthermia and little long-term change in cortical or striatal amines. Until very recently, the pharmacology of butylone was still unreported, although it was quite reasonably suggested that stimulant effects similar to those described in this section could be expected [130, 196]. A very recent animal study [126], however, has now demonstrated that butylone, together with methylone, results in hyperlocomotion in mice through activating serotonin receptors and increasing extra-cellular dopamine, together with inhibiting the uptake of these monoamines.

The metabolism of both butylone and methylone is relatively well known from several studies. Butylone principally undergoes demethylenation, O-methylation and beta-ketone reduction to form 4-OH-3MeO metabolites which become conjugated glucuronides/sulphates; N-dealkylation is subsidiary [197,198]. Methylone is either degraded to its partly conjugated primary amine form (MDC) or after demethylenation and O-methylation mostly to various hydroxylated/methoxylated and conjugated metabolites [199]; 26% of the dose ingested was present as metabolites in the urine after 48 hours. Within the last few years reliable methods of detecting these substances in blood and the aforementioned metabolites in urine [130, 197, 198, 200] now exist, although some questions remain on their sensitivity *vis-a-vis* actual doses taken by users.

Ethylone (bk-MDEA). It is also worth briefly considering ethylone which is closely related to methylone, and has recently been appearing on the illegal drugs market [131, 187]. Very little is documented on its pharmacological effects although, invariably, as for other DDs, there are anecdotal reports on various web forums. However, it can be reasonably inferred that it has stimulant effects closely resembling butylone and methylone [131]. The metabolism of ethylone has been elucidated [167] and its metabolites can be detected in the urine serving as a basis for forensic testing [131, 197] of this DD.

Pentylone (bk-MBDP). Has been found in recent DD shipments [67, 144, 137].

DISCUSSION

The reviewed DDs, from both articles, serve in part as the basis for the actions undertaken in Poland against DDs [4] and are consistent with the evidence-based strategy on Public Health as adopted by the Chief Sanitary Inspectorate, a central governmental authority subordinated to the Polish Ministry of Health, which is responsible for dealing with all aspects of public health. In line with this approach, whenever direct evidence is lacking, expert opinion is either sought out or used from *bona-fide* sources.

It has been suggested by some experts that certain individual drugs, e.g. mephedrone [201, 202] should be treated in similar ways to alcohol and tobacco, i.e. a reduction in harm could be achieved by regulating their use in controlled environments where, for example, clubs could be allowed to sell small amounts of drugs like mephedrone and ecstasy in a safe environment, similar to the way alcohol is sold. The justification for this being that there is no scientific argument for the effects of mephedrone and alcohol being viewed as being different. The view of the Polish authorities is that this interesting and novel, as well as politically controversial approach, may be flawed through being subjective in its analysis weightings. Although it may also be true that the harm caused by the biological effects of the given examples of mephedrone and alcohol *per se* may be similar, but this neglects the patterns of use and the level of public awareness of the respective dangers. Furthermore, it ignores the fact that DD abusers suffering and indeed sometimes dying through overdosing and/or mixing cocktails of drugs in conjunction with alcohol, taking medication and indeed even drinking strong coffee with the attendant risk of hypokalaemia [203], make diagnosis, management and treatment very difficult. It is often the case that clinicians do not actually know the reasons for a whole range of confusing symptoms, and analyses of taken samples is technically complex and requires a very high level of expert interpretation which is invariably not immediately available. It is felt that this is taking unacceptable risks with people's lives. Management of acute cases of DD toxicity is pragmatic and is often based on previous experience acquired in dealing with established drugs, such as amphetamines, ecstasy, LSD, etc. [204].

It is the considered opinion of the authors of the presented study that a far more effective course of action is constant vigilance through national and the EU-wide surveillance/monitoring systems already in place, followed by immediate action whenever a new DD substance has been identified. This being facilitated by having appropriate national legislation in place to allow an immediate ban to be implemented, followed by rapid and decisive enforcement action to be taken by the appropriate authorities. Evidence that actual bans are working at reducing harm can be seen in the case of mephedrone where a significant decrease of patients presenting with acute toxicity at a major UK teaching hospital has now been noted [115]. A novel method that holds promise in detecting and monitoring many new psychoactive substances is by measuring them in wastewater, which has been introduced by a UK drugs database agency [205] involved in the EC European Action on Drugs initiative.

Although a little beyond the scope of this paper, it should nevertheless be stressed that the most effective action against DD abuse is preventative, particularly in educating/informing youngsters and the general public. With this in mind, several information booklets have been published as an educational resource aimed at both at schools, colleges, GP surgeries and other healthcare establishments, as well as the public, primarily outlining in simple terms both the health/medical consequences and the legal position concerning DD abuse in Poland.

Concluding remarks and further discussion can be found in Part II of this review article.

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