Review

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GHB and synthetic cathinones: clinical effects and potential consequences

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Designer drugs belong to a group of legally or illegally produced substances that are structurally and pharmacologically very similar to illicit drugs. In the past, designer drugs were often used during all-night dance parties, but they are now consumed in multiple settings from college bars to parks to private house parties. Most of these club drugs can be bought on legal websites and home-delivered for private parties. Recently, legal highs have once again become a burning media issue across the world. Our review will focus on GHB and synthetic cathinones. Literature searches were conducted for the period from 1975 to July 2010 using PubMed, EMBASE, PsycInfo, Internet underground and governmental websites using the following keywords alone or in combination: designer drugs, club drugs, party drugs, GHB, synthetic cathinones, mephedrone, methylone, flephedrone, MDAI, and MDVP. Available epidemiological, neurobiological, and clinical data for each compound are described. There is evidence that negative health and social consequences may occur in recreational and chronic users. The addictive potential of designer drugs is not weak. Non-fatal overdoses and deaths related to GHB/GBL or synthetic cathinones have been reported. Clinicians must be careful with GBL or synthetic cathinones, which are being sold and used as substitutes for GHB and MDMA, respectively. Interventions for drug prevention and harm reduction in response to the use of these drugs should be implemented on the Internet and in recreational settings. Prevention, Information, Action, and Treatment are the main goals that must be addressed for this new potentially addictive problem.

Keywords: designer drugs; club drugs; party drugs; GHB; synthetic cathinones; mephedrone; methylone; flephedrone; MDAI; MDVP

Introduction

The terms designer drugs, club drugs, party drugs, designer party drugs, and synthetic drugs are frequently used synonymously.[1,2] The Drug Enforcement Administration (DEA) has noted that club drug terminology tends to have a glamorous aura. The appropriateness of the terms was discussed by the National Institute on Drug Abuse (NIDA) because the use of such drugs has spread beyond the club culture to different populations.[1,3]

Designer drugs belong to a group of legally or illegally produced substances that are structurally and pharmacologically very similar to an illicit substance (e.g. amphetamines, hallucinogenic substance).[4,5] Their classification also changes according to the setting in which they are used.[1] Such drugs include ecstasy (3,4-methylenedioxymethamphetamine) (MDMA), gamma-hydroxybutyrate (GHB) and its precursor chemicals (gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD)), mephedrone, methylone (a close structural analogue of MDMA), butylone (2-methylamino-1-(3,4-methylenedioxyphenyl)butane or MBDB), ketamine, d-lysergic acid diethylamide (LSD).[1,6–8] In the past, designer drugs were most often used during all-night dance parties (raves, free-parties) or in sex clubs,[8] but they are now consumed in multiple settings from college bars to parks to private house parties.[9,10]

There is a lack of epidemiological studies, but available data show that the use of club drugs is on the rise in Europe and elsewhere.[11,12] The clinical pharmacology of each drug is very different,[13] and the last few decades have seen a rise in patterns of polydrug use.[12] Combination with other designer drugs and/or alcohol, cocaine, cannabis, or sedatives is often the rule. Furthermore, combinations and patterns of use can also be quite different in groups who differ in terms of sociodemographic origin and sexual orientation.[9] Club drugs proliferated during the 1990s and remain as key substances used by young adults.[1] Studies about the use and the short- and long-term effects of these drugs in humans are evolving, but no conclusive evidence has yet been reported.

The main sources of information for the study of designer drugs are the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (reporting forms, risk assessment reports, drug profiles), Early Warning System (EWS) reports, the European School Project on Alcohol and Other Drugs Survey (ESPAD), National Reitox reports, underground Internet and governmental websites and discussion groups.[11,14]

The Internet has become a major problem because of its emergence as a new marketplace for psychoactive substances and its role in providing information on obtention, synthesis, extraction, identification, and substance use.[5,15,16] Furthermore, there have been no medical evaluations to determine the effects, risks and addictive potential of these compounds. Most club drugs can be bought on legal websites and home-delivered for private parties.[17]

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Because studies of MDMA, ketamine, and LSD have been extensively published in the literature, and because legal highs and designer party drugs have once again become a burning media issue across the world, our review will focus on GHB/GBL and synthetic cathinones (mephedrone, methylone, methedrone, butylone, MDAI, buphedrone, flephedrone, MDVP, MDAI). Literature searches were conducted for the period from 1975 to July 2010 using PubMed, EMBASE, PsycInfo, Erowid, underground Internet and governmental websites using the following key words alone or in combination: designer drugs, club drugs, party drugs, GHB/GBL, synthetic cathinones, mephedrone, methylone, flephedrone, MDAI, and MDVP.

Gamma-hydroxybutyrate (GHB)

Gamma-hydroxybutyrate (GHB) was first synthesized in 1874 by Zaytsevin, and the first human research on this drug was reported in the 1960s by Laborit.[18] GHB is an endogenous inhibitory neurotransmitter.[19] It is synthesized from GABA in cells containing glutamic acid decarboxylase, the marker of GABAergic neurons.[20] GHB is accumulated by the vesicular inhibitory amino acid transporter and released by depolarization via a calcium-dependent mechanism. GHB binds to GABAB and GHB-specific receptors,[21,22] which leads to an increase in dopamine and other neurotransmitters in the brain. An increase in prolactin and growth hormone levels has also been reported in humans.[23] GHB is a central nervous system (CNS) depressant, but its specific action has not yet been elucidated.[21]

Almost all psychoactive drugs that cause addiction in humans activate the mesocorticolimbic system by increasing dopamine release within the nucleus accumbens.[24–26] This dopaminergic system plays a critical role in motivational, emotional, contextual, and affective information processing of behaviour and drug reinforcement mechanisms.[27] GHB utilizes the same neurobiological mechanism and is thus a potentially addictive drug.[7]

GHB and its chemical analogues, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), were labelled, in the 1980s, as dietary supplements purported to enhance muscle growth, aid sleep, and improve sexual performance.[28] GHB was misused in the 1980s for its body-building effects and in the 1990s as a recreational drug at music venues.[29] Also at this time, reports of sexual assault (often referred to as date rape) facilitated by GHB brought the drug into the spotlight.[30–35]

GHB and its chemical analogues have many street names. The most commonly used are G or Liquid Ecstasy (Table 1). The comparison to ecstasy is due to the euphoric, disinhibiting and social effects, but the two substances are pharmacologically different.[29] When used as a recreational drug, GHB may be found as the sodium salt, which is a white crystalline powder dissolved in water to form an odourless and colourless solution.[36] Most of the time, it is ingested orally from small bottles. The intranasal or intravenous routes are less frequently used. One milliliter of liquid GHB is the common dosage and contains approximately one gram of GHB, although there may be variations in GHB concentration. During parties, the mean interval between GHB doses used was 5 h with a range of 30 min to 24 h.[29]

In Europe, GHB has been under surveillance since 2000. A year later, it was added to Schedule IV of the 1971 United Nations Convention on Psychotropic Substances for all European Union Member States. Despite the rapid control of the open sale of GHB, there was an emergent use of GBL, which is not under the control of the international drug control convention.[14] GBL and 1,4-BD are rapidly converted to GHB when ingested. GHB can be easily manufactured from GBL and 1,4-BD, which are widely used in the chemical industry and are commercially available, especially on the Internet, and can be found in wheel cleaners, cleaning solvents, multi-purpose stain removers, and chrome polish.[28,37] Prices of GBL vary between €24 and €59 per 250 ml, and street prices for 5 ml range from €2 to €8.[37]

Table 1. Market terms for GHB, GBL and 1,4BD

GHB	GBL	1,4BD
G		
Liquid Ecstasy	Blue Nitro	Review Trunt
Liquid X	Midnight Blue	Somatopro
Liquid E	Alloy cleaner	Serenity
Easy Lay	Wheel cleaner	Enliven
Scoop	Cleaner	
Fantasy	Magic stripper	
Cherry meth		
Growth hormone booster		
Woman viagra		
Natural sleep 500		
Organic Quaalude		
Biberones (Spain)		
Salt Water		
Soap		

A few European countries report lower prevalence of GHB than other illicit drugs.[37] In the Netherlands in 2007, a study reported a slight increase in the use of GHB in specific networks and regions. Among 15–16-year-old school students across Europe, the 2007 ESPAD survey reported a 1% or less lifetime prevalence of GHB use in most countries. Lifetime use of GHB/GBL ranges from 3% to 19% in surveys conducted in dance music settings and at popular music festivals (for review, EMCDDA[37]). In France, GHB use has been detected since 1999 by the TREND network (*Tendances Récentes et Nouvelles Drogues*/Recent Trends and New Drugs) in Paris, Marseille, Lille, the French-Belgian border and in Toulouse on the homosexual party scene.[38] The 8th TREND report indicated an increase in GHB use in 2006 and 2007, especially during after-parties. This increase in the recreational use of GHB has been accompanied by an acceptance of the accidents linked to this drug by the users and by the nightclubs, which have created recovery spaces called Chill Out rooms.[39] There is a clear lack of epidemiological data concerning GHB/GBL use, and the reported prevalence of use is certainly under-evaluated, especially due to the existence of hidden populations at homes and at parties.[40]

Because the first GHB/GBL use occurs in young adulthood, most users are likely to have tried other drugs (cannabis, cocaine, opiates, sedatives, etc.) before experimenting with GHB/GBL.[40]

GHB is rapidly absorbed, metabolized and eliminated with a plasma half-life of 27 min, and it is undetectable in the plasma after 6 h and in urine after approximately 12 h.[41–43]

Clinical effects of GHB are comparable with those of alcohol or benzodiazepines. These effects usually occur 15 min after ingestion and can last approximately 3–4 h.[44] According to Ward *et al*., a 0.5 gram dose is taken for relaxation and disinhibition, a 1 gram dose for euphoric effect and some stimulant-like effects and a 2 or 3 gram dose for deep sleep.[45]

In a recent controlled laboratory study in humans, Oliveto *et al*. found that GHB produced dose-related increases in subjective ratings of sedative-like, stimulant-like, positive mood and dissociative effects but produced no changes in psychomotor performance measures or blood pressure in 10 non-substance-abusing volunteers.[46] Doses greater than 50 mg/kg result in loss of consciousness and coma.[47,48] Other adverse effects include oversedation, anterograde amnesia, paradoxical agitation, slurred speech, irrational behaviour,[44] motor incoordination (G-napping), severe nausea, vomiting, gastrointestinal tract irritation, hyperthermia, and overdose (G-hole).[49–51] Most subjects reported that they would use GHB again despite severe negative consequences.[52] Driving under the influence of GHB and its major consequences are another major point not well recognized by users.[53]

The impact of GHB on several aspects of sexuality (increased desire and arousal, decreased inhibition, greater willingness to engage in sexual activity) is clearly recognized by all users, but the risk of unsafe sexual practices and sexually transmitted diseases is not appreciated.[52,54] Interactions between GHB, other recreational drugs and drugs commonly used in the management of HIV-positive patients can occur and may be associated with serious clinical consequences.[55] GHB is also known as a chemical submission agent due to its pharmacological properties. Despite widespread coverage of GHB in the media, alcohol and benzodiazepines are the drugs used most often in this context.[29,54]

GHB and its precursors can induce tolerance and dependence.[44] Although many GHB users will experience a mild withdrawal syndrome upon drug discontinuation, those with chronic GHB use can experience severe withdrawal. Severe withdrawal is characterized by central nervous system and autonomic dysfunction similar to that observed in other sedative withdrawal syndromes.[56,57] Withdrawal features were similar for GHB and its analogues. The median delay between last use and withdrawal presentation was 7.5 h for GHB, 72 h for GBL and 6 h for 1,4BD.[58,59]

The most common withdrawal symptoms were tremor, hallucinations, tachycardia, insomnia, anxiety, and hypertension. Other symptoms included agitation, diaphoresis, paranoia, confusion, delusions, delirium, nystagmus, rhabdomyolysis, and seizures. The duration of the withdrawal syndrome was 10 days for GHB, 6.5 days for GBL and 4 days for 1,4BD. Hospitalization may be required depending on the severity of the symptoms.[56,57]

Deaths have been attributed to GHB use, withdrawal or co-ingestion with other illicit drugs and/or alcohol. As a result of accident, injury, and respiratory compromise, deaths have also been reported.[60–63]

No randomized clinical trials have been conducted to identify the best pharmacological approach to treating withdrawal, but benzodiazepines are frequently used to manage this syndrome.[64]

Concerning the legal use of GHB, sodium oxybate (Xyrem oral solution) is the sodium salt of the gamma-hydroxybutyric acid. It was used as an anaesthetic for hospital use and it is approved in the USA for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy, and in the European Union for the treatment of narcolepsy with cataplexy.[65] It has also been tested in the treatment of alcohol withdrawal, Pakinson's disease, fibromyalgia syndrome, obstructive sleep apnea. Sodium oxybate is generally well tolerated and effective in the treatment of symptoms of narcolepsy with cataplexy. It differs from illicit GHB in accessibility, purity, and dosing. Post marketing and clinical experiences indicate a very low incidence of misuse, abuse and dependence.[66]

Synthetic cathinones

Cathinone, which was discovered approximately 15 years ago, is a stimulant alkaloid found in the leaves of the khat (*Catha Edulis)* bush. The plant grows in East Africa and southern Arabia, and it is frequently chewed because of its amphetamine-like effects.[67] Cathinone was found to be chemically similar to ephedrine, cathine and other amphetamines. The drug's maximum effect occurs after 15–30 min. Metabolism of cathinone is rapid, and only a small fraction of the molecule appears unchanged in the urine. Most cathinone is metabolized to norephedrine and is excreted in this form. The rate of inactivation is about the same as the rate of absorption, which limits the level of cathinone in the blood that can be attained by chewing the leaves. This compound is controlled by the UK 1971 Misuse of Drugs Act and is currently internationally classified as a Schedule 1 drug under the Convention on Psychotropic Substances[12] Its commerce is legal in Israel, Yemen, and in the Horn of Africa.

Synthetic cathinones belong to the so-called 'legal highs' group of drugs. These compounds, isolated from plant or fungal material, can be readily bought from the Internet without initial legal restrictions. But due to potential acute and chronic toxicity, these drugs are now forbidden in a number of countries. Their component chemicals may be structurally related to illegal drugs of abuse (e.g., amphetamine).[5] A recent study found that the methylcathinones are considerably more hydrophilic than the methylamphetamines, which may account for the higher doses that are needed to produce similar effects. Synthetic cathinones, which are considered to be ephedrone derivatives, include mephedrone, methylone, methedrone, flephedrone, buphedrone, butylone, and methylenedioxypyrovalerone (MDPV).[4,5] Mephedrone, methylone and MDPV seizures collectively represented over 97% of the synthetic cathinones seizures.[11] These drugs have many street names, which can be a source of confusion. Despite the increased availability of these legal highs on the Internet, little is known about the biology and the clinical pharmacology of these compounds.[12]

Mephedrone

Mephedrone, first described in 1929 by Saem de Burnaga Sanchez, is the fourth most commonly used drug (after cannabis, ecstasy, and cocaine) and the most commonly used 'legal high'.[68] Mephedrone use was first detected in November 2007 and was reported via the EMCDDA's Early Warning System in March 2008.[11]

Information regarding epidemiological data and the effects of mephedrone are limited to unconfirmed user reports and clinical case series. There are no published preclinical studies or human clinical pharmacology studies of mephedrone, and there are no pharmacological guidelines for acute and chronic intoxication.

Mephedrone is a water-soluble, white or coloured (yellowish, beige or brown) hydrochloride salt. Its common name is 4-methylmethcathinone (MMC or 4-MMC) and its main precursor, 4-methylpropiophenone, is available on the Internet.[16] Many street names for this drug exist around the world (Table 2).

Legal mephedrone production and distribution takes place in Asia. Mephedrone is commercially available in powder form via the Internet and smart shops. It is advertised and sold online as a

Table 2. Street names of Mephedrone

Mephedrone
• Meph, drone
• Meow or meow meow
• Miaow or miaow miaow,
• Bubble(s), bounce and subcoca
• Miaou miaou (France)
• Mef (Slovenia, Sweden)
• Mefi, mephisto, moonshine (Hungary)
• Flower Magic powder, flower power, special diamond, special gold (Romania)
• Rush (Belgium)
• MMC Hammer (Germany)
• Hurricane Charlie, Ketones, Dove (Ireland)

Table 3. Adverse effects of Mephedone

Most frequent adverse effects	Other adverse effects
Tachycardia	Dizziness
Hypertension	Tremor
Agitation	Stupor
Fatigue	Headache
Goose bumps	Chest pain
Facial flushing,	Dyspnoea
Restlessness	Nausea, vomiting, abdominal pain
Mydriasis	Renal pain
Loss of appetite	Nasal and throat irritation, sinusitis
Increased sweating ("mephedrone sweat")	Trismus, bruxism
Abnormal vision	Syndrome of inappropriate ADH secretion[72]

research chemical, plant food, plant feeder, bath salts, or vacuum freshener. Furthermore, some websites indicate that mephedrone is 'not for human use' to prevent potential control by authorities.[69] Mephedrone powder can be sold in retail (1, 5 or 10 grams) and/or in bulk quantities. The average price ranges from €9 to €17 per gram. The purity offered on the Internet can reach over 99%.[11] Mephedrone is a 'legal' alternative to MDMA, amphetamines, and cocaine.[16]

Oral, intranasal, intramuscular, intravenous, and rectal routes of administration have been reported. Oral (swallowing powder, capsules or tablets) and intranasal routes are predominant. Clinical effects usually occur 15–45 min after oral ingestion and last approximately 2–5 h. Effects usually occur 30 min after intranasal administration and last approximately 2–3 h. The high lasts approximately 10–15 min after intravenous injection, with an overall duration of 30 min.[70] Mixed routes (oral and intranasal, oral and rectal) have been reported during a single session. According to the Europol–EMCDDA Joint Report published in 2010, mephedrone was usually found in combination with synthetic cathinones (methylone, butylone, ethylcathinone, methoxymethcathinone, fluoromethcathinone). Furthermore, other substances found were MDMA and mCPP, lactose, and caffeine.[11] Mephedrone remains a key substance among 20–35-year-old male adults, predominantly from urban areas, in the recreational nightlife scene. Clinical effects of mephedrone are comparable with those of stimulants: euphoria, elevated mood, alertness, empathogenic effects, pleasurable rushing, sense of being sped up, enhanced music appreciation, and mild sexual stimulation. Higher dosage and more prolonged mephedrone use caused more severe unwanted effects.[16]

Adverse effects are summarized in Table 3.[70,71]

The main psychiatric adverse effects reported by the users were anxiety, dysphoria, depression, insomnia, hallucinations, paranoia, cognitive disorders (i.e. impaired short-term memory, impaired attention and concentration), delusions, suicidal ideations (especially with the intravenous route).[11,70,71]

There are no available animal studies that investigated the addictive potential of mephedrone, but case reports of dependence were reported by the UK National Drug Treatment Monitoring system. Subjects with high and frequent use of mephedrone report a major craving and tolerance for the drug.[68,73] The withdrawal syndrome is characterized by tremor, shivers, increased or decreased temperature, and a strong feeling of paranoia.[69]

In France, the nightlife scene did not include mephedrone use until March 2010. Recent media coverage (TV, radio, Internet, etc.), may have led to an increased awareness of the drug in the general population and potential users.[16]

Deaths have been attributed to mephedrone use and co-ingestion of mephedrone and other illicit drugs (i.e. heroin)[74] in many European countries (Sweden, the United Kingdom, Romania). Due to potential acute and chronic toxicity, mephedrone is now forbidden in a number of countries (Denmark, Finland, Sweden, Germany, Norway, France, Croatia, Estonia, Romania, and Israel). Other synthetic drugs have already emerged as successors to the banned mephedrone.[11,12,14,37]

Methylone

Methylone (3,4-methylenedioxy-*N*-methylcathinone) is a close structural analogue of MDMA, differing by the addition of a ß-ketone group (ßk-MDMA).[13] This drug is the second, most popular designer drug and is often combined with mephedrone.[11] Cozzi *et al*. found that methylone potently inhibits plasma membrane catecholamine transporters *in vitro*, but in contrast to MDMA, it weakly inhibits the vesicular monoamine transporter.[75] A preclinical study showed that methylone has psychoactive effects similar to those of MDMA and it can be used as a substitute for MDMA in rats trained to discriminate between MDMA and saline.[76] Little is known about the pharmacokinetics of methylone; and there are two major metabolic pathways for this drug.[13][77]

Methylone was reported for the first time in 2004 as a liquid solution sold as a vanilla-scented room odorizer.[78] A recent study found it sold in plastic tubes containing 5 ml of liquid called Explosion via the Internet and in head shops.[79] The compound mainly exists in powder form and in tablets. The average price ranges from €10 to €20 per gram.[12]

Very little epidemiological data for this drug have been gathered. Similar to mephedrone, there is no significant clinical literature on the effects of methylone. On user websites, subjects reported average doses of 100 to 200 mg of methylone. These doses were reported to produce a calm euphoria, alertness, restlessness, and a strong sense of empathy with mild stimulation.[80] An antidepressant action has been reported by Shulgin (http://www.cognitiveliberty.org/shulgin/adsarchive/cathinone.htm).

Adverse effects are quite similar to those of mephedrone. Somatic adverse effects include tachycardia, hypertension, hy-

perthermia, sweating, mydriasis, nystagmus, nausea, vomiting, trismus, and bruxism. Psychiatric adverse effects include anorexia, anxiety, derealisation/depersonalisation, impaired short-term memory, psychosis, hallucinations and suicidal ideations.[12]

No deaths have been attributed to methylone use alone or to co-ingestion with other illicit drugs.[12]

Methylone first appeared at the end of 2004 in the Netherlands and, as in the United States, it is not a scheduled substance.[81] Methylone has been illegal in Sweden since 2007 and in the UK since April 2010.[12] There are currently no reports on the toxicity and the harmfulness of this designer drug.

Methedrone

Methedrone [4-methoxymethcathinone or PMMC (para-methoxymethcathinone)] is the cathinone derivative of PMMA (paramethoxymethamphetamine or bk-PMMA).[12] Illicit use of PMMA in humans could have serotoninergic neurotoxic effects. An animal study found that the stimulating effects produced by MDMA and PMMA are similar but non-identical and that PMMA is the less stimulating of the two.[82]

Clinical effects include increased sociability, euphoria, disinhibition, increased energy and stimulation. Mydriasis, polypnea, and hyperthermia are the main physiological responses. Despite the lack of published clinical studies, health risks are possible due to the similarity of the drug's pharmacological profile to that of PMMA.[12] Methedrone was reported for the first time via the EWS in October 2009. Two deaths were partly attributed to methedrone in Sweden.[12,83] This compound is under control in Sweden and in Romania.

Flephedrone

Archer *et al*. identified a new compound in capsules marketed as plant feeders available from the internet. The capsules contain 3′-fluoromethcathinone (3-FMC), caffeine and a methylamine salt. Flephedrone (4′-fluoromethcathinone or 4-FMC), along with its structural isomer (3-FMC), began to be sold as a party drug in 2008 by Internet-based companies.[84] Due to important seizures in several Member States, 4-FMC was officially reported for the first time via the EWS in December 2008.[12] Flephedrone has weaker stimulant effects and has often been encountered as an ingredient in ecstasy tablets, probably due to the lack of the chemical precursor BMK. Its toxicity is not well established; however, it appears to act like mephedrone and other amphetamines.[84]

Butylone

Butylone [ß-keto-N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (ßk-MBDB)] is the alpha-ethyl homologue of MDMA.[79] It was first synthesized by Koeppe *et al*. in 1967. MBDB has been available at least since 1994, but its popularity on the synthetic drugs market is marginal. MBDB is also known as Methyl-J and Eden.[8]

MBDB metabolism is similar to MDMA metabolism. The acute pharmacological effects of MBDB in the rat include an increase in serotonin release in the brain, an inhibition of serotonin and noradrenaline reuptake, a modest increase in dopamine release and an inhibition of dopamine reuptake. Aerts *et al*. reported that MBDB was three times less likely to cause serotonergic brain deficits than MDMA.[85] This result is not negligible because in animals, serotonergic brain deficits after exposure to MDMA have been linked to the degeneration of serotonergic nerve terminals.[13,86]

The rewarding properties of MBDB appear to be smaller than those of MDMA, as suggested by an animal study. MBDB effects are comparable to those of MDMA, although the latter is more potent.[8,87]

MBDB has been reported to have novel central nervous system effects with neither stimulant nor hallucinogenic properties. MBDB and MDMA are reported to be generally similar in effect with slight differences in potency.[13]

MBDB effects last 4–6 h with noticeable after-effects lasting for 1–3 hours. The main effects of MBDB in humans are a mild euphoria, a pleasant state of introspection, greatly facilitated interpersonal communication and a pronounced sense of empathy and compassion between subjects.[8] Severe adverse effects have not been published. The addictive potential appears to be small in comparison to MDMA.[8] Deaths have been reported in relation to MBDB misuse.[88]

Buphedrone

We are not aware of any published animal, epidemiological or clinical studies of buphedrone. Information is available via the Internet and user reports from drug forums.

Buphedrone (α-methylamino-butyrophenone) was first synthesized in 1928. Its effects are similar to those of methcathinone and its toxicity is not well established.[89]

Methylenedioxypyrovalerone (MDVP)

Methylenedioxypyrovalerone (MDVP) was first detected in June 2007 in Germany.[90] It was reported via the EWS at the end of 2008. As a drug variant of pyrovalerone, this compound acts by releasing and inhibiting the reuptake of the monoamine neurotransmitters and is reported to have amphetamine-like stimulant effects.[90]

MDVP is a grey-coloured substance with a granular consistency (chemical form of its free base) or a white powder (hydrochloride salt form). It can be sold via the Internet as a research chemical.[90]

We are not aware of any published animal, epidemiological or clinical studies of MDVP.

Routes of administration are usually oral or intranasal (the most common route). Effects usually occur 15–30 min after oral ingestion and can last approximately 2–7 hours. After intranasal use, effects usually occur 5–20 min after administration and can last approximately 2–3.5 h. The effects of MDPV are usually compared to those of amphetamines or other stimulants. Adverse effects are comparable to those of mephedrone or other synthetic cathinones.[91] Abuse of pyrovalerone has been reported in drug addicts,[92] so MDVP addiction may be possible. From user reports and clinical cases, MDPV is known to be associated with compulsive use.

5,6-Methylenedioxy-2-aminoindane (MDAI)

5,6-Methylenedioxy-2-aminoindane (MDAI), developed in the 1990s, is an analogue of MDMA with low neurotoxicity that is a highly selective serotonin-releasing agent *in vitro*.[86,93,94] In 2009, MDAI became available on the research chemical market via the Internet. In April 2010, there was a press rumour that MDAI will emerge as a successor to mephedrone, which was banned in a number of countries.[95] MDAI, often found in powder form, can be used via the oral, rectal, or intranasal route. According to users, the cost of the chemical is about twice that of mephedrone. It produces mild entactogen effects and is significantly weaker and less stimulating than MDMA in humans. Health risks are possible.[96]

Conclusion

The addiction landscape has to take GBL/GHB and synthetic cathinones into account. Designer drugs have become a noticeable part of the drug scene in the EU, Australia and the USA. The Internet has become a new marketplace for these party drugs and also plays a crucial role in the spread of these new drugs.[16] Actual methods of controlling street drugs cannot cope with this current internet environment.

The ease of obtaining of GBL or synthetic cathinones, their use in private house parties, their moderate cost and their 'legal' status risks attracting more and more drug users.[12] Media coverage of mephedrone and GBL has certainly influenced people to try them.[97] Users of these drugs should be aware that just because a substance is being advertised as legal does not make it safe or actually legal. Another important point is that new chemicals are synthesized, marketed and legally sold as soon as previous compounds are banned, which is especially true for the synthetic cathinones.

As reported in our review, there is an important lack of epidemiological, animal, and clinical data concerning designer drugs. There is evidence that negative health and social consequences may occur in recreational and chronic users. The addictive potential of designer drugs is not weak. Non-fatal overdoses and deaths related to GHB/GBL and synthetic cathinones have been reported.[61,69,70,98]

Clinicians must be careful with GBL or synthetic cathinones, which are being sold and used as substitutes for GHB and MDMA, respectively. Interventions for drug prevention and harm reduction in response to the use of these drugs should be implemented on the internet and in recreational settings. Prevention, Information, Action, and Treatment are the main goals that must be addressed for this new potentially addictive problem.

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