

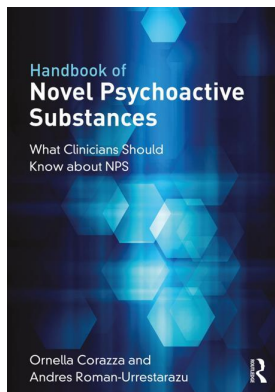
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Access details: *subscription number*

Publisher: *Routledge*

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Handbook of Novel Psychoactive Substances What Clinicians Should Know About NPS

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NPS

Publication details

<https://www.routledgehandbooks.com/doi/10.4324/9781315158082-3>

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Published online on: 17 Oct 2018

How to cite :- Máté Kapitány-Fövény, Aviv M. Weinstein, Zsolt Demetrovics. 17 Oct 2018, *NPS* from: Handbook of Novel Psychoactive Substances, What Clinicians Should Know About NPS Routledge
Accessed on: 30 Nov 2021

<https://www.routledgehandbooks.com/doi/10.4324/9781315158082-3>

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3 NPS

Epidemiology, User Group Characteristics, Patterns, Motives, and Problems

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Introduction

The rise of novel psychoactive substances (NPS) started approximately two decades ago, initiated by the appearance of cathinone derivatives, piperazines, and ketamine- (or phencyclidine) type substances and followed by the spread of synthetic opioids and synthetic cannabinoids (e.g., Stogner, 2015; Rivera, Vance, Rushton, & Arnold, 2017; Zawilska, 2017). Web-based drug trafficking and rapid online information sharing (such as “psychonaut” networking sites) increased the speed and amplitude of the drug market’s fluctuation (Smith & Garlich, 2013; Gilani, 2016) and made it a challenging task to reliably monitor emerging trends in terms of production, compounds, distribution, purchase, or consumption patterns. In this novel drug scene, user experiences and reports on the subjective and somatic effects of NPS have gained enhanced importance in addiction research. International research collaborations, such as the ReDNet Project or the Psychonaut Web Mapping Project, began to examine social network sites, video sharing sites and various online user reports to identify new trends and drug use patterns, providing an opportunity for almost real-time monitoring (e.g., Deluca et al., 2012; Corazza et al., 2013).

The growing number of online drug shops, the new trend of home production, the temporary legal status, and the relatively cheap price of these substances increased the availability of NPS. Therefore, the popularity of these substances is principally explained by practical or even economical aspects of their use, such as the temporary absence of legal risks; the low cost; their easy availability via the Internet (Cottencin, Rolland, & Karila, 2014); their attractive, multicoloured packaging and exotic brand names; or the fact that they are often not easily detectable in urine and blood samples (Fattore & Fratta, 2011). Presumed purity of NPS can also be mentioned as one of their main benefits for users. As an example, despite different physical characteristics of various synthetic cannabinoid products, definitely high purities (ranging between 75% and 100%) of JWH-018 and JWH-073 were found (Ginsburg, McMahon, Sanchez, & Javors, 2012), although it is also addressed that the more severe withdrawal syndrome of synthetic cannabinoids in comparison to cannabis could be due to the fact that these synthetic products may contain heterogeneous compounds, such as amphetamine-like substances (Nacca et al., 2013) or even synthetic opioids, like O-desmethyltramadol (Dresen et al., 2010). Pharmacokinetical characteristics of NPS also increase their reputation among the users. For instance, in case of cathinones, the high blood-brain barrier permeability of especially mephedrone and MDPV was proven in an in vitro model (Simmler, Rickli, Hoener, & Liechti, 2014), whereas increased reinforcer efficacy and abuse liability of methylone

was found by employing intravenous self-administration and intracranial self-stimulation in rats (Watterson et al., 2012). Yet, research regarding NPS pharmacokinetics in humans is lacking.

The heterogeneity of NPS user groups was further increased by the phenomenon of drug change, especially among injecting drug users (IDUs) who shifted from formerly banned substances to legal highs. Injection of synthetic cathinones has been identified at a substantial level in Hungary and Romania and as a localized phenomenon in Austria, Belgium, the Czech Republic, France, Germany, Ireland, Poland, Spain, and the United Kingdom (EMCDDA, 2014). Many studies have already described the effects of different risk behaviours, such as felony convictions (Domier, Simon, Rawson, Huber, & Ling, 2000), difficulty in controlling violent behaviour (Zweben et al., 2004), suicide attempts (Darke & Kaye, 2004; Marshall, Galea, Wood, & Kerr, 2011), sexually transmitted infections (Tyndall et al., 2003; Cheng et al., 2010), social stigma (Semple, Patterson, & Grant, 2004), higher rates of unemployment (White et al., 2006), and patterns of harmful drug use associated with intravenous stimulant use.

This chapter aims to provide an overview of the available information regarding NPS use epidemiology and give answers to some relevant questions (e.g., the main patterns and motives of NPS use; the subjective and somatic experiences characterizing NPS consumption, and the most frequently associated harms) by using synthetic cathinones, synthetic cannabinoids, and GHB/GBL as our benchmarks.

Synthetic Cathinones

Epidemiology

The first online reports about mephedrone occurred in 2003 (Power, 2009); however, in that time, it was mainly purchased via online drug shops (e.g., Roussel, Perrin, Herard, Chevance, & Arpino, 2009; Camilleri, Johnston, Brennan, Davis, & Caldicott, 2010). Its popularity as a commonly consumed substance started to spread in the recreational drug scene only after 2007 (Psychonaut Web Mapping Research Group, 2009). The growing popularity of mephedrone can be attributed to the wide availability of this substance because of the globalization of the Internet and web-based marketing. Another possible reason for mephedrone's popularity is that—according to users' reports—it can give a better quality high than other stimulants (e.g., Winstock & Mitcheson, 2010). Furthermore, mephedrone's popularity increased when MDMA's and cocaine's purity fell (e.g., EMCDDA, 2011; Schneider & Meys, 2011; Sindicich, Cassar, & Burns, 2011) and when the availability of MDMA decreased (EMCDDA, 2010; e.g., Brunt, Poortman, Niesink, & van den Brink, 2011). Followed by its ban in all the EU member states, mephedrone was replaced with other cathinones, such as MDPV and later penthedrone.

Epidemiological data regarding the prevalence of synthetic cathinone use is limited, especially in the general population. The 2010/2011 British Crime Survey identified a 1.4% lifetime prevalence of mephedrone use in England and Wales (Smith & Flatley, 2011), the 2015 National Survey on Addiction Problems in Hungary indicated 0.6% lifetime prevalence of mephedrone use (Paksi, Magi, Felvinczi, & Demetrovics, 2016), and the US National Survey of Drug Use and Health described a 0.5% lifetime prevalence for a merged category of phenethylamines, cathinones, and euphoric stimulant

consumption (Palamar, Martins, Su, & Ompad, 2015). The latest 2017 US Monitoring the Future study showed a 0.5%, 0.4%, and 0.6% prevalence of synthetic stimulant (bath salts) use among 8th, 10th, and 12th graders respectively last year (Johnston et al., 2018), whereas the 2015 European School Survey Project on Alcohol and Other Drugs (ESPAD) showed higher rates (e.g. 2.5% in Hungary) of lifetime cathinone consumption (Elekes, 2016; ESPAD Group, 2016).

Studies that assessed non-probability convenience samples among specific sub-populations identified much higher prevalence rates. For instance, 63.8% of South London's gay club-goers reported lifetime mephedrone consumption in 2011 (Wood, Measham, & Dargan, 2012). Among regular Australian psychostimulant users, a 19–23% lifetime prevalence was found for mephedrone, 10% for methylone, and 5% for MDPV use in 2012 (Sindicich & Burns, 2012). The results of the latest 2017 Global Drug Survey study (Winstock, Barratt, Ferris, & Maier, 2017) indicated a 1.9% lifetime mephedrone use. A 3.3% lifetime mephedrone consumption was found in a mixed Italian sample of adolescent and young adult respondents from both urban and rural areas (Martinotti et al., 2015).

Subjective and Somatic Effects

In recent years, several studies examined the typical subjective and somatic effects of mephedrone (Newcombe, 2009; Psychonaut Web Mapping Research Group, 2009; Dargan, Albert, & Wood, 2010; Winstock & Marsden, 2010; Brunt et al., 2011; Winstock et al., 2011a, 2011b; Freeman et al., 2012), as well as the characteristics of its use (Winstock, Marsden, & Mitcheson, 2010; Lea, Reynolds, & De Wit, 2011). Based on these studies, the main desired effects of this NPS include euphoria, friendliness, enhanced empathy, talkativeness, decreased hostility—as entactogen properties—increased sexual desire, mood enhancement, increased insight, improved concentration, high self-confidence, or increased alertness and energy.

The most common unwanted or adverse effects consist of dry mouth, hot flushes, tachycardia, muscular tension, bruxism/jaw clench, suppressed appetite and anorexia, nausea and vomiting, respiratory difficulties and dyspnea, numbness and periferic neuralgia, painful joints and extremities, dizziness and vertigo, chest pain and angina, tremors, or palpitations. Mephedrone-induced subjective experiences might be categorized into the following factors: (1) positive emotions, (2) sensibility, (3) physical symptoms, (4) psychological symptoms, (5) stimulant effects, and (6) psychedelic effects (Kapitány-Fövény, Kertész et al., 2013). Mephedrone can function as an alternate for MDMA and other entactogen stimulants, which provides an explanation for its popularity among club-goers (Moore, Dargan, Wood, & Measham, 2013).

In comparison to mephedrone and other cathinones, MDPV contains a pyrrolidine ring in its chemical structure, which gives MDPV potent actions, blocking the uptake at dopamine and norepinephrine transporters (Marusich et al., 2014). In some studies (Cameron et al., 2013), MDPV was found to be more potent than cocaine, with longer lasting effects as well. Users often call it 'MP4' or 'music', street names of this substance. 4-MEC, a 'second-generation' mephedrone analogue, also became popular after the legislative ban on mephedrone. 4-MEC produces large increases in extracellular 5-HT (*5-hydroxytryptamine: serotonin*) (Saha et al., 2015); however, alongside methylone, it was found to be less potent than other cathinones (Araújo et al., 2015).

After the zenith of mephedrone's and MDPV's popularity, pentadone became the most frequently used cathinone, cited as 'crystal' or 'penta crystal' by its users. It acts as a reuptake inhibitor for dopamine and norepinephrine, the same mechanism of action as methylphenidate (Simmler, Rickli, Hoener, & Liechti, 2014), the chemical compound of ADHD-medication: Ritalin and Concerta. However, in the case of synthetic cathinones, potential "off-target" sites of neuropharmacological action are still underexplored (Baumann et al., 2014). Considering further effects of synthetic cathinone-derivatives, human studies are still lacking, as the majority of the published papers are using animal models. Nevertheless, MDPV is considered to create cocaine-like psychoactive effects, lasting for about three to four hours (Baumann et al., 2013), with severe and hardly tolerable come-down effects and adverse symptoms, including suicidality and disturbing hallucinations. Subjective effects of methylone include euphoria, alertness, enhanced empathy, restlessness (Karila, Megarbane, Cottencin, & Lejoyeux, 2015), thought acceleration, reduced fatigue, and increased locomotor activity (Karila, Billieux, Benyamina, Lançon, & Cottencin, 2016).

Toxicity and Side Effects

Regarding the toxicity of synthetic cathinones, cardiac, psychiatric, and neurological symptoms are the most commonly reported toxic effects of these NPS (Prosser & Nelson, 2017). In the case of mephedrone, agitation, confusion or psychosis, chest pain, nausea, palpitations, peripheral vasoconstriction, and headache (James et al., 2011) were found to be relevant consequences of intoxication, along with tachycardia, anxiety, mydriasis, hypertension, and tremor. In recent years, a growing body of evidence confirmed mephedrone's ability to induce comatose states or even death (Maskell, De Paoli, Seneviratne, & Pounder, 2011; Schifano, Corkery, & Ghodse, 2012; Adamowicz, Tokarczyk, Stanaszek, & Slopianka, 2013). Similarly to mephedrone, the overdose of other cathinones may result in comparable adverse states. Linked to MDPV overdose, cerebral edoema, cardio-respiratory collapse, myocardial infarction, anoxic brain injury, and death were reported (Ross, Reisfield, Watson, Chronister, & Goldberger, 2012). The number of fatal intoxications due to excessive MDPV consumption—and mostly caused by cardiac arrhythmia—also increased over the past few years (Murray, Murphy, & Beuhler, 2012; Wyman et al., 2013). The classic serotonin syndrome causes a considerable rate of synthetic cathinone-related lethality (Zaami et al., 2018). Furthermore, MDPV users more frequently experience excited delirium syndrome (ExDS) than either mephedrone or methylone users (the '3Ms') because of its high potency as a dopamine transporter reuptake inhibitor (Baumann et al., 2013; Karch, 2015).

Some studies documented Parkinsonism as well in patients following chronic parental use of methcathinone, as explained by the manganese contamination of these homemade products (Iqbal, Monaghan, & Redmond, 2012). Renal and hepatic failure, rhabdomyolysis, and hyperthermia are further frequently occurring (Wood, Greene, & Dargan, 2011; Borek & Holstege, 2012) adverse consequences of synthetic cathinone use.

One study (Institóris et al., 2017) examined the prevalence of psychoactive substance use (including NPS consumption) among DUID (driving under the influence of drugs) drivers in 2014 and 2015 and found that positive tests for cathinones (pentadone and alpha-PVP) occurred in 21 to 28 percent of all the cases, indicating an elevated risk for road traffic injuries.

With regard to NPS-induced psychiatric symptoms and states, under the influence of synthetic cathinones, violent acts and unpredictable behaviour are common consequences. Users lose touch with reality, and dissociative experiences and drug-induced psychotic states occur frequently (James et al., 2011; Andrásy & Asztalos, 2013). Psychotic episodes or persistent psychosis may be present independently of either family or individual history of any psychiatric disorder (Dragogna, Oldani, Buoli, & Altamura, 2014). Such psychotic states are described as presenting with coloured visual and auditory hallucinations with menacing or paranoid contents and visual patterns and disturbances (Bajaj, Mullen, & Wylie, 2010). In some cases, anxiety and repeated bursts of inappropriate laughter were observed (Kyle, Iverson, Gahagowni, & Spencer, 2011).

Mephedrone-induced catatonia was also identified in a case without significant medical history (Kolli, Sharma, Amani, Bestha, & Chaturvedi, 2013). Low mood and other symptoms of depression were linked to mephedrone consumption as well (Bajaj et al., 2010). As psychostimulants, synthetic cathinones affect learning and memory processes, although at different levels. For instance, in comparison to methylone, mephedrone more intensely reduces working memory (den Hollander et al., 2013), while MDPV also has the potential to produce memory loss, accompanied by severe anxiety, suicidal ideation, and aggression (Ross et al., 2012). Further and mainly user-reported adverse effects of synthetic cathinones include bruxism, headache, and chest pain related to panic-like states (Dargan, Albert, & Wood, 2010; Van Hout & Bingham, 2012).

Former injectors of opioids and various psychostimulants who switched to inject cathinones (e.g., mephedrone, pentedrone, and MDPV) with unknown short and long-term effects on users health and wellbeing (e.g., Dickson, Vorce, Levine, & Past, 2010; DrugScope, 2012; Rácz, Csák, Faragó, & Vadász, 2012; Csák, Demetrovics, & Rácz, 2013) experienced further harm. The intravenous use of mephedrone—compared, for instance to injecting heroin use—is typically associated with a much higher frequency of daily injecting (DrugScope, 2012), which might lead to the rapid damage of syringes and therefore to muscle and vein injuries as well as a greater risk of infections. As powder mephedrone is highly soluble in water, it can easily be dissolved and then injected intravenously or intramuscularly. Adverse consequences of cathinone injecting include skin erosion, endocarditis, localized infections, thrombosis, thrombophlebitis, a burning sensation at the injection site, and increases in HCV and HIV infection rates (Botescu, Abagiu, Mardarescu, & Ursan, 2012). The use of synthetic cathinones was also linked to an enhanced risk of unsafe sex among men who have sex with men (MSM) (Zawilska, 2014).

User Experiences

Profiling User Groups

Users of NPS often constitute a hidden subpopulation, which is hard to reach in terms of both research and treatment (Palamar et al., 2015). Existing research, however, helps in describing this population with regard to its main sociodemographic characteristics. Mephedrone users are recurrently found to be males as a majority (e.g., Winstock & Marsden, 2010; Winstock et al., 2010; Carhart-Harris, King, & Nutt, 2011; Lea et al., 2011), ranging between 56% (Lea et al., 2011) and 84% (Carhart-Harris et al., 2011) of the assessed samples, mostly in their twenties (Winstock & Marsden,

2010; Winstock et al., 2010; Carhart-Harris et al., 2011; Lea et al., 2011; Winstock et al., 2011b). However, as the cited studies predominantly assessed non-probability/non-representative and self-selected samples, we might need to consider and interpret these results with caution.

Considering their educational level, available data suggest that users often have completed high school or even a college/university degree (e.g., Dargan et al., 2010; Lea et al., 2011). Regarding co-ingested substances, MDMA, amphetamines, cocaine, ethanol, and cannabis are most frequently mentioned concomitantly used drugs (Newcombe, 2009; Matthews & Bruno, 2010; Winstock et al., 2011b).

Patterns of Use

Recently, a number of studies have examined the characteristics of mephedrone use, including the frequency of use, the route of administration, the ways users usually purchase this substance, and the typical amount of mephedrone consumed (Dargan et al., 2010; Matthews & Bruno, 2010; Carhart-Harris et al., 2011; Lea et al., 2011; Winstock et al., 2011a; Winstock et al., 2011b). Mephedrone is most commonly administered in either an oral way (e.g., Matthews & Bruno, 2010) or by snorting the substance (e.g., Winstock et al., 2011a, 2011b), while intravenous use is found to be considerable only by a few studies (e.g., Kapitány-Fövény, Mervó, Kertész et al., 2015). Oral use is the main route of administration in case of methylone (Karila et al., 2016), whereas injecting MDPV, pentedrone and α -PHP use was reported to be common among clients of needle exchange programs (Csák et al., 2013; Péterfi et al., 2018). The main location of cathinone consumption is the setting of bars and clubs (Lea et al., 2011). The average dosage of mephedrone consumed is reported to vary between 500 mg/day (e.g., Carhart-Harris et al., 2011) and 1000 mg/day (e.g., Winstock et al., 2011b).

Motives of Use

Prosser and Nelson (2017) highlighted that synthetic cathinones are mainly consumed for social and economic reasons rather than their stimulant properties. Karila and colleagues (2015) further emphasize the relevance of synthetic cathinones' falsely legal image, low cost, and easy distribution as additional reasons for their use. Curiosity, replacing other drugs, and easy availability were further motives reported by others (e.g., Kapitány-Fövény, Farkas et al., 2017).

The assessed reasons of cathinone use highlight the leading role of practical or economical aspects and not psychopharmacological preferences (e.g., effect duration or intensity). Broadly speaking, legislative status and easy availability became more relevant than the drug effect itself. This assumption may partly be justified by the fact that a significant decline in NPS use prevalences was observed by certain research groups (e.g., Kikura-Hanajiri, Kawamura, & Goda, 2014; Smyth, Lyons, & Cullen, 2017) as a result of local legislative efforts.

A self-medication purpose may also be attributed to synthetic cathinone consumption. As similar psychostimulants (such as MDMA) might produce beneficial or even therapeutic effects (Mithoefer, Grob, & Brewerton, 2016; Yazar-Klosinski & Mithoefer, 2017) in case of certain disorders (e.g., PTSD, depression, anxiety), it might be a well-established hypothesis to assume that some cathinone users aim to treat themselves by using NPS-type stimulants.

Synthetic Cannabinoids

Epidemiology

Synthetic cannabinoid compounds are usually marketed as herbal mixtures under different brand names—e.g., Spice, K2, Kronik, Northern Lights, Herbal Incense, Zeus, Puf, Tai High, Cloud 9, or Mojo—(Barratt, Cakic, & Lenton, 2013; Mills, Yepes, & Nugent, 2015) and often labelled as legal highs because of their temporary legal status (Fattore & Fratta, 2011). Currently, these are the majorly consumed NPS, with 169 different types detected by the EMCDDA (EMCDDA, 2017a, 2017b). The vast number of synthetic cannabinoids, the variability of their chemical compounds, and their rapid emergence in the drug market make these NPS hard to detect or respond to in a timely manner.

Considering the prevalence of their use in the general population, the US National Survey of Drug Use and Health (Palamar et al., 2015) identified an approximately 0.5% lifetime synthetic cannabinoid consumption, and the 2015 National Survey on Addiction Problems in Hungary showed a 1.9% lifetime prevalence (Paksi et al., 2016). Among the adolescent population, the 2017 Monitoring the Future study observed a dramatic decline in annual prevalence rates through the past 5 years, reaching a 2%, 2.7%, and 3.7% past-year prevalence among 8th, 10th, and 12th graders (Johnston et al., 2018). Slightly higher rates were documented by the ESPAD research group in Europe (ESPAD Group, 2016), reporting an approximately 4% lifetime synthetic cannabinoid use among 15- to 16-year-old participants. The 2014/2015 Canadian Student Tobacco, Alcohol, and Drugs Survey showed a 4% annual prevalence among 7th and 12th graders (Health Canada, 2016), whereas 2.4% of Australian high-school students reported lifetime use of synthetic cannabinoids (Champion, Teeson, & Newton, 2016).

Non-probability subpopulation studies indicated either similar or much higher consumption frequencies. Among the mixed sample of Italian adolescent and young adult respondents, a 1.2% lifetime synthetic cannabinoid use was reported (Martionotti et al., 2015). The 2017 Global Drug Survey study (Winstock et al., 2017) resulted in a 5.8% lifetime synthetic cannabinoid use. Adult inpatients of Scotland's general psychiatric wards reported a 23.1% of lifetime synthetic cannabinoid consumption (Stanley, Mogford, Lawrence, & Lawrie, 2016).

Subjective and Somatic Effects

Similarly to the psychoactive compound of cannabis, Δ^9 -tetrahydrocannabinol (THC), the compound of synthetic cannabinoids, also binds to the CB1 and CB2 receptors. Their main effects therefore are produced by CB1 receptor agonism (Cooper, 2016). However, some studies highlighted that the pharmacodynamic and pharmacokinetic properties of synthetic cannabinoids can be different from THC, as they bind to CB1 and CB2 with higher affinity (Wiley et al., 1998); furthermore, some synthetic cannabinoids have a longer half-life than in the case of naturally occurring cannabinoids (Liechti, 2015).

As various compounds are marketed under the same name or brand, it is difficult to reliably describe the subjective and somatic effects of synthetic cannabinoids in general or even distinct products per se. Nevertheless, adverse effects, such as anxiety, agitation, loss of appetite, irritability, dry mouth, diaphoresis, restlessness, palpitations, decreased motor coordination, nausea, cough, sleep disruptions, fatigue, dysphoria, and psychosis were reported by several studies since the appearance of these products (e.g., Cooper & Haney,

2008; Barratt et al., 2013; Spaderna, Addy, & D'Souza, 2013; Gunderson, Haughey, Ait-Daoud, Joshi, & Hart, 2014; Hermanns-Clausen et al., 2016). Users naturally do not consume synthetic cannabinoids for their unwanted effects. Desired and reinforcing effects of synthetic cannabinoids include euphoria, a feeling of wellbeing, relaxation, an intense high, elevated mood, and cannabimimetic effects experienced at greater intensity (Fattore & Fratta, 2011; Bonar, Ashrafioun, & Ilgen, 2014). User reports have parallels to the findings of in vivo studies—mostly carried out with rodents—indicating that exposure to synthetic cannabinoids produces much more intense effects, as these CB1/CB2 agonist products are sometimes 100 times more potent than THC (e.g., Dalton, Wang, & Zavitsanou, 2009). Based on the results of Winstock and Barratt (2013), although synthetic cannabinoids have less sedating effects than natural cannabis, users are still less able to function after their consumption compared to the use of cannabis. Table 3.1 summarizes the main findings regarding the effects of synthetic cannabinoids.

Toxicity and Side Effects

Besides the adverse effects already listed among the main subjective and somatic effects of these NPS, further studies explored the risks and adverse consequences associated with the use of synthetic cannabinoids. Castaneto and colleagues (2014) assessed a sample of emergency department (ED) patients and found that the most common symptoms of synthetic cannabinoid intoxication—besides the aforementioned ones—were short-term memory and cognitive impairment, psychosis, slurred speech, shortness of breath, hypertension, tachycardia (up to 180 bpm), chest pain, muscle twitches, skin pallor. Mild leucocytosis, hypokalemia, and hyperglycemia were also observed. In some cases with serious complications—e.g., seizures—intubation was also required. Regarding the increased risk of synthetic cannabinoid-induced psychosis, these substances may act as full cannabinoid receptor agonists, producing unwanted effects and symptoms, and

Table 3.1 Reported desired and unwanted subjective and somatic effects of synthetic cannabinoids

<i>Somatic</i>		<i>Psychological</i>	
<i>Desired Effects</i>	<i>Unwanted Adverse Effects</i>	<i>Desired Effects</i>	<i>Unwanted Adverse Effects</i>
Shorter effect duration	Loss of appetite	Euphoria	Anxiety
Increased energy	Dry mouth	Feeling of wellbeing	Agitation
Quicker time to peak onset of effect	Diaphoresis	Relaxation	Irritability
	Palpitations	Intense high	Restlessness
	Decreased motor coordination	Elevated mood	Sleep disruptions
	Cough	Cannabimimetic effects experienced at greater intensity	Fatigue
		Talkativeness	Dysphoria
			Psychosis
			Paranoid states

Note: *Effects are collected out of the following studies:* Cooper and Haney (2008); Fattore and Fratta (2011); Barratt et al. (2013); Spaderna et al. (2013); Winstock and Barratt (2013); Kapitány-Fövény, Farkas et al. (2013); Bonar et al. (2014); Gunderson et al. (2014); Hermanns-Clausen et al. (2016).

because of the fact that synthetic cannabinoids do not contain cannabidiol, which may function as a protective agent against psychosis, it is considered to be a potential explanation for the higher rates of psychotic cases (Weinstein, Rosca, Fattore, & London, 2017) as compared to natural cannabis.

Cognitive impairments due to the repeated use of synthetic cannabinoids were identified by Cohen and colleagues (2017) as well. Based on their results, synthetic cannabinoid users—as compared to recreational natural cannabis users—showed worse cognitive outcomes regarding the accuracy, response time, and recall of memories. Furthermore, synthetic cannabinoid users were characterized by higher rates of depression and anxiety. The consumption of synthetic cannabinoids additionally causes impairment in skills and cognitive functions that are necessary for safe driving, such as fine motor skills or reaction times (Musshoff et al., 2014), although in a similar way as natural cannabis.

Nacca and colleagues (2013) described the withdrawal syndrome of synthetic cannabinoids to be similar to but more severe than that of natural cannabis. Andrassy and Asztalos (2013) delineated both the psychiatric and organic adverse health effects of synthetic cannabinoids, including intense hallucinations, acute renal failure, and developmental pathology of the embryo in the first two weeks of childbearing. Sherpa and colleagues (2015) observed multi-organ failure and various metabolic derangements in the case of a 45-year-old synthetic cannabinoid user, including myocardial infarction, subarachnoid haemorrhage, reversible cardiomyopathy, and acute rhabdomyolysis.

User Experiences

Profiling User Groups

The majority of synthetic cannabinoid users are found to be males in their twenties (Barratt et al., 2013; Castaneto et al., 2014; Gunderson et al., 2014; Caviness, Tzilos, Anderson, & Stein, 2015), with rates of male respondents varying between 67% (Caviness et al., 2015) and 81% (Gunderson et al., 2014). Some studies (e.g., Caviness et al., 2015) describe that not being enrolled in school is associated with frequent use of synthetic cannabinoids, whereas others (e.g., Castaneto et al., 2014) state that at least high school education characterizes the user group of this NPS. The findings of relevant adolescent studies, such as Monitoring the Future or the European School Survey Project on Alcohol and Other Drugs, indicate that high-frequency use of synthetic cannabinoids is a significant thread in this subpopulation as well (ESPAD Group, 2016; Johnston et al., 2018). Gunderson and colleagues (2014) highlighted the ethnical diversity of synthetic cannabinoid users but also delineated that the majority of their sample consisted of white and black respondents. However, a study assessing a community sample of young adults (Caviness et al., 2015) found that synthetic cannabinoid use is not significantly associated with the indicator of ethnicity or sexual orientation.

With regard to concomitant substance use, tobacco, alcohol, and cannabis are the most common co-ingested substances (Barratt et al., 2013; Caviness et al., 2015).

Patterns of Use

Primary sources of synthetic cannabinoid purchase are head shops, Internet—web-based marketing—and friends or acquaintances (Barratt et al., 2013). Consumed quantities are usually higher than that of cannabis (Kapitány-Fövény, Farkas et al.,

2013). However, just like in the case of cannabis, synthetic cannabinoids are mostly consumed in an oral way: users are smoking or using a vaporizer (Gunderson et al., 2014). In the case of water pipe or bong usage, a greater number of unwanted side effects were reported by users (Barratt et al., 2013). Synthetic cannabinoids are usually obtained as a white powder. Nevertheless, many other forms are available, including dark-brown powder, gel, or resin (Ginsburg et al., 2012). Several users purchase pure synthetic cannabinoids to extract and spray on a plant material (Rosenbaum, Carreiro, & Babu, 2012).

Motives of Use

The popularity of synthetic cannabinoids can be attributed to their intense effects, low price, and the fact that most urine drug tests are unable to detect them as well as their once legal status (Vandrey, Dunn, Fry, & Girling, 2012; Gunderson et al., 2014; Winstock & Barratt, 2013). Further reported reasons include shorter effect duration (varying between ten minutes and one hour), easy availability (online purchase and home production), and more intense, sometimes stimulant-like effects (Kapitány-Fövény, Farkas et al., 2013). Some patients additionally report that they consider synthetic cannabinoids to be safer, as a false illusion of synthetic cannabinoids being natural substances and also a decreased risk perception about the potential dangers of their consumption. Winstock and Barratt (2013) also found that synthetic cannabinoids have shorter effect duration and are characterized by a quicker time to peak onset of their effects as compared to naturally occurring cannabis. However, according to their additional findings, the majority of the users prefer cannabis and not synthetic products, as the consumption of synthetic cannabinoids is associated with a higher number of unwanted effects, including hangover symptoms and paranoid states.

Gunderson and colleagues (2014) described common reasons for the onset or continuation of synthetic cannabinoid consumption. To experience a cannabis-like, yet novel feeling of 'high', to avoid drug use detection, to mimic the habits of friends, easy availability, and low price were the most frequently mentioned reasons among the participants of their study as well. Curiosity, recreational purposes, and seeking therapeutic effects are further reasons for the first synthetic cannabinoid use, described by Barratt and colleagues (2013).

GHB

Epidemiology

GHB, a naturally occurring compound of mammalian central nervous system and peripheral tissue (Bessman & Fishbein, 1963; Roth, 1970; Mamelak, 1989; Tunnicliff, 1992), was first synthesized by Henri Laborit in 1960 (Laborit, Jouany, Gerard, & Fabiani, 1960). Since then, GHB has been used as a general anaesthetic and sedative in the treatment of narcolepsy (e.g., Broughton & Mamelak, 1979; Scharf, Brown, Woods, Brown, & Hirschowitz, 1985; Mamelak, Scharf, & Woods, 1986; Scrima, Hartman, Johnson, Thomas, & Hiller, 1990; Lammers et al., 1993) and alcohol- (e.g., Gallimberti et al., 1989, 1992; Nimmerrichter, Walter, Gutierrez-Lobos, & Lesch, 2002; Korninger, Roller, & Lesch, 2003; Nava et al., 2007) and opiate withdrawal syndrome and dependence (Gallimberti et al., 1993, 1994; Rosen, Pearsall, Woods, & Kosten, 1997). The

abuse liability of this chemical and the presence of a possible GHB dependence was empirically demonstrated (e.g., Galloway et al., 1997; Gonzalez & Nutt, 2005; Caputo, Vignoli, Maremmani, Bernardi, & Zoli, 2009).

Athletes and bodybuilders started to use GHB (or its precursor, GBL) in the 1980s (e.g., Michael & Hall, 1994) in order to improve their performance, as GHB may even double the secretion of growth hormone (Galloway et al., 1997; Van Cauter et al., 1997). Widespread use of this substance as a recreational drug began in the 1990s (Galloway et al., 1997; Kam & Yoong, 1998; Nicholson & Balster, 2001), and according to some more recent studies conducted in dance music settings and in homosexual sub-populations, GHB is still a popular recreational substance (Palamar & Halkitis, 2006; Halkitis, Palamar, & Mukherjee, 2007; Hillebrand, Olszewski, & Sedefov, 2008). Despite its remarkable history both as a medication and an illicit substance, GHB is also considered to be an NPS, as its popularity among recreational drug users rose in the 2000s.

With regard to the epidemiology of GHB use in the general population, the 2004 National Drug Strategy Household Survey indicated a 0.5% lifetime GHB consumption in Australia (Degenhardt & Dunn, 2008). Among the participating countries of the 2005 WHO Questionnaire, the highest lifetime prevalence (6.7%) was reported by the Czech Republic (WHO, 2006). A 0.7% lifetime prevalence was found by the 2015 National Survey on Addiction Problems in Hungary (Paksi et al., 2016). Considering the results of further studies that assessed non-representative subsamples, the highest GHB use prevalence was identified among MSM and women who have sex with women (WSW). Halkitis and Palamar (2006) described a 29% four-month prevalence of GHB use among a subsample of club drug-using MSM. A lifetime prevalence of 9.4% was reported by WSW (Parsons, Kelly, & Wells, 2006) and 15.1% by MSM club-goers (Kelly, Parsons, & Wells, 2006) in another study; 18.1% of club-attending MSM showed actual use of GHB (Ramchand, Fisher, Griffin, Becker, & Iguchi, 2013). More recently, an increased frequency of GHB intake was also linked to chemsex events; 19.5% of sex-party-attending gay and bisexual men (GBM) had a history of lifetime GHB consumption (Hammoud et al., 2018).

Subjective and Somatic Effects

The dose-dependent main subjective and somatic effects of GHB include a mixture of stimulant- and sedative-like effects, such as energy boosting, a feeling of drunkenness, drowsiness, and relaxation (Palamar & Halkitis, 2006; Sumnall, Woolfall, Edwards, Cole, & Beynon, 2008; Oliveto et al., 2010). These effects follow not only a dose dependent but also a biphasic time profile with initial stimulant-like effects and latter sedative effects (Abanades et al., 2007; Oliveto et al., 2010). Oliveto and colleagues (2010) stated that GHB at doses of 0.32 to 3.2 g/70 kg might produce dissociative and sedating effects with some but less inherent stimulant-like effects in humans. Pleasant mood, heightened energy, euphoria, relaxation, and increased sociability were reported as the most preferred effects of GHB, whereas nausea or sickness, blackouts, vertigo, fatigue, or weakness were found to be the most typical unwanted effects (Kapitány-Fövényi, Mervó, Corazza et al., 2015). Many studies that dealt with GHB's effects have focused on its impact on human sexual behaviour, which is linked to either unintentional GHB intake (drug facilitated sexual assaults) or intentional and mainly recreational GHB use. In the past decade, the misuse of GHB as a potential 'date-rape drug' provoked the widest

media and societal interest (Jansen & Theron, 2006; Karila et al., 2009). According to a systematic review by Németh, Kun, and Demetrovics (2010) on the involvement of GHB in sexual assaults reported by 11 articles between 1961 and 2009, this substance was detected in 0.2–4.4% of all reported sexual assaults. Even though this number might be an underestimation due to some specific factors (Németh et al., 2010), authors concluded that media reports about GHB-involved sexual assaults might be over-sensitive and misleading, as they turn attention away from other substances which may also play a more relevant and more frequent role in these crimes. Nevertheless, due to the specific disinhibitory effect of GHB (Laborit, 1972), the relationship between its use and sexuality remained a diffuse research topic.

As the first one to describe it, Laborit identified four sexual-enhancing effects of GHB: disinhibition, heightened sense of touch (i.e., increase in tactile sensitivity), enhancement of male erectile capacity, and more intense orgasm (Laborit, 1972). In the past decades, both qualitative or observational and quantitative studies have dealt with or mentioned the sexual correlates of the intentional and mainly recreational use of GHB (Laborit, 1972; Miotto et al., 2001; Palamar & Halkitis, 2006; Barker, Harris, & Dyer, 2007; Lee & Levounis, 2008; Sumnall et al., 2008; Stein et al., 2011; Kapitány-Fövény, Mervó, Corazza et al., 2015). Based on these studies, GHB's effects on human sexuality include increased sexual desire or arousal, sexual disinhibition, increased intensity or a new quality of orgasm, heightened sense of touch (tactility), enhanced sexual intimacy or psychological and social connection, the enhancement of male erectile capacity, or an increased attraction to others. A possibility of heightened sexual risk-taking, a greater willingness to engage in sexual activities, and a greater risk of unsafe sex were also found to be relevant consequences of GHB intake. Therefore GHB's effects, and especially its ability to decrease social inhibitions, may also promote high-risk sexual behaviours associated with increased probability of HIV infection (Romanelli, Smith, & Pomeroy, 2003), mostly among club-attending MSM.

Toxicity and Side Effects

GHB's toxicity is well described by the literature. Dose-dependent effects of GHB can mainly be explained by its affinity for two receptors in the brain. At low doses, GHB might bind to the GHB-specific receptor (e.g., Maitre et al., 1990), and by doing so, it inhibits presynaptic dopamine release and evokes stimulant-like effects (Feigenbaum & Howard, 1996). At higher doses, GHB stimulates the GABA_B receptor, resulting in an increase in dopamine levels and inducing depressant effects (Xie & Smart, 1992). High oral doses of GHB (typically greater than 60 mg/kg) can result in coma, which usually lasts up to four hours (Mamelak, 1989).

Clinical toxicological studies often use the Glasgow Coma Scale (GCS) scores (Teasdale & Jennett, 1974) in order to indicate overall impairment of neurocognitive states. GHB intoxicated patients frequently score less than eight (out of a maximum of 15 points) on the GCS (e.g., Sporer, Chin, Dyer, & Lamb, 2003; Krul & Girbes, 2011; Kapitány-Fövény, Zacher et al., 2017). In these cases, clinicians should protect the patient's airway through endotracheal intubation; a longer period of time to recover is expected (Lu & Erickson, 2010), although it has also been demonstrated that patients, even with a score of three on GCS usually spontaneously regain consciousness within five hours of GHB ingestion (Chin, Sporer, Cullison, Dyer, & Wu, 1998). Another important

indicator of clinical toxicology is the Poisoning Severity Score (PSS) (Persson, Sjöberg, Haines, & Pronczuk de Garbino, 1998), which grades the severity of acute poisoning due to administration of different chemicals, including psychoactive substances. As a result of a toxicology database analysis of GHB intoxication cases, severe poisonings were found to occur more frequently among male patients; however, severe poisonings were not common in general (Kapitány-Fövény, Zacher et al., 2017).

GHB withdrawal, which—similarly to alcohol—often includes symptoms such as anxiety, tremor, agitation, delirium, seizures, or even death (Rosenberg, Deerfield, & Baruch, 2003; Choudhuri, Cross, Dargan, Wood, & Ranjith, 2013) has also been associated with Wernicke-Korsakoff syndrome (Friedman, Westlake, & Furman, 1996), characterized by symptoms like confusion, ataxia, and loss of muscle coordination, abnormal eye movements and nystagmus, loss of memory, paranoia, and hallucinations. In these cases, Korsakoff psychosis results from permanent damage of specific brain areas associated with memory functions, due to Wernicke encephalopathy.

Patients with various psychiatric disorders show an elevated risk of developing comorbid substance use disorder (SUD) and vice versa. This connection between substance use and psychiatric problems was demonstrated in the case of GHB as well (Martinotti et al., 2014). High relapse rates (i.e., 85–89%) regarding GHB-dependent patients (Dijkstra, de Weert van Oene, Verbrugge, & De Jong, 2013) indicate that GHB has a severe addiction potential. Besides its use and dependence potential (Galloway et al., 1997)—as described by DSM-IV but not DSM-5 terminology—GHB may induce confusion, incoherent speech and short-term memory loss; symptoms that make individual psychotherapy hardly feasible, if not impossible. High-risk behaviours are often connected to GHB intake. Comorbid impulsivity leading to risky situations, such as driving or engaging in sexual activities under the influence of this substance, was linked to GHB consumption in these cases (Kim, Anderson, Dyer, Barker, & Blanc, 2007). Anxiety after reducing use, persisting for over one year, insomnia, depression, and irritability are further psychiatric symptoms mostly occurring as a consequence of GHB withdrawal (Stein et al., 2011). GHB withdrawal might be effectively treated with benzodiazepines, but recent studies suggest the therapeutic use of baclofen (Lingford-Hughes et al., 2016).

At higher doses, GHB use may also induce or increase paranoia with auditory and tactile delusions (Couper & Marinetti, 2002), as comorbid psychiatric disorders, anxiety, and depression are most typically linked to GHB use (e.g., Miotto et al., 2001).

User Experiences

Profiling User Groups

As available studies highlight, GHB users are most typically young adults in their twenties (e.g., Miotto et al., 2001; Degenhardt, Darke, & Dillon, 2003; Sumnall et al., 2008; Brunt et al., 2013; Wisselink, Kuijpers, & Mol, 2013) or early thirties (e.g., Barker et al., 2007; Lee & Levounis, 2008; Oliveto et al., 2010; Stein et al., 2011), and the vast majority—approximately two-thirds or more of them—are reported to be males (e.g., Miotto et al., 2001; Lee & Levounis, 2008; Sumnall et al., 2008; Stein et al., 2011; Brunt et al., 2013; Wisselink et al., 2013), with a range between 73.3% (Brunt et al., 2013) and 94.1% (Lee & Levounis, 2008). GHB is highly popular within the MSM community,

mostly because of its capability of inducing disinhibition and enhancing sexual desire (Palamar & Halkitis, 2006).

Considering their educational backgrounds and living conditions, mixed results were published, as GHB users were presented to have low education level and a high rate of unemployment by some papers (e.g., Brunt et al., 2013), while other studies reported that well-educated people with stable employment and moderately high income (Degenhardt et al., 2003; Barker et al., 2007; Lee & Levounis, 2008) are also found among them.

GHB is frequently co-ingested with ethanol, MDMA, amphetamines, cocaine, cannabis, and sometimes opioids (Rosen et al., 1997; Miotto et al., 2001; Sumnall et al., 2008; Brunt et al., 2013). As Barker and colleagues (2007) reported, heavy GHB users are more likely to mix GHB with MDMA or crystal methamphetamine.

Patterns of Use

GHB is mostly consumed within the user's home (Sumnall et al., 2008), or—as a club drug—in the setting of nightlife environment and social gatherings (Barker et al., 2007). As its street name, “liquid ecstasy” also suggests, users almost exclusively orally consume GHB in liquid form. Although it is also available as a powder, GHB is mainly distributed as a clear and odourless liquid with a salty or soapy taste, usually stored in mini shampoo bottles. Other forms of use—e.g., snorting or injecting—are reported by only a minority of users (Barker et al., 2007). Recreational users usually take smaller doses in order to experience stimulant-like effects.

Motives of Use

According to the findings of Sumnall and colleagues (2008), the most frequently reported reasons or functions of GHB use are recreational purposes, sexual enhancement, increased sociability and the exploration of altered states of consciousness. An altered state of mind, excluding everyday problems, and recreational purposes were found to be the most relevant reasons for consuming GHB by Kapitány-Fövény, Mervó and Corazza colleagues (2015). The desired sexual effects of GHB also increased its reputation among users who often take this NPS as an aphrodisiac.

For those who consume GHB for body image enhancement purposes (Brennan & Van Hout, 2014), its anabolic muscle-building properties and its ability to facilitate weight loss might function as the main motives for repeated use.

Palamar and Halkitis (2006) described how the short effect duration of GHB, its capability of producing an energy boost, its role as sleep assistance, the increase in libido, and its limited and tolerable after-effects make this substance a preferable choice for its users.

Conclusions

By providing this overview of the various characteristics related to the use of synthetic cathinones, synthetic cannabinoids, and GHB, we might conclude that the consumption of these NPS is a phenomenon that typifies adolescent and young adults and mostly males. Each of these drugs holds significant risk of inducing severe overdose, which—in some cases—might lead to fatal intoxication. Main reasons and motives of their use derive from the specificities of the transforming drug market, such as easy availability

(e.g., online purchase and home production), low price, and temporary legal status. Still, the primary explanation for the popularity of these NPS may be their potential to substitute for formerly banned psychoactive substances. Synthetic cathinones were found to be effective substitutes of mainly MDMA (Brunt et al., 2011; Carhart-Harris et al., 2011; Winstock et al., 2011a; Kapitány-Fövény, Kertész et al., 2013). GHB is often consumed as an alternative of alcohol (Johnson & Griffiths, 2013), while a vast number of cannabis users switched to smoking synthetic cannabinoids (e.g., Winstock & Barratt, 2013; Gunderson et al., 2014).

Regarding the detection of NPS, a number of studies dealing with the utility or feasibility of novel detection methods has recently been published (e.g., Archer, Hudson, Wood, & Dargan, 2013; Armenta et al., 2015; Cannart, Storme, Franz, Auwärter, & Stove, 2016). With an increasing access to these drug testing tools, users' expectations of avoiding NPS detection will be eliminated. Recent data, however, suggest that users started to experiment with various techniques (e.g., shampoos or hair cleansers to affect the results of hair analyses) in order to pass drug detection (Marrinan et al., 2017).

It is important to further explore the motives of NPS users, especially in terms of psychotherapy and the establishment of NPS-specific therapeutic guidelines as well. Studies that dealt with therapeutic approaches related to NPS use and intoxication were mainly presenting options of emergency interventions, including the goals of reducing agitation and psychosis, supporting renal perfusion (Banks, Worst, & Sprague, 2014), or treating the withdrawal syndrome (Busardò & Jones, 2015; Cooper, 2016). These studies were therefore focusing on the adverse outcomes of NPS use. Studies that assess the efficacy of different treatment methods—both psychotherapy and pharmacotherapy—in the case of NPS users are lacking. Available findings however suggest that NPS users often face more severe somatic and psychiatric symptoms than users of formerly banned substances (e.g., Kapitány-Fövény, Farkas et al., 2017), which emphasizes the need for specific and regular screening of NPS use among the clients of either inpatient or outpatient treatment facilities.

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