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Abstract: The purpose of this review is to identify emerging or new psychoactive substances (NPS) by undertaking an online survey of the UK NPS market and to gather any data from online drug fora and published literature. Drugs from four main classes of NPS were identified: psychostimulants, dissociative anaesthetics, hallucinogens (phenylalkylamine-based and lysergamide-based materials) and finally benzodiazepines. For inclusion in the review the 'user reviews' on drugs fora were selected based on whether or not the particular NPS of interest was used alone or in combination. NPS that were use alone were considered. Each of the classes contained drugs that are modelled on existing illegal materials and are now covered by the UK New Psychoactive Substances Bill in 2016.

Suggested Reviewers:

An overview of Emerging and New Psychoactive Substances in the United Kingdom

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*Highlights (for review)

Emerging New Psychoactive Substances are reviewed from user for a and available literature

Four classes, namely psychostimulants, lefetamine-based compounds, hallucinogens and benzodiazepines are covered

The effects of each of these materials and doses are described

Abstract

The purpose of this review is to identify emerging or new psychoactive substances (NPS) by undertaking an online survey of the UK NPS market and to gather any data from online drug fora and published literature. Drugs from four main classes of NPS were identified: psychostimulants, dissociative anaesthetics, hallucinogens (phenylalkylamine-based and lysergamide-based materials) and finally benzodiazepines. For inclusion in the review, the ‘user reviewers’ on drugs fora were selected based on whether or not the particular NPS of interest was used alone or in combination. NPS that were used alone were considered.

Each of the classes contained drugs that are modelled on existing illegal materials and will be covered by the UK New Psychoactive Substances Bill in 2016.

Keywords: New Psychoactive Substances, Psychostimulants, Lefetamine, Hallucinogens, LSD Derivatives, Benzodiazepines

1. Introduction

New Psychoactive Substances (NPS), also inaccurately known as ‘legal highs’, are those materials which lie in the grey area of legislative control in most countries and are used recreationally by psychonauts and at raves. According to the European Monitoring Centre for Drugs and Drug Addiction’s (EMCDDA) March 2015 report, the number of NPS is continuously increasing every year putting pressure on National Agencies to monitor these newly emerging drugs and to find solutions to reduce their harms [1]. The emergence of NPS has established itself as a global phenomenon appearing in some 94 countries worldwide as of December 2013 [2]. Furthermore, some NPS have much higher potency than the older drugs they are designed to replace while some are difficult to detect in body fluids [3]. NPS have rarely been studied for the purposes they are being used for and therefore pose a considerable and significant threat to the health of society.

2. Methods

The NPS names were entered as keywords into the search engines Google and PubMed. Around ten of the most relevant results on Google were considered and all relevant literature on PubMed was taken into account for each substance. Information was gathered from manufacturer’s websites, drug fora such as Bluelight, UK Chemical Research, Drugs-Forum, Reddit, TripSit and PsychonautWiki.

3. Results and discussion

3.1. Psychostimulants

3-Fluorophenmetrazine (3-FPM;(1)), also known as PAL-539 (Fig. 1), has recently emerged in the online market of ‘research chemicals’ and is currently legal to possess and supply in

the UK as long as it is not for human consumption [4]. This compound is a relatively new substance and there are currently no scientific studies or literature pertaining to it. Psychonaut Wiki and drug fora such as Bluelight refer to the amphetamine-like its properties and 3-FPM is a close relative to the now no longer used anorectic drug phenmetrazine (**2**), the chemical backbone of which can be likened to amphetamine with the terminal amine in a morpholine ring. According to Psychonaut Wiki, 3-FPM has not been used in humans prior to 2014, however, psychonaut communities who have experience with the drug have put up rough ‘guidelines’ for its use. These suggest that a longest duration of action of 5-8 hours occurs when taken orally with a dose of 25-50 mg orally or 20-35 mg as insufflation for what is referred to as a ‘common’ effect [5].

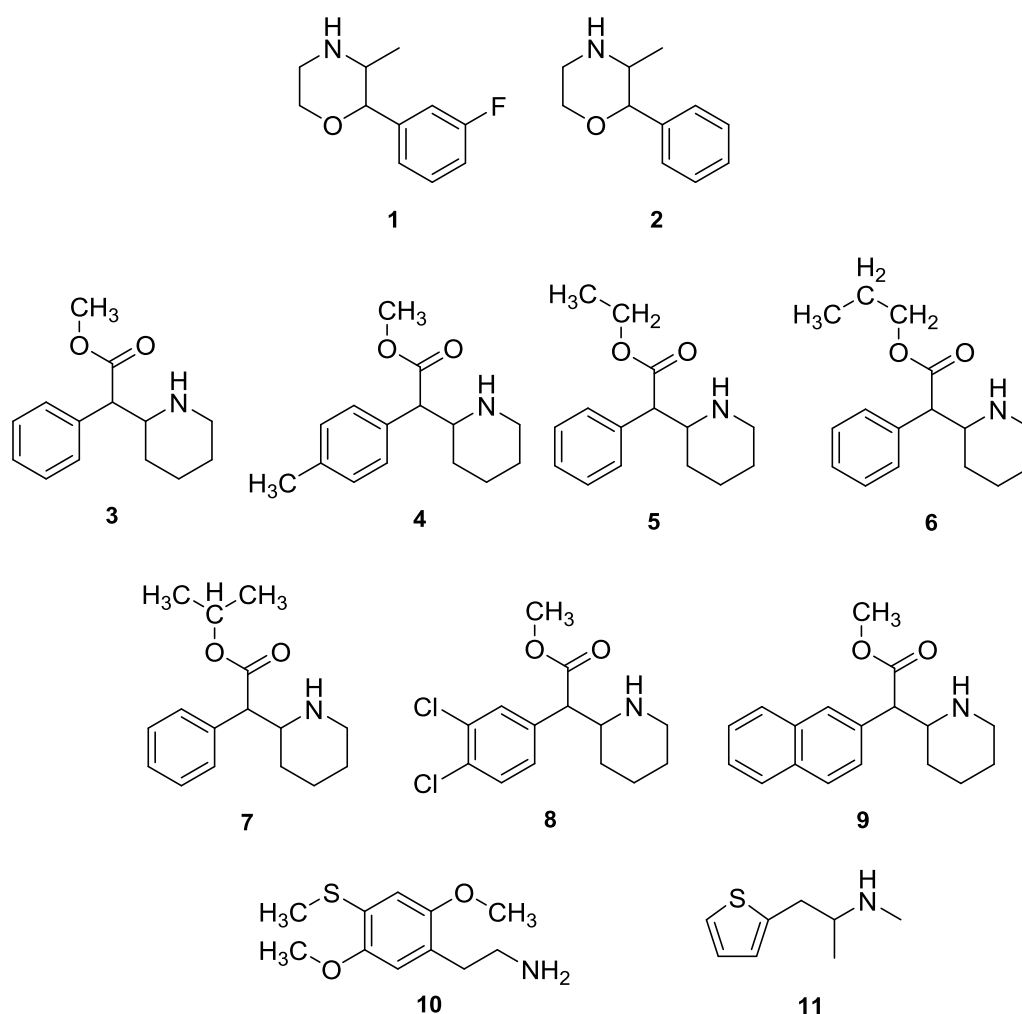


Fig. 1. The structures of commonly encountered psychostimulants

Physical effects described are increased energy levels, vasoconstriction, loss of thermoregulation, appetite suppression and an increased heart rate. Cognitive effects included increased motivation, focus and euphoria. Nonetheless, the stimulant effect was described as being less than that induced by substituted amphetamine compounds and users have referred to 'flu-like' symptoms with shivers [4,6]. Most of its effects could be inferred from the effects associated with phenmetrazine and other amphetamine-like drugs; therefore, part of this review will include some closely related compounds to which 3-FPM is related.

Phenmetrazine is of the phenylmorpholine class of compounds and was developed as an appetite suppressant (anorectic) to be used in conjunction with a low caloric intake diet in the short-term treatment of exogenous obesity [7]. It was marketed under the trade name Preludin and was allegedly used by the Beatles early during their career to cope with long hours of performance. It is an indirect-acting sympathomimetic agent with central stimulant effects, and its mode of action and effects are similar to those of dextroamphetamine [7, 8]. Due to its high potential for abuse, considered to be more potent than amphetamine, it was withdrawn from the market [9]. It has been used recreationally and abused in Sweden in the 1950's and in the USA in the 1960's and 1970's before being removed completely from the market [10]. The mechanism of action is highly similar to amphetamine by blocking the noradrenaline and dopamine re-uptake transporters in the brain which leads to their prolonged presence and hence prolonged stimulation of post-synaptic receptors at the synapse [11, 12].

Ritalin or methylphenidate (**3**) analogues such as 4-Me-TMP (**4**), made its appearance on the NPS market in April 2015 as a methylphenidate (**3**) replacement for the recently banned methylphenidate analogues EPH (**5**), PPH (**6**), IPH (**7**), 3,4-CTMP (**8**) and HDMP-28 (**9**) [13]. However, 4-Me TMP did not last long among psychonauts as it also was soon put under a Temporary Class Drug Order which took effect on the 27th of June 2015 following

recommendations made by the [UK Advisory Council on the Misuse of Drugs \(ACMD\)](#), based on its similarity to methylphenidate in effects and inferred adverse effects [14,15].

Currently there are no scientific studies specific to 4Me-TMP as a recreational drug. A search on Pubmed using the keywords '4Me-TMP', '4-Methylmethylphenidate' returned no results as of 26th of October 2015. Pharmacological data is limited with records of 4Me-TMP as one of the analogues of methylphenidate investigated in the treatment of cocaine dependence. It was found to be slightly more potent than methylphenidate at inhibiting the binding of [³H]-WIN35 428, a cocaine analogue used in research on the dopamine transporter [16, 17].

In psychonaut communities, 4Me-TMP has gained popularity as a psychostimulant during its short span of 'legality'. Users described it as the only 'research chemical' with effects closest to methylphenidate with a relatively lower potency that is concordant with available scientific pharmacological data [18]. Information regarding its effects in the human body can only be gleaned from reports of trips as posted or discussed on drug fora. Users reported euphoria, decreased appetite and need for sleep, increased alertness and focus and sexual arousal as positive and desired effects. Negative effects included increased sweating, tremors and tachycardia, however, the degree of the effects was subjective to the user. Depending on the dose administered, 4Me-TMP was reported to be recreational resulting in a clear head and enabling users to improve performance during work or study. Some users have recognised that as a methylphenidate analogue, 4Me-TMP may also have addictive potential, although so far, no compulsion to re-dose has been reported [19, 20].

4Me-TMP has been mainly taken orally or by insufflation and oral doses vary from a recommended threshold of 25 mg to 90-125 mg as a heavy dose, with an onset of action within minutes and a duration of action of 4-6 hours. For insufflation, doses are smaller with a threshold of 10mg and a heavy dose of over 70 mg with an onset of action within minutes and a duration of action of 2-5 hours. Doses are sometimes 'boosted' after 3 hours of

administration for a prolonged effect [18, 19, 21, 22]. Varying degrees of harm from drug-drug interactions when using methylphenidate are also warned of on the Tripsit website. For instance, concomitant use of stimulants and tramadol are said to increase the risks of seizures and are qualified as dangerous. Increased risk of serotonin syndrome is noted with simultaneous use with monoamine oxidase inhibitors and 2C-T-x compounds (e.g. **10**). Excessive anxiety with persistent thought-loop is also purported to occur when 4Me-TMP is used with psychedelics such as mescaline. 4Me-TMP as a psychostimulant is also said to decrease the perception of drunkenness and increase the risk of drinking excessively till the passing out point [21].

The fora threads on 4Me-TMP are relatively short possibly because of its short span of use as an NPS. Nevertheless, users have so far reported few negative effects and are positive about 4Me-TMP with people still seeking it out. New posts appear to come from users who are apparently based outside the UK for example in Sydney [18], which suggests that 4Me-TMP has spread globally. For the time being, there is still no scientific evidence specific to 4Me-TMP (26th October 2015) apart from its inferred effects from structural similarity to methylphenidate, to validate its permanent ban under UK law.

Methiopropamine (**11**) as an NPS was first reported following a seizure in Finland in January 2011[23]. Its synthesis however, dates back to the 1940s when it was synthesised by Blicke and Burckhalter as an analogue of methamphetamine, where the phenyl ring was substituted with a thiophene ring in order to compare effects on blood pressure [24].

Since its appearance online as a research chemical in late 2010, methiopropamine has become an established NPS used recreationally and evading control under the UK legislation until a temporary class drug order at the end of 2015. According to an internet snapshot study conducted in June 2013 in accordance with EMCDDA methodology, it was found that methiopropamine is readily available over the internet with 45% of vendors identified as

being UK-based. It is sold mainly in powder form in amounts ranging from 150 mg to 4 kg [25]. This NPS was also detected in pooled urine collected from urinals placed in Central London on Friday and Saturday nights in 2012 as part of a pilot study to understand prevalence of NPS use [26]. It was also detected in the blood samples from drivers in Norway [27].

An analysis of the metabolites of methiopropamine from rat and human urine by GC-MS and LC-HR-MS was conducted by Welter et al 2013. This proposed that methiopropamine underwent a combination of *N*-methylation and hydroxylation at the side-chain and thiophene ring respectively before glucuronidation and sulfation. The CYP450 enzymes involved were CYP1A2, CYP2C19, CYP2D6 and CYP3A4 [28].

It seems that users have been utilizing methiopropamine as a performance enhancer to cope with work, study and bereavement as well as recreationally [31, 32, 38]. Methiopropamine is being ingested orally, smoked, used as an insufflation, taken rectally or injected intravenously by psychonauts depending on the effects desired. For instance, small doses of 10 mg taken 3 hourly by IV injection to maintain a high or a bolus of 40-50 mg for a 'rush' have been suggested [32]. The threshold dose is noted as 10 mg with a 60 mg+ dose as being heavy. Onset of action is within 30-60 minutes with the effects peaking at 2-4 hours, with a coming down that lasts 2-3 hours and an afterglow experienced for 1-3 hours [33]. Insufflation is reported to leave a bad taste which may be due to the sulfur atom in the molecule but provides the same intense rush as IV injection with a shorter duration of action [32]. An analysis of the pyrolysis products of methiopropamine under the same conditions when smoked by users found that they were mostly the same as methamphetamine. However, other products were also formed such as beta-keto-methiopropamine, whose properties are unknown, *N*-methyl methiopropamine which is psychoactive, 2-methylthiophene which is

toxic and a bicyclic tetrahydropyridine compound with a structure similar to the anti-platelet drug clopidogrel [29].

As an analogue of methamphetamine, methiopropamine has also been reported to induce similar effects. This was supported by a study of neurochemical profiling of NPS by Iversen et al (2013) in which methiopropamine was found to be a potent inhibitor of noradrenalin, dopamine and to a lesser extent serotonin re-uptake comparable to amphetamine [30]. Users report an increased alertness, energy and focus, sexual arousal and euphoria on drug fora which is described as a ‘rush of adrenaline’. Side-effects also noted were high-blood pressure, tachycardia, anxiety, sweating and shaking, nausea, dehydration, difficulty urinating and a significant loss of appetite and sleep which could last for days. Quite a few users also reported chest pain, palpitations and headaches sometimes comparable to a heart-attack. Users recommended taking multivitamins, drinking plenty of water and *Gingko biloba* for its vasodilating effects to minimise the harmful effects of methiopropamine. Negative effects were said to increase with repeated dosing and to cause hallucinations at high dose. Chronic use multiple times a day and/or over several consecutive days was reported to cause psychosis, hallucinations and heightened fear and anxiety, depression and aggressive behaviour on withdrawal [31–39]. Methiopropamine was also regarded as highly addictive with a strong compulsion to re-dose and binge accompanied by a loss of inhibition at high doses. This addictive character was suggested to be in part a psychological need to feel the ‘intense euphoric rush’ by users [35, 32]. Tolerance was also said to build up very quickly with loss of positive or desired effects [38, 39]. In drug fora, prospective users are warned not to binge on methiopropamine and an awareness of its potentially-life threatening side-effects seems to be prevalent [31-39].

Methiopropamine use has already claimed lives as it continues to gain followers despite some discouraging user reviews online [32, 39]. In 2012, two methiopropamine-related deaths

were first reported in the UK [23] while the first ever case in Australia was reported in 2015 where a post-mortem investigation found 38mg/L of methiopropamine in the blood of the deceased [40]. Acute toxicity related to methiopropamine where 400ng/ml was found in urine, has also been reported. In that particular case, however, the user bought their samples from a Central London market stall under the name of ‘Quicksilver’. Considering that the only reference to ‘Quicksilver’ in a recreational drug context that could be found online was of methoxetamine, it is possible that the victim may not have been aware of what they were ingesting [41].

Methiopropamine is appealing to many users as a euphoric psychostimulant that can be employed in multiple situations in spite of its notorious side-effects. Use will probably continue to spread worldwide via its boundary-less cyber foothold unless any action is taken whether in terms of legislative control or harm reduction and drug use education measures.

3.2.Lefetamine-derived dissociative anaesthetics

Following the UK ban in February 2013 on all arylcyclohexylamines in an attempt to curtail the spread of PCP and ketamine analogues, a new class of dissociative anaesthetics known as diarylethylamines based on lefetamine (**12**) among which can be found ephenidine (**13**), diphenidine (**14**) and methoxyphenidine (**15**), hit the NPS market as crystals, powder and pellets to circumvent the law [42] (Fig. 2).

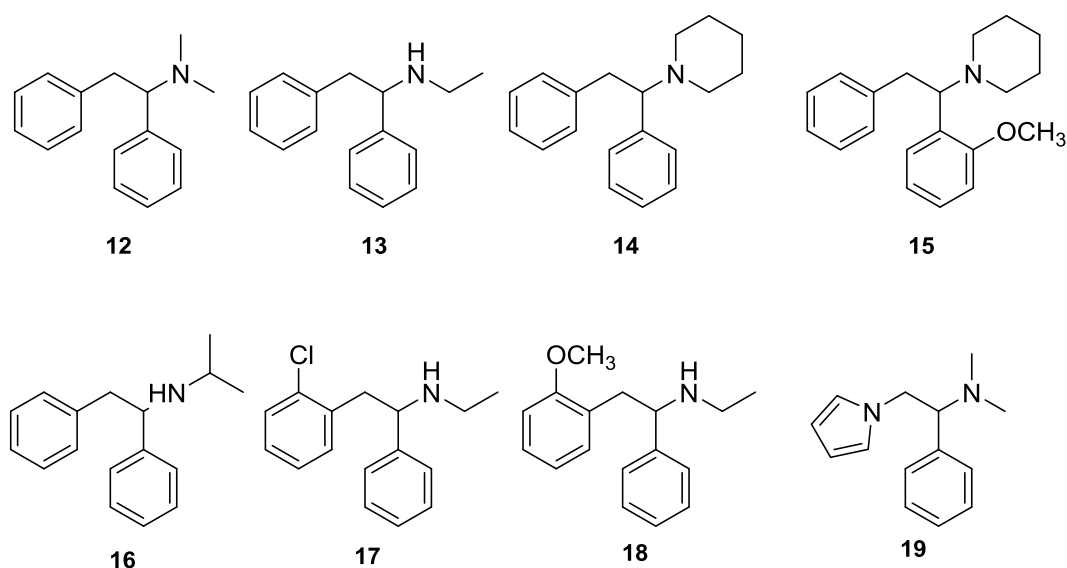


Fig. 2. Lefetamine-derived dissociative anaesthetics

Diarylethylamines, which are far from being novel, have actually been synthesised and documented as far back as 1924 [43]. Diarylethylamines are in fact, analogues of the now withdrawn and controlled drug lefetamine (**12**), which was introduced as an opioid analgesic in the 1940s and marketed as Santenol [44].

However, despite their structural resemblance to lefetamine, these diarylethylamines do not have the same pharmacological activity, mimicking instead the effects of PCP and ketamine, and their respective analogues function by uncompetitive NMDA-receptor antagonism and are being marketed as their legal replacement by online chemical vendors [43, 45]. Indeed, from a thread on Bluelight, it seems that lefetamine and lefetamine-derivatives have been compared to the arylcyclohexylamines PCP and ketamine and their use as possible recreational drugs was discussed as early as 2006 [46].

While these compounds have been gaining in popularity across the psychonaut communities, again little is known about them. Most of the information reported about their physiological effects in humans comes from online drug fora and some from cases of NPS poisoning sent to emergency services. So far, Sweden has already classified them as hazardous to human health [47] and this review seeks to bring an overview of the information available so far.

Ephenidine (**13**), first appeared on the NPS scene in 2008 when it was seized alongside NPDPA (**16**), another lefetamine derivative, by the German police. Nonetheless its amphetamine-like stimulant properties had already been described in the 1940s [48]. From the metabolites collected from rat urine, it was inferred that ephenidine was completely metabolised and most likely underwent a combination of *N*-alkylation, mono- and bis-hydroxylation of the benzyl ring followed by methylation of one of the two hydroxyl group metabolites at phase 1, and hydroxylation of the phenyl ring after *N*-dealkylation, glucuronidation and sulfation of all hydroxylated metabolites in phase 2 [48]. Since the metabolism of ephenidine has been found to involve at least four CYP-450 enzymes to varying degrees, it has been purported that ephenidine may not give rise to significant drug-drug or drug-food interactions [44].

In the Psychonaut communities, a thread was first dedicated to ephenidine and other related dissociative NPS in late December 2014 on Bluelight. However, it seems that ephenidine is only recently starting to gain wider acceptance and popularity according to the drug fora studied [49, 50]. Often, reference is made to its smooth or ‘silk-like’ come-up compared to other dissociative anaesthetics [52] but also of a tendency to feel dehydrated. The experience is also viewed as much more positive with a greater cornucopia of visual stimulation and hallucinations and also as less ‘out-of-body’ at regular doses. In some cases, users reported its effects as more ‘spiritual’ or ‘magical’ with an enhanced appreciation for music and colours [51, 52, 50]. One user even stated that ephenidine surpasses ketamine, PCP and all other dissociatives [53]. Ephenidine has also been reported to have mild psychedelic effects while scarcely affecting ‘*functioning as a person*’ [56]. Furthermore, it was also seen as an alternative to ketamine and methoxetamine by another user [57].

Psychonauts have been administering the drug orally, rectally, by sniffing or vaping and by the IV route. Doses employed are sometimes seen to be quite high, ranging from 150mg to

600 mg in some cases to achieve desired effects, though websites such as Psychonaut Wiki indicates a threshold of 60mg with a 200 mg+ dose being seen as ‘heavy’ [50, 54]. This suggests that ephenidine might be less potent or that the negative effects are more tolerable. Ephenidine is also reported to have a slow onset depending on individuals ranging from 10-30 minutes to 1.5-3 hours but also a longer duration of action of 5-7 hours [50, 54, 55]. Full recovery from the dissociative effects also seem to vary among individuals with some still feeling wobbly after 15 hours after a 250 mg dose while others took a full 24 hours to recover after a 200 mg dose [55]. This may of course be as a result of the quality of the product as well as individual pharmacogenomic responses.

Overall, most ‘user reviews’ appear in favour of ephenidine with apparently no distressing mental stimulation and a more enjoyable trip with seemingly no negative effects except for residual dissociative effects post use. Nonetheless, ephenidine is regarded as having a potential for addiction and prospective users are warned to use it carefully [57].

On the side, two other variants of ephenidine that so far seem to be less popular among psychonaut communities are 2-chloro-ephenidine(**26**) and 2-MeO-ephenidine(**27**) [49].

Diphenidine (**14**) was first synthesised in 1924 by Christiaen who used a modified Brulyants reaction which would later be used by Maddox to synthesise PCP [43]. Though it was launched earlier than methoxyphenidine, it is less popular [58].

As a diarylethylamine, diphenidine has been investigated for neuroprotective effects on neurones in the hippocampus as described in a 1989 patent and furthermore its ability to suppress cough as an antitussive agent in dogs has also been studied. These past observed properties are what might have made it a candidate as a research chemical [59]. The NMDA-receptor antagonist effect has recently been confirmed in-vivo using rat hippocampal slices and was found to be similar to ketamine in reducing NMDA-mediated field excitatory post-synaptic potentials at 30 μ M [59]. Though not of the same chemical class, diphenidine

definitely does act as a pharmacological analogue to the dissociative drug ketamine. Dopamine and serotonin re-uptake inhibition and mu-opioid receptor affinity are purported by vendors but have however, not been studied [60].

According to Tripsit, a normal dose of diphenidine would be approximately 85-110mg, with an onset of action of 10-30 minutes, a duration of 2-5 hours and an 'after-glow' effect of up to 4-24 hours [61]. The most common route of administration is oral or sublingual. Blocked nose or inflamed sinuses have been reported with insufflation, although it is believed to have a quicker onset of action by this route requiring a fifth of the oral dose [63, 61].

Diphenidine is described as mildly stimulating and mostly amnesia-inducing, crippling the recall ability of the user which may potentially cause loss of control over one's own behaviour [62]. An example is that of a previous ketamine user who overdosed on diphenidine orally at 310mg, was violent with the paramedics who came to take him to hospital and could not remember any of what had happened [63]. Other effects noted are those of sensory dissociation, loss of inhibition, and significant visual and internal hallucinations. Several users also reported high blood pressure and tachycardia. This was reflected in non-fatal intoxication cases of diphenidine observed in Sweden [61, 45]. Diphenidine has not been very popular with many users reporting negative and sometimes both physiologically and psychologically troubling experience described by one user as being '*sucked down into a shrieking vortex of insanity*' [58]. Of most concern is the steep dose response curve reported with a rapid build-up of tolerance at higher doses and high addiction potential, which is described as very compulsive [63, 45, 64]. Diphenidine has even been described as 'evil' by another user [64].

Methoxyphenidine (**15**), is also member of the diarylethylamine group that has been screened for the potential treatment of neurotoxic injury according to a 1989 patent [66]. Methoxyphenidine appeared shortly after diphenidine and gained a rapid rise in popularity

relative to the latter despite an initial dearth of reports of previous human use of the compound [58]. Methoxyphenidine has been and is still being used extensively by the psychonaut communities.

However, while it is being marketed by online vendors as a replacement for methoxetamine and ketamine, the effects of methoxyphenidine are reported to be qualitatively closer to those of dextromethorphan, an antitussive which has been abused. Subjective physical effects which include tactile disconnection, a spontaneous tactile sensation described as ‘body high’ and loss of motor control are reported to increase with increasing dosage and are reported to feel like those induced by dextromethorphan [67].

Furthermore, the cognitive effects are seen as different from all other dissociatives with the user still being in control and less confused even at higher dosages to bring about the same subjective intensity when using methoxetamine, dextromethorphan or ketamine [58, 67]. A methoxyphenidine experience has been qualified as ‘introspective’ by one user-blogger [70]. An in-depth review of harm reduction and online consumerism of methoxyphenidine among psychonauts conducted by Van Hout and Hearne supported that its effects are perceived as unique and result in a more ‘clear-headed’ sensation. It was also viewed as much better than diphenidine in that it is less ‘havoc-provoking’ with more enjoyable effects [58].

Routes of administration are oral, sublingual, rectal, insufflation and by IV [58]. Insufflations are said to irritate the nasal mucosa significantly [68, 70] and a numbness of the tongue is said to occur with IV administration and is therefore not the most favoured route [58]. Psychoactive effects are said to start at a dose ranging from 30 to 50 mg with 150+ mg being regarded as giving strong effects. The onset starts from 30 to 60 minutes with a duration of action of between 6-8 hours and after-effects are described as ‘after-glow’ of 1-3 hours [67, 69]. Sometimes, even at higher doses of 200 mg, some users reported being reasonably lucid [56]. Whilst a steep-dose response curve has been reported, it is also said

that re-dosing is unnecessary as there is not much enhancement of positive effects but instead a higher risk of experiencing negative side-effects such as amnesia [43, 68]. Nevertheless, the dose-response effect of methoxyphenidine is reported as inconsistent and unpredictable with different users experiencing a differing degree of intoxication/side-effects at the same dosage [68]. Novice users as well as users who are experienced with dissociatives are often advised to start at the lowest dose as even with past dissociative usage, the effects of methoxyphenidine have been reportedly experienced as strong [70, 71].

On drug fora, users are reminded not to ‘push too far’ with this compound as it has been reported to cause chest pains, palpitations, tachycardia, high blood pressure and sometimes seizures requiring hospitalization [43, 56, 58, 70]. Indeed, during a relatively short span of use, cases of methoxyphenidine-related deaths and acute toxicity have already been reported [45, 65, 66]. An acute toxicity case of a 53 year old Caucasian male presented with hypertension at 220/125 mmHg and tachycardia of 112 bpm was treated with lorazepam, whilst an enlarged heart was found at the autopsy of two of the fatal cases attributed to methoxyphenidine [65, 66]. The acute toxicity case also developed opisthotonus and horizontal nystagmus upon losing consciousness before reaching a Glasgow Coma Scale of 10 [65].

Despite the grave side-effects of methoxyphenidine that are possible, its positive effects of mood-elevation and as a brain stimulant with ‘responsible’ use were seen as important enough to lead psychonauts to speculate about its medicinal potential as an antidepressant and in psychotherapy [58].

Possible further lefetamine-based dissociative anaesthetics may find their roots in previously studied analogues of lefetamine as suggested by one Bluelight thread dating back to 2008 which briefly discusses DMPP (**19**), a compound investigated for analgesic properties [72].

On the whole, the psychoactive agents, ephenidine, diphenidine and methoxyphenidine are an emerging class of dissociative anaesthetics that have not been explored in that sense before. Their effects are being widely reported by psychonaut communities, definitely warrants further investigation and it is reasonable to expect new lefetamine analogues on the NPS market in the future.

3.3. Phenylalkylamine hallucinogens

Alexander Shulgin was the first to synthesise the phenylalkylamine hallucinogens 2C-B (**20**) (Fig. 3), DOB and DOM and described their syntheses and effects in PiHKAL [73]. While DOM and DOB were already established, 2C-B really flourished in the recreational drug use sphere in the mid-1980s as the best alternative to LSD and psilocybin [74, 75]. However, the 2C-B class were soon banned in the US in 1985 and placed in Schedule 2, as Class B drugs in the UK. However, 2C-B still found its way into raves being often disguised as MDMA.

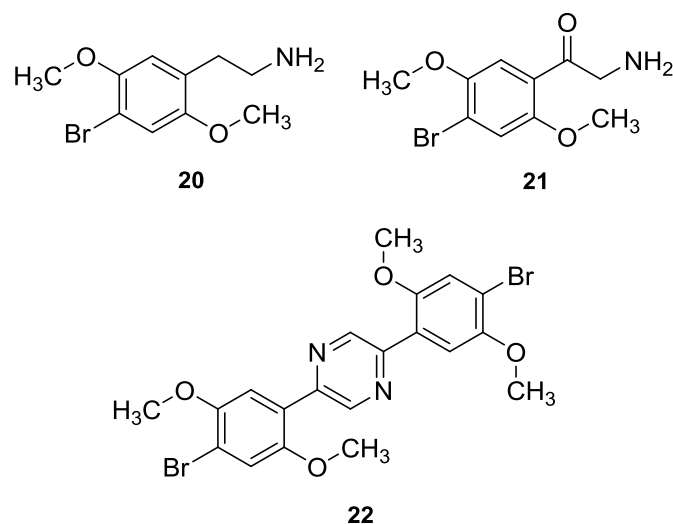


Fig. 3. Commonly encountered phenylalkylamine hallucinogens in this study

In recent years, as an attempt to find a legal substitute to 2C-B, vendors have come up with bk-2C-B (**21**) also known as beta-keto 2C-B, which hit the shelves of online head-shops in mid-2013 being sold as powder or crystals. Because of its structure, bk-2C-B is not regulated to date in the UK or Ireland though it can be considered as the beta-keto analogue or a

cathinone analogue of 2C-B [76]. bk-2C-B appeared online in 2007 in a Bluelight forum thread discussing its potential as a future 'legal-high' replacement for 2C-B focusing on its possible dimerization (**22**) which could lead to inactivity of the compound in-vivo[77]. An even earlier appearance can be traced back to 2004 in a paper published by Glennon et al as an intermediate in the synthesis of beta-oxygenated analogues of a 5-HT_{2A} serotonin receptor agonist investigated in the treatment of intraocular pressure [78].

Analogous to 2C-B, bk-2C-B is deemed to be active at serotonergic receptors although scientific pharmacological data are limited. It was gathered from anecdotal evidence posted on drug fora that bk-2C-B provides a psychedelic experience comparable to 2C-B [77], curiously though no article on bk-2C-B is yet available on Psychonaut Wiki. From other sources, users describe typical psychedelic effects of visual hallucinations, sensory enhancement and sometimes a greater appreciation of food and music is mentioned with euphoria and empathogenic experiences. [77, 79, 80]. Predominantly bk-2C-B is viewed as having scarce negative effects and seems to be appreciated though it is not always a favourite regarded by a few as 'bland' or 'empty' with little excitement and some users said they still prefer 2C-B. The quality of the trip is said to be dependent on the state of mind prior to taking the drug [77, 82, 81].

It is also said to be 10 times less potent than 2C-B, initially requiring higher doses for the same effect but past a 150 mg dose, a steep dose-response curve is reached which warrants careful proceeding. The drug has a threshold of 50-60 mg and a 150 mg+ dose is seen as heavy while many users report that a proper 'trip' is achieved at 100 mg. The drug has been taken orally, rectally and insufflated with encapsulation of an oral dose preferred over dissolution in water to avoid the aforementioned dimerization. Reports indicate that it has an onset of action of 20-70 minutes and a duration of 8-12 hours [77, 79, 82]. However, the effects of bk-2C-B have also been reported as inconsistent, one report even describing it as

‘Russian Roulette’ as the onset and duration of action were not always predictable at a given dose [83]

Despite being apparently relatively ‘safe’, there has been a report of a 25 year-old male user with no previous history of heart disease who experienced a cardiac arrest following a dose of 140 mg of bk-2C-B. The person suffered amnesia lasting two days after re-gaining consciousness and suffering from severe rhabdomyolysis [84]. Indeed, from several posts, psychonauts state that they are not willing or that it is not necessary to try a dose above 100-120 mg as they deemed that the desired effects do not increase significantly and that it might be more dangerous to do so [77,82].

It is to be noted that despite being on the market since mid-2013 and showing similarity of action to 2C-B from drug forum posts, bk-2C-B has not conquered the recreational field of psychonauts in spite of being qualified as a ‘good chemical’.

3.4 Psychdelics: LSZ and 1P-LSD

NPS analogues of the classic psychedelic LSD (**23**) include two potent analogues LSZ (**24**) and 1P-LSD (**25**) (Fig. 4). Very little scientific data exists regarding their pharmacological properties while they have been widely adopted by the psychonaut community ever since their appearance on the NPS market.

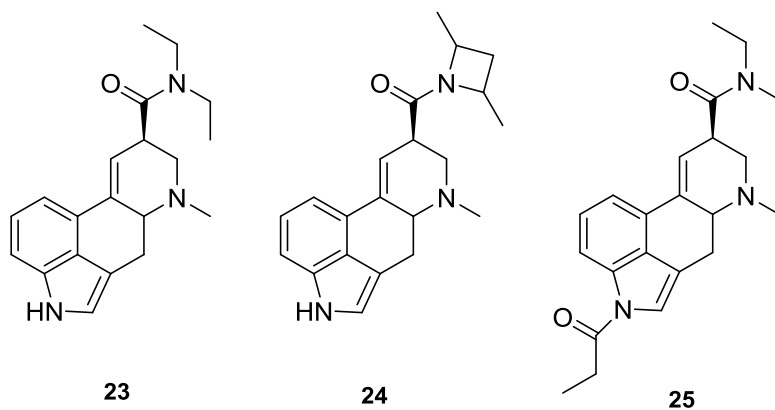


Fig. 4. The structures of LSZ and 1P-LSD

LSZ is currently classified as a Class A Schedule 1 Drug in the UK since 6th January 2015 on recommendation of the ACMD based on the fact that LSZ is an analogue of the controlled drug LSD and as a tryptamine-based drug it will have similar effects [85]. LSZ was synthesised and documented back in the early 2000's by Nichols et al (2002) as a conformationally constrained analogue of LSD. It was found that the *S, S* isomer of LSZ was slightly more potent than LSD itself and showed greater binding affinity to 5-HT_A receptors in rats, therefore being responsible for its hallucinogenic properties [86]. It appeared on the NPS highs market 7 years later in 2009 [87].

1P-LSD however, is only a recent addition to the lysergamide family, appearing in January 2015 and has apparently been designed to provide an alternative to LSZ as it was banned. 1P-LSD is also believed to be slightly more potent than its parent drug LSD [88]. This was demonstrated in a study in mice by Brandt et al where it was found to display approximately 38% more potency than LSD [89].

Both LSZ and 1P-LSD have been marketed in the form of blotters containing usually 150 micrograms of the substance which is placed under the tongue in a similar fashion to LSD. 1P-LSD is also available in tablet or ampoule forms [98]. Threshold dosage for LSZ is said to be 80 micrograms and between 150-300 micrograms to achieve a common effect. The onset of action is 90-120 minutes with a duration of action lasting from 7 to 10 hours. After-effects can be felt for up to 1 to 3 hours [90]. On the other hand, 1P-LSD seems to be more potent with a threshold dose of 50 micrograms and 150+ micrograms as a heavy dosing. The onset of action is also faster, starting at around half the time and a much longer duration of action lasting up to 12 hours with after-effects lasting up to 24 hours [88].

Users report mostly similar effects to those of LSD with experiences such internal-external visual hallucinations, loss of ego, empathy, euphoria, increased tactile sensation and

perception alteration. Tripping experiences are subjective and varied with the occurrence of a positive experience more likely with a ‘positive mindset’ and a negative experience more likely with the opposite or with exposure to an object of fear and/or disdain during tripping. Users also sometimes reported ‘self-realisation’ or ‘spiritual’ experiences whilst tripping. The effects have been reported to significantly alter cognitive functions enough to endanger the user if in a potentially unsafe situation in that state such as walking on roads. Physical manifestations are sweating, chills, pupil dilation, nausea and decreased appetite. Overall, however, most trip reports of LSZ or 1P-LSD are positive with users often reporting a more positive outlook on life afterwards and an agreeable experience they are willing to repeat. So far, no acute toxicity cases or hospitalisation were reported with either LSZ or 1P-LSD. Both LSZ and 1P-LSD are deemed to have no addictive potential and very low toxicity by users [88, 90-101]. One user, however, did report excessive nausea after taking a significant dose of 600 micrograms of LSZ but acknowledged to having overdosed [95].

It seems that to date, lysergamides remain popular amongst psychonauts with uses ranging from recreational to introspective to spiritual. Furthermore, their ‘apparent safety’ and low addiction and recoverable tolerance make them a drug of choice of this community.

3.5 Benzodiazepines: flubromazepam

Benzodiazepines are used in the psychonaut community to temper the effects of stimulants and hallucinogenic drugs to ‘come down’ while some people may use them as self-medication for anxiety disorders when they cannot get a prescription. Benzodiazepines are also used in the clinical setting to treat cases of acute toxicity related to NPS use [102]. However, benzodiazepines are also used recreationally and the scheduling of the etizolam and phenazepam in 2012 led to the advent of new designer benzodiazepines made available to the public through online vendors. Flubromazepam (**26**) is the second of the class to be put on the market and was a drug candidate described first in 1962 by Sternbach et al. Its

potency is said to be possibly higher than those of bromazepam, diazepam and nitrazepam [102,103].

Research into the pharmacokinetics and pharmacodynamics of flubromazepam is pretty scarce with only one study found on Pubmed at the time this review where one of the authors actually ingested 4mg of the drug to obtain data [103]. Flubromazepam has been reported as having a half-life of more than 106 hours with metabolites detectable by LC-MS/MS for up to 28 days after consumption. However, detection of the drug with immunochemical assays were difficult and may indicate that its detection in drug-facilitated crimes may not be conclusive [103].

The effects reported in psychonaut drug fora are typical of benzodiazepines such as muscle relaxant, anxiolytic, hypnotic and sedation and amnesia noted at higher doses. For some users, flubromazepam is regarded as more anxiolytic than hypnotic and for others the reverse was true. The routes of administration employed seem to be mainly oral, sublingual and rectal as the drug comes mainly as pellets of 4 mg or 8 mg. Flubromazepam indeed seems to be quite potent with a threshold dose of 3-5 mg and a heavy dose of 16+ mg. However, the onset of action is not immediate, taking between 30 minutes and even up to 6 hours before any effect is noted. This has led many to overdose on their first attempt with unpleasant consequences. The effects are also reported to last for up to a few days. Users seem to recognise that this long duration of action can have potential impact on safety when driving or operating machinery. The danger of cumulative toxicity with reported dosage is also mentioned as is its addictive potential [104-108]. One user even reported withdrawal symptoms as soon as after one week's use [109]. Concomitant use with other depressants such as alcohol or GBH is warned against to avoid potential respiratory depression [104].

Nonetheless, flubromazepam is regarded as one of the 'best' NPS benzodiazepines with the effects viewed as pleasant with a few cases of appreciated mild psychedelic effects reported.

Due to its apparent greater perceived effects than diazepam, some users have discussed its use in treating alcohol withdrawal instead of the latter [106]. Furthermore, awareness of the difficulty to detect in immunochemical assays is already causing some benzodiazepine users to consider it to escape drug-testing [110].

Whether or not flubromazepam's potential as a useful drug candidate can be revived is yet to be determined with the lack of research on this substance. Meanwhile flubromazepam continues to remain in the confines of the grey area of legislative control along with other and emerging designer benzodiazepines without any reliability of safety of use.

4. Conclusion

From this review, the dire lack of pharmacological data available on these substances was obvious as was their popularity of use among psychonauts. A trend observed in most of the compounds selected was their origin from old patents and papers on drug candidates which have not been developed further and which can be found online. Not only was the wealth of scientific information exploited by research chemical vendors themselves, but also actively discussed by psychonauts on drug fora even before the appearance of these NPS on the legal high market as is the case of bk-2C-B or lefetamine-based drugs. As such, it makes sense to consider the content on drug fora as well as previous or abandoned drug candidates to try and spot upcoming NPS. Furthermore, it should be noted that trip reporting on drug fora provides a wealth of information on the effects of NPS on the human body albeit by subjective views, and may also be a trend-setter in the development of future NPS. Another interesting issue was that NPS were discussed not only as recreational drugs but for their therapeutic value in treating conditions such as depression and anxiety, for instance, in the case of ephenidine. Of concern, is the very strong addiction potential of some drugs reviewed such as diphenidine or the potentially hazardous and easily overdosed psychostimulants and psychedelics and the

ease of access to them. It should be noted that acute toxicity cases requiring hospitalization and even deaths ensuing from NPS use have also been well reported.

In any case, NPS which represent a largely unknown and rapidly expanding territory in an era of globalization and instantaneous access to information through the World Wide Web, will not be easy to conquer nor overlook. It may not be completely surprising if the next generation of antidepressants, psychotherapy counselling aid or the next schizophrenia-modelling drugs were to come from NPS nor would it be surprising if the next addictive or crime-facilitating drug were to come from the NPS as well.

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Abstract

The purpose of this review is to identify emerging or new psychoactive substances (NPS) by undertaking an online survey of the UK NPS market and to gather any data from online drug fora and published literature. Drugs from four main classes of NPS were identified: psychostimulants, dissociative anaesthetics, hallucinogens (phenylalkylamine-based and lysergamide-based materials) and finally benzodiazepines. For inEach of the classes contained drugs that are modelled on existing illegal materials and will be covered by the UK New Psychoactive Substances Bill in 2016.

Keywords: New Psychoactive Substances

1. Introduction

New Psychoactive Substances (NPS), also inaccurately known as ‘legal highs’ are those materials which lie in the grey area of legislative control in most countries and are used recreationally by psychonauts and at raves. According to the European Monitoring Centre for Drugs and Drug Addiction’s (EMCDDA) March 2015 report, the number of NPS is continuously increasing every year putting pressure on National Agencies to monitor these newly emerging drugs and to find solutions to reduce their harms [1]. The emergence of NPS has established itself as a global phenomenon appearing in some 94 countries worldwide as of December 2013 [2]. Furthermore, some NPS have much higher potency than the older drugs they are designed to replace while some are difficult to detect in body fluids [3]. NPS have rarely been studied for the purposes they are being used for and therefore pose a considerable and significant threat to the health of society.

2. Methods

The NPS names were entered as keywords into the search engines Google and PubMed. Around ten of the most relevant results on Google were considered and all relevant literature on PubMed was taken into account for each substance. Information was gathered from manufacturer’s websites, drug fora such as Bluelight, UK Chemical Research, Drugs-Forum, Reddit, TripSit and PsychonautWiki.

3. Results and discussion

3.1. Psychostimulants

3-Fluorophenmetrazine (3-FPM;(1)), also known as PAL-539, has recently emerged in the online market of ‘research chemicals’ and is currently legal to possess and supply in the UK as long as it is not for human consumption [4]. This compound is a relatively new substance and there are currently no scientific studies or literature pertaining to it. Psychonaut

Wiki and drug fora such as Bluelight refer to the amphetamine-like its properties and 3-FPM is a close relative to the now no longer used anorectic drug phenmetrazine (2), the chemical backbone of which can be likened to amphetamine with the terminal amine in a morpholine ring. According to Psychonaut Wiki, 3-FPM has not been used in humans prior to 2014, however, psychonaut communities who have experience with the drug have put up rough 'guidelines' for its use. These suggest that a longest duration of action of 5-8 hours occurs when taken orally with a dose of 25-50mg orally or 20-35 mg as insufflation for what is referred to as a 'common' effect [5]. Physical effects described are increased energy levels, vasoconstriction, loss of thermoregulation, appetite suppression and an increased heart rate. Cognitive effects included increased motivation, focus and euphoria. Nonetheless, the stimulant effect was described as being less than that induced by substituted amphetamine compounds and users have referred to 'flu-like' symptoms with shivers [4,6]. Most of its effects could be inferred from the effects associated with phenmetrazine and other amphetamine-like drugs; therefore, part of this review will include some closely related compounds to which 3-FPM is related.

Phenmetrazine is of the phenylmorpholine class of compounds and was developed as an appetite suppressant (anorectic) to be used in conjunction with a low caloric intake diet in the short-term treatment of exogenous obesity [7]. It was marketed under the trade name Preludin and was allegedly used by the Beatles early during their career to cope with long hours of performance. It is an indirect-acting sympathomimetic agent with central stimulant effects, and its mode of action and effects are similar to those of dextroamphetamine [7, 8]. Due to its high potential for abuse, considered to be more potent than amphetamine, it was withdrawn from the market [9]. It has been used recreationally and abused in Sweden in the 1950's and in the USA in the 1960's and 1970's before being removed completely from the market [10].

The mechanism of action is highly similar to amphetamine by blocking the noradrenaline and dopamine re-uptake transporters in the brain which leads to their prolonged presence and hence prolonged stimulation of post-synaptic receptors at the synapse [11, 12].

Ritalin or methylphenidate (3) analogues such as 4-Me-TMP (4), made its appearance on the NPS market in April 2015 as a methylphenidate (3) replacement for the recently banned methylphenidate analogues EPH (5), PPH (6), IPH (7), 3,4-CTMP (8) and HDMP-28 (9) [13]. However, 4-Me-TMP did not last long among psychonauts as it also was soon put under a Temporary Class Drug Order which took effect on the 27th of June 2015 following recommendations made by the UK Advisory Council on the Misuse of Drugs (ACMD), based on its similarity to methylphenidate in effects and inferred adverse effects [14,15].

Currently there are no scientific studies specific to 4Me-TMP as a recreational drug. A search on Pubmed using the keywords '4Me-TMP', '4-Methylmethylphenidate' returned no results as of 26th of October 2015. Pharmacological data is limited with records of 4Me-TMP as one of the analogues of methylphenidate investigated in the treatment of cocaine dependence. It was found to be slightly more potent than methylphenidate at inhibiting the binding of [³H]-WIN35 428, a cocaine analogue used in research on the dopamine transporter [16, 17].

In psychonaut communities, 4Me-TMP has gained popularity as a psychostimulant during its short span of 'legality'. Users described it as the only 'research chemical' with effects closest to methylphenidate with a relatively lower potency that is concordant with available scientific pharmacological data [18]. Information regarding its effects in the human body can only be gleaned from reports of trips as posted or discussed on drug fora. Users reported euphoria, decreased appetite and need for sleep, increased alertness and focus and sexual arousal as positive and desired effects. Negative effects included increased sweating, tremors and tachycardia, however, the degree of the effects was subjective to the user. Depending on the dose administered, 4Me-TMP was reported to be recreational resulting in a clear head and

enabling users to improve performance during work or study. Some users have recognised that as a methylphenidate analogue, 4Me-TMP may also have addictive potential, although so far, no compulsion to re-dose has been reported [19, 20].

4Me-TMP has been mainly taken orally or by insufflation and oral doses vary from a recommended threshold of 25mg to 90-125mg as a heavy dose, with an onset of action within minutes and a duration of action of 4-6 hours. For insufflation, doses are smaller with a threshold of 10mg and a heavy dose of over 70 mg with an onset of action within minutes and a duration of action of 2-5hours. Doses are sometimes 'boosted' after 3 hours of administration for a prolonged effect [18,19,21,22]. Varying degrees of harm from drug-drug interactions when using methylphenidate are also warned of on the Tripsit website. For instance, concomitant use of stimulants and tramadol are said to increase the risks of seizures and are qualified as dangerous. Increased risk of serotonin syndrome is noted with simultaneous use with monoamine oxidase inhibitors and 2C-T-x compounds(e.g. **10**)while combinations with NBOMe, cocaine, dextromethorphan and methoxetamine are recognised as causing excessive sympathetic stimulation and posing unnecessary stress on the heart. Excessive anxiety with persistent thought-loop is also purported to occur when 4Me-TMP is used with psychedelics such as mescaline. 4Me-TMP as a psychostimulant is also said to decrease the perception of drunkenness and increase the risk of drinking excessively till the passing out point [21].

The fora threads on 4Me-TMP are relatively short possibly because of its short span of use as an NPS. Nevertheless, users have so far reported few negative effects and are positive about 4Me-TMP with people still seeking it out. New posts appear to come from users who are apparently based outside the UK for example in Sydney [18], which suggests that 4Me-TMP has spread globally. For the time being, there is still no scientific evidence specific to 4Me-

TMP (26th October 2015) apart from its inferred effects from structural similarity to methylphenidate, to validate its permanent ban under UK law.

Methiopropamine

Methiopropamine (**11**) as an NPS was first reported following a seizure in Finland in January 2011[23]. Its synthesis however, dates back to the 1940s when it was synthesised by Blicke and Burckhalter as an analogue of methamphetamine, where the phenyl ring was substituted with a thiophene ring in order to compare effects on blood pressure [24].

Since its appearance online as a research chemical in late 2010, methiopropamine has become an established NPS used recreationally and evading control under the UK legislation until a temporary class drug order at the end of 2015. According to an internet snapshot study conducted in June 2013 in accordance with EMCDDA methodology, it was found that methiopropamine is readily available over the internet with 45% of vendors identified as being UK-based. It is sold mainly in powder form in amounts ranging from 150mg to 4kg [25]. This NPS was also detected in pooled urine collected from urinals placed in Central London on Friday and Saturday nights in 2012 as part of a pilot study to understand prevalence of NPS use [26]. It was also detected in the blood samples from drivers in Norway [27].

An analysis of the metabolites of methiopropamine from rat and human urine by GC-MS and LC-HR-MS was conducted by Welter et al. This proposed that methiopropamine underwent a combination of *N*-methylation and hydroxylation at the side-chain and thiophene ring respectively before glucuronidation and sulfation. The CYP450 enzymes involved were CYP1A2, CYP2C19, CYP2D6 and CYP3A4 [28].

It seems that users have been utilizing methiopropamine as a performance enhancer to cope with work, study and bereavement as well as recreationally [31, 32, 38]. Methiopropamine is being ingested orally, smoked, used as an insufflation, taken rectally or injected intravenously

by psychonauts depending on the effects desired. For instance, small doses of 10mg taken 3 hourly by IV injection to maintain a high or a bolus of 40-50mg for a 'rush' have been suggested [32]. The threshold dose is noted as 10mg with a 60mg+ dose as being heavy. Onset of action is within 30-60minutes with the effects peaking at 2-4 hours, with a coming down that lasts 2-3 hours and an afterglow experienced for 1-3 hours [33]. Insufflation is reported to leave a bad taste which may be due to the sulfur atom in the molecule but provides the same intense rush as IV injection with a shorter duration of action [32]. An analysis of the pyrolysis products of methiopropamine under the same conditions when smoked by users found that they were mostly the same as methamphetamine. However, other products were also formed such as beta-keto-methiopropamine, whose properties are unknown, *N*-methyl methiopropamine which is psychoactive, 2-methylthiophene which is toxic and a bicyclic tetrahydropyridine compound with a structure similar to the anti-platelet drug clopidogrel [29].

As an analogue of methamphetamine, methiopropamine has also been reported to induce similar effects. This was supported by a study of neurochemical profiling of NPS by Iversen et alin which methiopropamine was found to be a potent inhibitor of noradrenalin, dopamine and to a lesser extent serotonin re-uptake comparable to amphetamine [30]. Users report an increased alertness, energy and focus, sexual arousal and euphoria on drug fora which is described as a 'rush of adrenaline'. Side-effects also noted were high-blood pressure, tachycardia, anxiety, sweating and shaking, nausea, dehydration, difficulty urinating and a significant loss of appetite and sleep which could last for days. Quite a few users also reported chest pain, palpitations and headaches sometimes comparable to a heart-attack. Users recommended taking multivitamins, drinking plenty of water and *Gingko biloba* for its vasodilating effects to minimise the harmful effects of methiopropamine. Negative effects were said to increase with repeated dosing and to cause hallucinations at high dose. Chronic

use multiple times a day and/or over several consecutive days was reported to cause psychosis, hallucinations and heightened fear and anxiety, depression and aggressive behaviour on withdrawal [31–39]. Methiopropamine was also regarded as highly addictive with a strong compulsion to re-dose and binge accompanied by a loss of inhibition at high doses. This addictive character was suggested to be in part a psychological need to feel the ‘intense euphoric rush’ by users [35, 32]. Tolerance was also said to build up very quickly with loss of positive or desired effects [38, 39]. In drug fora, prospective users are warned not to binge on methiopropamine and an awareness of its potentially-life threatening side-effects seems to be prevalent [31-39].

Methiopropamine use has already claimed lives as it continues to gain followers despite some discouraging user reviews online [32, 39]. In 2012, two methiopropamine-related deaths were first reported in the UK [23] while the first ever case in Australia was reported in 2015 where a post-mortem investigation found 38mg/L of methiopropamine in the blood of the deceased [40]. Acute toxicity related to methiopropamine where 400ng/ml was found in urine, has also been reported. In that particular case, however, the user bought their samples from a Central London market stall under the name of ‘Quicksilver’. Considering that the only reference to ‘Quicksilver’ in a recreational drug context that could be found online was of methoxetamine, it is possible that the victim may not have been aware of what they were ingesting [41].

Methiopropamine is appealing to many users as a euphoric psychostimulant that can be employed in multiple situations in spite of its notorious side-effects. Use will probably continue to spread worldwide via its boundary-less cyber foothold unless any action is taken whether in terms of legislative control or harm reduction and drug use education measures.

II. LEFETAMINE-DERIVED DISSOCIATIVE ANAESTHETICS

Following the UK ban in February 2013 on all arylcyclohexylamines in an attempt to curtail the spread of PCP and ketamine analogues, a new class of dissociative anaesthetics known as diarylethylamines based on lefetamine (**12**) among which can be found ephenidine (**13**), diphenidine (**14**) and methoxyphenidine (**15**), hit the NPS market as crystals, powder and pellets to circumvent the law [42]. Diarylethylamines, which are far from being novel, have actually been synthesised and documented as far back as 1924 [43]. Diarylethylamines are in fact, analogues of the now withdrawn and controlled drug lefetamine (**12**), which was introduced as an opioid analgesic in the 1940s and marketed as Santenol [44].

However, despite their structural resemblance to lefetamine, these diarylethylamines do not have the same pharmacological activity, mimicking instead the effects of PCP and ketamine, and their respective analogues function by uncompetitive NMDA-receptor antagonism and are being marketed as their legal replacement by online chemical vendors [43, 45]. Indeed, from a thread on bluelight, it seems that lefetamine and lefetamine-derivatives have been compared to the arylcyclohexylamines PCP and ketamine and their use as possible recreational drugs was discussed as early as 2006 [46].

While these compounds have been gaining in popularity across the psychonaut communities, again little is known about them. Most of the information reported about their physiological effects in humans comes from online drug fora and some from cases of NPS poisoning sent to emergency services. So far, Sweden has already classified them as hazardous to human health [47] and this review seeks to bring an overview of the information available so far.

Ephenidine (13), (N-ethyl-1, 2-diphenylethylamine (NEDPA))

Ephenidine first appeared on the NPS scene in 2008 when it was seized alongside NPDPA (**16**), another lefetamine derivative, by the German police. Nonetheless its amphetamine-like stimulant properties had already been described in the 1940s [48]. From

the metabolites collected from rat urine, it was inferred that ephedrine was completely metabolised and most likely underwent a combination of *N*-alkylation, mono- and bis-hydroxylation of the benzyl ring followed by methylation of one of the two hydroxyl group metabolites at phase 1, and hydroxylation of the phenyl ring after *N*-dealkylation, glucuronidation and sulfation of all hydroxylated metabolites in phase 2 [48] Since the metabolism of ephedrine has been found to involve at least four CYP-450 enzymes to varying degrees, it has been purported that ephedrine may not give rise to significant drug-drug or drug-food interactions [44].

In the Psychonaut communities, a thread was first dedicated to ephedrine and other related dissociative NPS in late December 2014 on Bluelight. However, it seems that ephedrine is only recently starting to gain wider acceptance and popularity according to the drug fora studied [49, 50]. Often, reference is made to its smooth or ‘silk-like’ come-up compared to other dissociative anaesthetics [52] but also of a tendency to feel dehydrated. The experience is also viewed as much more positive with a greater cornucopia of visual stimulation and hallucinations and also as less ‘out-of-body’ at regular doses. In some cases, users reported its effects as more ‘spiritual’ or ‘magical’ with an enhanced appreciation for music and colours [51, 52, 50]. One user even stated that ephedrine surpasses ketamine, PCP and all other dissociatives [53]. Ephedrine has also been reported to have mild psychedelic effects while scarcely affecting ‘*functioning as a person*’ [56]. Furthermore, it was also seen as an alternative to ketamine and methoxetamine by another user [57].

Psychonauts have been administering the drug orally, rectally, by sniffing or vaping and by the IV route. Doses employed are sometimes seen to be quite high, ranging from 150mg to 600 mg in some cases to achieve desired effects, though websites such as Psychonaut Wiki indicates a threshold of 60mg with a 200 mg+ dose being seen as ‘heavy’ [50, 54]. This suggests that ephedrine might be less potent or that the negative effects are more tolerable.

Ephedrine is also reported to have a slow onset depending on individuals ranging from 10-30 minutes to 1.5-3 hours but also a longer duration of action of 5-7 hours [50, 54, 55]. Full recovery from the dissociative effects also seem to vary among individuals with some still feeling wobbly after 15 hours after a 250 mg dose while others took a full 24 hours to recover after a 200 mg dose [55]. This may of course be as a result of the quality of the product as well as individual pharmacogenomic responses.

Overall, most 'user reviews' appear in favour of ephedrine with apparently no distressing mental stimulation and a more enjoyable trip with seemingly no negative effects except for residual dissociative effects post use. Nonetheless, ephedrine is regarded as having a potential for addiction and prospective users are warned to use it carefully [57].

On the side, two other variants of ephedrine that so far seem to be less popular among psychonaut communities are 2-chloro-ephedrine(**26**) and 2-MeO-ephedrine(**27**) [49].

Diphenidine (14)(1-(1,2-Diphenylethyl)piperidine)

Diphenidine (**14**) was first synthesised in 1924 by Christiaen who used a modified Brulyants reaction which would later be used by Maddox to synthesise PCP [43]. Though it was launched earlier than methoxyphenidine, it is less popular [58].

As a diarylethylamine, diphenidine has been investigated for neuroprotective effects on neurones in the hippocampus as described in a 1989 patent and furthermore its ability to suppress cough as an antitussive agent in dogs has also been studied. These past observed properties are what might have made it a candidate as a research chemical [59]. The NMDA-receptor antagonist effect has recently been confirmed in-vivo using rat hippocampal slices and was found to be similar to ketamine in reducing NMDA-mediated field excitatory post-synaptic potentials at 30 μ M [59]. Though not of the same chemical class, diphenidine definitely does act as a pharmacological analogue to the dissociative drug ketamine.

Dopamine and serotonin re-uptake inhibition and mu-opioid receptor affinity are purported by vendors but have however, not been studied [60].

According to Tripsit, a normal dose of diphenidine would be approximately 85-110mg, with an onset of action of 10-30 minutes, a duration of 2-5 hours and an ‘after-glow’ effect of up to 4-24 hours [61]. The most common route of administration is oral or sublingual. Blocked nose or inflamed sinuses have been reported with insufflation, although it is believed to have a quicker onset of action by this route requiring a fifth of the oral dose [63, 61].

Diphenidine is described as mildly stimulating and mostly amnesia-inducing, crippling the recall ability of the user which may potentially cause loss of control over one’s own behaviour [62]. An example is that of a previous ketamine user who overdosed on diphenidine orally at 310mg, was violent with the paramedics who came to take him to hospital and could not remember any of what had happened [63]. Other effects noted are those of sensory dissociation, loss of inhibition, and significant visual and internal hallucinations. Several users also reported high blood pressure and tachycardia. This was reflected in non-fatal intoxication cases of diphenidine observed in Sweden [61, 45]. Diphenidine has not been very popular with many users reporting negative and sometimes both physiologically and psychologically troubling experience described by one user as being ‘*sucked down into a shrieking vortex of insanity*’ [58]. Of most concern is the steep dose response curve reported with a rapid build-up of tolerance at higher doses and high addiction potential, which is described as very compulsive [63, 45, 64]. Diphenidine has even been described as ‘evil’ by another user [64].

Methoxyphenidine (15), 1-[1-(2-methoxyphenyl)-2-phenylethyl] piperidine

Methoxyphenidine is also member of the diarylethylamine group that has been screened for the potential treatment of neurotoxic injury according to a 1989 patent [66]. Methoxyphenidine appeared shortly after diphenidine and gained a rapid rise in popularity

relative to the latter despite an initial dearth of reports of previous human use of the compound [58]. Methoxyphenidine has been and is still being used extensively by the psychonaut communities.

However, while it is being marketed by online vendors as a replacement for methoxetamine and ketamine, the effects of methoxyphenidine are reported to be qualitatively closer to those of dextromethorphan, an antitussive which has been abused. Subjective physical effects which include tactile disconnection, a spontaneous tactile sensation described as ‘body high’ and loss of motor control are reported to increase with increasing dosage and are reported to feel like those induced by dextromethorphan [67].

Furthermore, the cognitive effects are seen as different from all other dissociatives with the user still being in control and less confused even at higher dosages to bring about the same subjective intensity when using methoxetamine, dextromethorphan or ketamine [58, 67]. A methoxyphenidine experience has been qualified as ‘introspective’ by one user-blogger [70]. An in-depth review of harm reduction and online consumerism of methoxyphenidine among psychonauts conducted by Van Hout and Hearne supported that its effects are perceived as unique and result in a more ‘clear-headed’ sensation. It was also viewed as much better than diphenidine in that it is less ‘havoc-provoking’ with more enjoyable effects [58].

Routes of administration are oral, sublingual, rectal, insufflation and by IV [58]. Insufflations are said to irritate the nasal mucosa significantly [68, 70] and a numbness of the tongue is said to occur with IV administration and is therefore not the most favoured route [58]. Psychoactive effects are said to start at a dose ranging from 30 to 50mg with 150+ mg being regarded as giving strong effects. The onset starts from 30 to 60 minutes with a duration of action of between 6-8hours and after-effects are described as ‘after-glow’ of 1-3hours [67, 69]. Sometimes, even at higher doses of 200mg, some users reported being reasonably lucid [56]. Whilst a steep-dose response curve has been reported, it is also said

that re-dosing is unnecessary as there is not much enhancement of positive effects but instead a higher risk of experiencing negative side-effects such as amnesia [43, 68]. Nevertheless, the dose-response effect of methoxyphenidine is reported as inconsistent and unpredictable with different users experiencing a differing degree of intoxication/side-effects at the same dosage [68]. Novice users as well as users who are experienced with dissociatives are often advised to start at the lowest dose as even with past dissociative usage, the effects of methoxyphenidine have been reportedly experienced as strong [70, 71].

On drug fora, users are reminded not to ‘push too far’ with this compound as it has been reported to cause chest pains, palpitations, tachycardia, high blood pressure and sometimes seizures requiring hospitalization [43, 56, 58, 70]. Indeed, during a relatively short span of use, cases of methoxyphenidine-related deaths and acute toxicity have already been reported [45, 65, 66]. An acute toxicity case of a 53 year old Caucasian male presented with hypertension at 220/125mmHg and tachycardia of 112bpm was treated with lorazepam, whilst an enlarged heart was found at the autopsy of two of the fatal cases attributed to methoxyphenidine [65, 66]. The acute toxicity case also developed opisthotonus and horizontal nystagmus upon losing consciousness before reaching a Glasgow Coma Scale of 10 [65].

Despite the grave side-effects of methoxyphenidine that are possible, its positive effects of mood-elevation and as a brain stimulant with ‘responsible’ use were seen as important enough to lead psychonauts to speculate about its medicinal potential as an antidepressant and in psychotherapy [58].

Possible further lefetamine-based dissociative anaesthetics may find their roots in previously studied analogues of lefetamine as suggested by one Bluelight thread dating back to 2008 which briefly discusses DMPP (**19**), a compound investigated for analgesic properties [72].

On the whole, the psychoactive agents, ephenidine, diphenidine and methoxyphenidine are an emerging class of dissociative anaesthetics that have not been explored in that sense before. Their effects are being widely reported by psychonaut communities, definitely warrants further investigation and it is reasonable to expect new lefetamine analogues on the NPS market in the future.

III. PHENYLALKYLAMINE HALLUCINOGENS

bk-2C-B

Alexander Shulgin was the first to synthesise the phenylalkylamine hallucinogens 2C-B (**20**), DOB and DOM and described their syntheses and effects in PiHKAL [73]. While DOM and DOB were already established, 2C-B really flourished in the recreational drug use sphere in the mid-1980s as the best alternative to LSD and psilocybin [74, 75]. However, the 2C-B class were soon banned in the US in 1985 and placed in Schedule 2, as Class B drugs in the UK. However, 2C-B still found its way into raves being often disguised as MDMA.

In recent years, as an attempt to find a legal substitute to 2C-B, vendors have come up with bk-2C-B(**21**)also known as beta-keto 2C-B, which hit the shelves of online head-shops in mid-2013 being sold as powder or crystals. Because of its structure, bk-2C-B is not regulated to date in the UK or Ireland though it can be considered as the beta-keto analogue or a cathinone analogue of 2C-B [76]. bk-2C-B appeared online in 2007 in a Bluelight forum thread discussing its potential as a future ‘legal-high’ replacement for 2C-B focusing on its possible dimerisation (**22**) which could lead to inactivity of the compound in-vivo[77]. An even earlier appearance can be traced back to 2004 in a paper published by Glennon et al as an intermediate in the synthesis of beta-oxygenated analogues of a 5-HT_{2A} serotonin receptor agonist investigated in the treatment of intraocular pressure [78].

Analogous to 2C-B, bk-2C-B is deemed to be active at serotonergic receptors although scientific pharmacological data are limited. It was gathered from anecdotal evidence posted on drug fora that bk-2C-B provides a psychedelic experience comparable to 2C-B [77], curiously though no article on bk-2C-B is yet available on Psychonaut Wiki. From other sources, users describe typical psychedelic effects of visual hallucinations, sensory enhancement and sometimes a greater appreciation of food and music is mentioned with euphoria and empathogenic experiences. [77,79,80]. Predominantly bk-2C-B is viewed as having scarce negative effects and seems to be appreciated though it is not always a favourite regarded by a few as 'bland' or 'empty' with little excitement and some users said they still prefer 2C-B. The quality of the trip is said to be dependent on the state of mind prior to taking the drug [77, 82, 81].

It is also said to be 10 times less potent than 2C-B, initially requiring higher doses for the same effect but past a 150mg dose, a steep dose-response curve is reached which warrants careful proceeding. The drug has a threshold of 50-60mg and a 150mg+ dose is seen as heavy while many users report that a proper 'trip' is achieved at 100mg. The drug has been taken orally, rectally and insufflated with encapsulation of an oral dose preferred over dissolution in water to avoid the aforementioned dimerisation. Reports indicate that it has an onset of action of 20-70 minutes and a duration of 8-12 hours [77, 79, 82]. However, the effects of bk-2C-B have also been reported as inconsistent, one report even describing it as 'Russian Roulette' as the onset and duration of action were not always predictable at a given dose [83]. Despite being apparently relatively 'safe', there has been a report of a 25 year-old male user with no previous history of heart disease who experienced a cardiac arrest following a dose of 140mg of bk-2C-B. The person suffered amnesia lasting two days after re-gaining consciousness and suffering from severe rhabdomyolysis [84]. Indeed, from several posts, psychonauts state that they are not willing or that it is not necessary to try a dose above 100-

120mg as they deemed that the desired effects do not increase significantly and that it might be more dangerous to do so [77,82].

It is to be noted that despite being on the market since mid-2013 and showing similarity of action to 2C-B from drug forum posts, bk-2C-B has not conquered the recreational field of psychonauts in spite of being qualified as a ‘good chemical’.

IV. PSYCHEDELICS – LSZ AND 1P-LSD

NPS analogues of the classic psychedelic LSD (**23**) include two potent analogues LSZ (**24**) and 1P-LSD(**25**). Very little scientific data exists regarding their pharmacological properties while they have been widely adopted by the psychonaut community ever since their appearance on the NPS market.

LSZ; (**24**) (8 β)-8-[[*(2S,4S)*-2,4-Dimethylazetid-1-yl]carbonyl]-6-methyl-9,10-didehydroergoline

LSZ is currently classified as a Class A Schedule 1 Drug in the UK since 6th January 2015 on recommendation of the ACMD based on the fact that LSZ is an analogue of the controlled drug LSD and as a tryptamine-based drug it will have similar effects [85]. LSZ was synthesised and documented back in the early 2000’s by Nichols et al as a conformationally constrained analogue of LSD. It was found that the *S, S* isomer of LSZ was slightly more potent than LSD itself and showed greater binding affinity to 5-HT_A receptors in rats, therefore being responsible for its hallucinogenic properties [86]. It appeared on the NPS highs market 7 years later in 2009 [87].

1P-LSD; (**25**) (6*aR,9R*)-4-propionyl-N,N-diethyl-7-methyl-4,6,6*a*,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide

1P-LSD is only a recent addition to the lysergamide family, appearing in January 2015 and has apparently been designed to provide an alternative to LSZ as it was banned. 1P-LSD is also believed to be slightly more potent than its parent drug LSD [88]. This was demonstrated

in a study in mice by Brandt et al where it was found to display approximately 38% more potency than LSD [89].

Both LSZ and 1P-LSD have been marketed in the form of blotters containing usually 150 micrograms of the substance which is placed under the tongue in a similar fashion to LSD. 1P-LSD is also available in tablet or ampoule forms [98]. Threshold dosage for LSZ is said to be 80micrograms and between 150-300micrograms to achieve a common effect. The onset of action is 90-120minutes with a duration of action lasting from 7 to 10 hours. After-effects can be felt for up to 1 to 3 hours [90]. On the other hand, 1P-LSD seems to be more potent with a threshold dose of 50 micrograms and 150+ micrograms as a heavy dosing. The onset of action is also faster, starting at around half the time and a much longer duration of action lasting up to 12 hours with after-effects lasting up to 24hours [88].

Users report mostly similar effects to those of LSD with experiences such internal-external visual hallucinations, loss of ego, empathy, euphoria, increased tactile sensation and perception alteration. Tripping experiences are subjective and varied with the occurrence of a positive experience more likely with a 'positive mindset' and a negative experience more likely with the opposite or with exposure to an object of fear and/or disdain during tripping. Users also sometimes reported 'self-realisation' or 'spiritual' experiences whilst tripping. The effects have been reported to significantly alter cognitive functions enough to endanger the user if in a potentially unsafe situation in that state such as walking on roads. Physical manifestations are sweating, chills, pupil dilation, nausea and decreased appetite. Overall, however, most trip reports of LSZ or 1P-LSD are positive with users often reporting a more positive outlook on life afterwards and an agreeable experience they are willing to repeat. So far, no acute toxicity cases or hospitalisation were reported with either LSZ or 1P-LSD. Both LSZ and 1P-LSD are deemed to have no addictive potential and very low toxicity by users

[88,90-101]. One user, however, did report excessive nausea after taking a significant dose of 600micrograms of LSZ but acknowledged to having overdosed [95].

It seems that to date, lysergamides remain popular amongst psychonauts with uses ranging from recreational to introspective to spiritual. Furthermore, their ‘apparent safety’ and low addiction and recoverable tolerance make them a drug of choice of this community.

V. BENZODIAZEPINES– FLUBROMAZEPAM

Benzodiazepines are used in the psychonaut community to temper the effects of stimulants and hallucinogenic drugs to ‘come down’ while some people may use them as self-medication for anxiety disorders when they cannot get a prescription. Benzodiazepines are also used in the clinical setting to treat cases of acute toxicity related to NPS use [102]. However, benzodiazepines are also used recreationally and the scheduling of the etizolam and phenazepam in 2012 led to the advent of new designer benzodiazepines made available to the public through online vendors. Flubromazepam (**26**) is the second of the class to be put on the market and was a drug candidate described first in 1962 by Sternbach et al. Its potency is said to be possibly higher than those of bromazepam, diazepam and nitrazepam [102,103].

Research into the pharmacokinetics and pharmacodynamics of flubromazepam is pretty scarce with only one study found on Pubmed at the time this review where one of the authors actually ingested 4mg of the drug to obtain data. Flubromazepam has been reported as having a half-life of more than 106 hours with metabolites detectable by LC-MS/MS for up to 28 days after consumption. However, detection of the drug with immunochemical assays were difficult and may indicate the potential use of flubromazepam in drug-facilitated crimes or in situations where drug-testing is performed [103].

The effects reported in psychonaut drug fora are typical of benzodiazepines such as muscle relaxant, anxiolytic, hypnotic and sedation and amnesia noted at higher doses. For some

users, flubromazepam is regarded as more anxiolytic than hypnotic and for others the reverse was true. The routes of administration employed seem to be mainly oral, sublingual and rectal as the drug comes mainly as pellets of 4mg or 8mg. Flubromazepam indeed seems to be quite potent with a threshold dose of 3-5mg and a heavy dose of 16+ mg. However, the onset of action is not immediate, taking between 30minutes and even up to 6 hours before any effect is noted. This has led many to overdose on their first attempt with unpleasant consequences. The effects are also reported to last for up to a few days. Users seem to recognise that this long duration of action can have potential impact on safety when driving or operating machinery. The danger of cumulative toxicity with reported dosage is also mentioned as is its addictive potential [104-108]. One user even reported withdrawal symptoms as soon as after one week's use [109]. Concomitant use with other depressants such as alcohol or GBH is warned against to avoid potential respiratory depression [104].

Nonetheless, flubromazepam is regarded as one of the 'best' NPS benzodiazepines with the effects viewed as pleasant with a few cases of appreciated mild psychedelic effects reported. Due to its apparent greater perceived effects than diazepam, some users have discussed its use in treating alcohol withdrawal instead of the latter [106]. Furthermore, awareness of the difficulty to detect in immunochemical assays is already causing some benzodiazepine users to consider it to escape drug-testing [110].

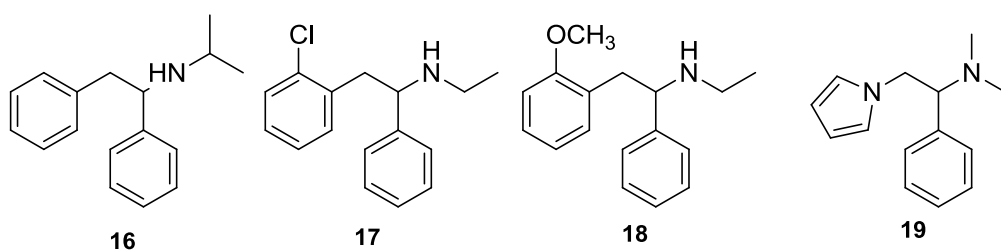
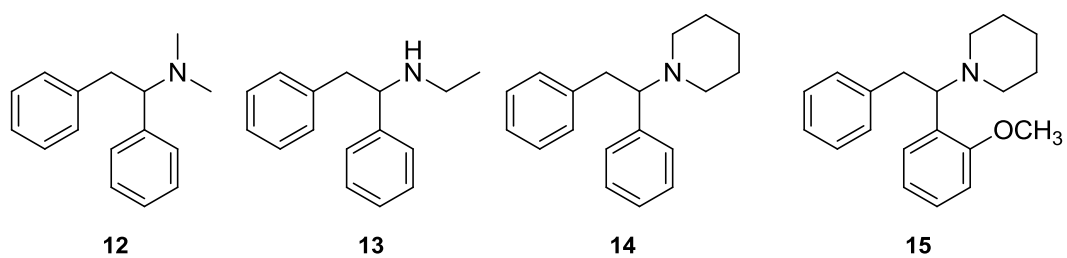
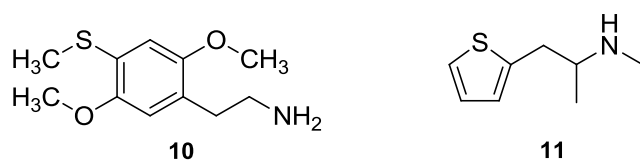
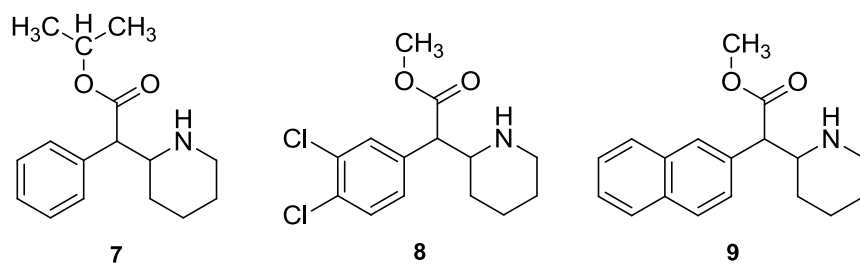
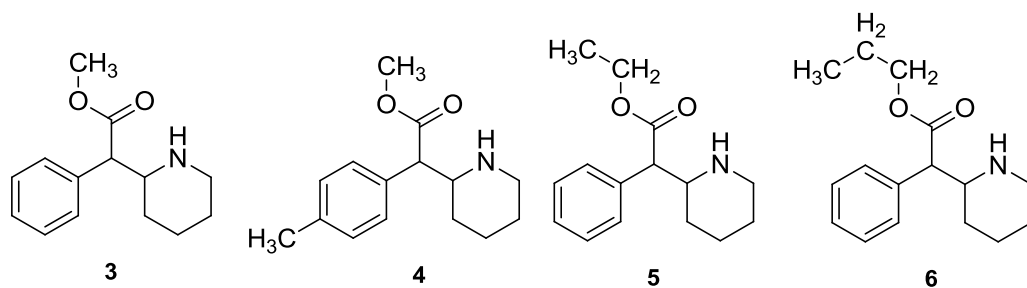
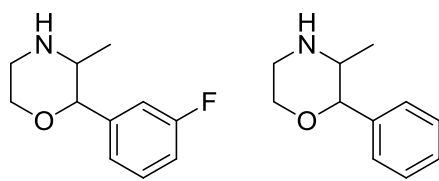
Whether or not flubromazepam's potential as a useful drug candidate can be revived is yet to be determined with the lack of research on this substance. Meanwhile flubromazepam continues to remain in the confines of the grey area of legislative control along with other and emerging designer benzodiazepines without any reliability of safety of use.

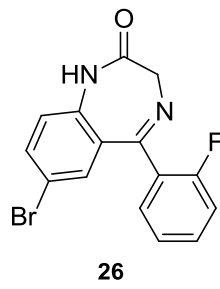
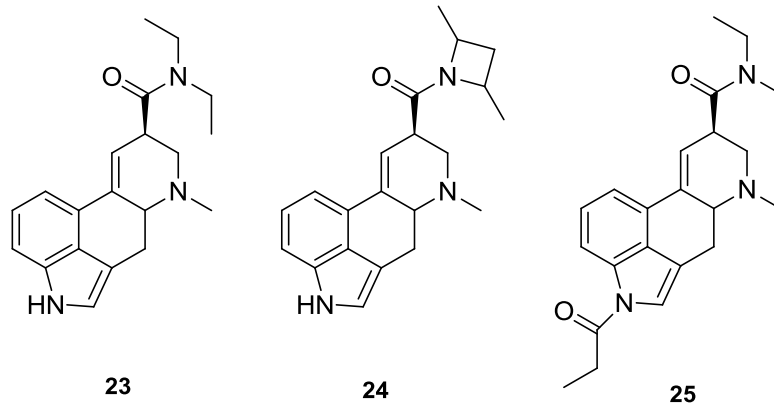
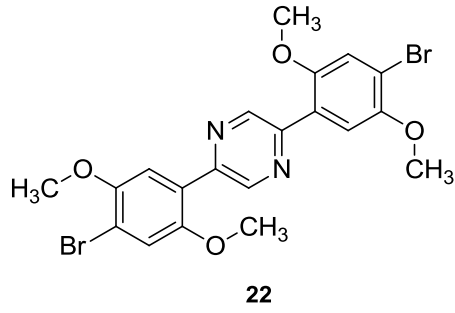
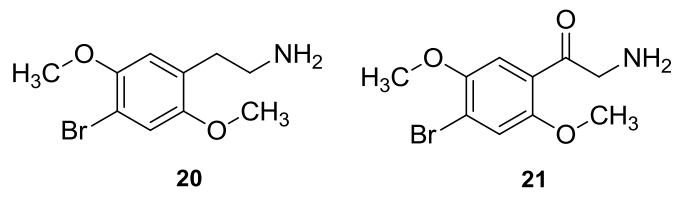
4. CONCLUSION

From this review, the dire lack of pharmacological data available on these substances was obvious as was their popularity of use among psychonauts. A trend observed in most of the

compounds selected was their origin from old patents and papers on drug candidates which have not been developed further and which can be found online. Not only was the wealth of scientific information exploited by research chemical vendors themselves, but also actively discussed by psychonauts on drug fora even before the appearance of these NPS on the legal high market as is the case of bk-2C-B or lefetamine-based drugs. As such, it makes sense to consider the content on drug fora as well as previous or abandoned drug candidates to try and spot upcoming NPS. Furthermore, it should be noted that trip reporting on drug fora provides a wealth of information on the effects of NPS on the human body albeit by subjective views, and may also be a trend-setter in the development of future NPS. Another interesting issue was that NPS were discussed not only as recreational drugs but for their therapeutic value in treating conditions such as depression and anxiety, for instance, in the case of ephedrine. Of concern, is the very strong addiction potential of some drugs reviewed such as diphenidine or the potentially hazardous and easily overdosed psychostimulants and psychedelics and the ease of access to them. It should be noted that acute toxicity cases requiring hospitalization and even deaths ensuing from NPS use have also been well reported.

In any case, NPS which represent a largely unknown and rapidly expanding territory in an era of globalization and instantaneous access to information through the World Wide Web, will not be easy to conquer nor overlook. It may not be completely surprising if the next generation of antidepressants, psychotherapy counselling aid or the next schizophrenia-modelling drugs were to come from NPS nor would it be surprising if the next addictive or crime-facilitating drug were to come from the NPS as well.





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