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ORIGINAL ARTICLE

# Self-medication with Novel Psychoactive Substances (NPS): a Systematic Review

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**Abstract**
Currently, novel psychoactive substance (NPS) use presents a challenging issue for authorities. To effectively tackle the use of NPS, a deeper understanding of the motivations of those who use NPS is required. Evidence suggests that a subset of NPS users declare their use as 'self-medicating'; however, there is a paucity of research in this area. The aim of this review is to provide an overview and synthesis of the research concerning self-medication with novel psychoactive substances (NPS). Seven databases (EMBASE, MEDLINE, APA PsychInfo, Global Health, PubMed, Scopus, and Google Scholar) were searched using a search strategy compromising 600 + NPS terms, yielding 3563 articles, 24 of which met the search criteria. Two independent reviewers screened the articles and appraised the quality of the included studies. The results were synthesised using a narrative synthesis approach. We identified 22 NPS being used for self-medication. We found that (1) self-medication with NPS occurs mainly for anxiety, depression, and ADHD; (2) links between cluster headaches, the use of psychedelic NPS, and anxiety and novel benzodiazepines were evident; (3) novel benzodiazepine use by young individuals represents particular concern. There is a need for greater knowledge within healthcare professions concerning self-medication practices with NPS. Primary qualitative research is needed to address the underlying motivations behind this phenomenon.

**Keywords** Novel psychoactive substances (NPS) · Self-medication · Psychedelics · Depression · Anxiety · Substance use

The United Nations Office on Drugs and Crime (UNODC) defines novel psychoactive substances (NPS) as 'substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat' (United Nations Office On Drugs And Crime, 2013). As a category, NPS are constantly in a state of flux,

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with new substances becoming available on the drug market each year. In this respect, a 'new' or 'novel' substance may have existed for a significant amount of time, but only just become popular on the drug market. Some have expressed a desire to detach legality from the definition of NPS given the transient and highly heterogenous nature of NPS substances (Peacock et al., 2019; Potter & Chatwin., 2017).

NPS span several different substance classes including synthetic cannabinoids, cathinones, opioids, psychedelics, and benzodiazepines, often mirroring classic street drugs (Shafi et al., 2020). Currently, novel benzodiazepine use has been highlighted as an area of significant concern (Advisory Council on the Misuse of Drugs, 2016; Høiseth et al., 2016; Jolliff, 2020; Moosmann et al., 2015; Pendkar et al., 2019). The continued appearance of NPS remains a complicated issue for governments. In 2021, the European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction, 2022) identified 52 novel compounds, raising the total number of currently monitored NPS above 880. The constant evolution of NPS is a significant issue for authorities (Baumeister et al., 2015) and often means that pharmacological profiles of emerging substances are inadequately understood. Initially, governments would attempt to ban newly emerging chemicals as they arise (Seddon, 2014); however, producers would alter the NPS substance and quickly circumvent the legislation, leading to a costly and time-consuming game of 'cat-and-mouse'. In response, many countries such as the UK and Poland introduced 'blanket ban' legislation (Neicun et al., 2019). This approach has attracted criticism for its potential to ban benign or useful substances and overall the effectiveness has been unclear (Deen et al., 2021; Deligianni et al., 2020; Humphries, 2022; European Monitoring Centre for Drugs and Drug Addiction, 2022; Reuter & Pardo, 2017; Webb et al., 2019). The globalised nature of NPS use means that the issue remains complex (Sedefov et al., 2013) and more recently has been complicated by the emergence of the dark web, affording NPS a different route to proliferate (Hill, 2020).

Estimates for the prevalence of NPS use are low (Palamar et al., 2015); however, research has suggested that use may be increasing disproportionately in young people and those with mental health issues (Neicun et al., 2021). Therefore, adequately defining the reasons individuals choose to use NPS remains paramount. Previously, motivations for NPS use have been shown to include self-exploration, an interest in novel pharmacology, enhanced social bonding, pleasure, convivence, legality, and perceived safety (Andersson & Kjellgren, 2017; Martin & Anette, 2016; Soussan & Kjellgren, 2016; Soussan et al., 2018a).

Research has indicated that some individuals using NPS define their use as self-medication (Martin & Anette, 2016; Mason & Kuypers, 2018; Soussan et al., 2018b). Self-medication can be defined as 'choosing and using substances to treat self-diagnosed symptoms and diseases without consulting a doctor'. This worldwide phenomenon is practiced by most to some degree, with governments beginning to encourage self-medication practices for minor issues (Porteous et al., 2005), highlighting the active role individuals can take in their own healthcare (Bennadi, 2013). Self-medication also presents the risk of significant adverse effects, such increased antibiotic resistance (Pagán et al., 2006).

Self-medication can include a range of behaviour such as the use of illicit substances or non-prescribed medication, the misuse of prescribed medication, or the use of supplements. Estimating prevalence can therefore be difficult, and estimates vary greatly (2–92%) (Shehnaz et al., 2014); however, those who are young (Fetensa et al., 2021) or with unmet health issues (Harris & Edlund, 2005; Smith et al., 2021) have been shown to be more likely to self-medicate. Evidence suggests that self-medication with drugs and alcohol is commonplace in the general population (Bolton et al., 2009; Robinson et al., 2009a, 2009b). Almost a quarter (24.1%) of those suffering from mood

disorders self-medicate (Bolton et al., 2009) and higher rates of NPS use have been shown in individuals with psychiatric disorders (Jones et al., 2016; Martinotti et al., 2014). These behaviours could be explained through the self-medication hypothesis (SMH) (E. J. Khantzian, 1985; Edward J. Khantzian, 1997, 2003).

Literature focusing on self-medication with NPS is currently scarce; however, indications from online discussion boards like Bluelight (2023) or Reddit (2023) implicate the discussion of a multitude of NPS in the self-medication of various disorders such as ADHD (Anonymous, 2022, 2023), anxiety, depression, and pain. Understanding this gap in the literature is fundamental in providing a basis for future research. Accordingly, an in-depth systematic review was conducted to understand what is currently known regarding self-medication with NPS. The present review could help healthcare professionals understand which NPS are being used to self-medicate, which disorders are likely to be self-medicated, and which populations may be vulnerable.

## Methods

The current review involved structured and systematic searches for original peer-reviewed literature. It was registered (CRD42022325244) with PROSPERO and guided by the 'enhancing transparency in reporting the synthesis of qualitative research' (ENTREQ) protocol (Appendix S2) (Tong et al., 2012). This was a deviation from the registered protocol as this was subsequently identified as better suited. No current or ongoing systematic reviews on self-medication with NPS were identified.

### Research Question

This systematic review aimed to assess which NPS were being used to self-medicate, which disorders were being self-medicated, and what motivations underlie self-medication practices. Our research question was informed using an adapted SPIDER model. The SPIDER model was adapted to inform the parameters of the study, including Sample (anyone using NPS for self-medication), Phenomenon of Interest (self-medication), Design (any), Evaluation (NPS used, experiences), and Research type (primary research).

### Definitions

NPS were defined according to the UNODC definition, excluding the non-medical use of prescription substances. Additionally, we focused on synthetic NPS and excluded plant-derived substances such as kratom, for which systematic reviews have already been completed. This allowed for a more directed discussion. Individuals were deemed to be self-medicating if they reported 'using NPS substances to treat a self-diagnosed or professionally diagnosed disorder or symptoms or this disorder without consulting a doctor'. Research involving those within homeless and prison populations was excluded.

### Search Strategy and Eligibility Criteria

A pilot search was conducted in May 2022. Our search strategy was informed by a semi-comprehensive list of 600 + NPS, combined with several 'self-medication' synonyms using Boolean operators (Appendix 1). Seven databases (EMBASE, MEDLINE, APA PsychInfo, Global Health, PubMed, Scopus, and Google Scholar) were searched between 04/04/22 and 05/02/23. The search was supplemented by cross-checking references and grey literature from relevant institutions and organisations including Gov.uk, Office of National Statistics, NDTMS, EMCDDA, and GDS. Studies not written in English, in vitro, or animal studies were excluded. There were no restrictions on date, age, or gender.

### Screening, Selection, and Data Extraction

Abstract screening and full-text reviews were conducted by two independent reviewers (TH, RP), with discrepancies discussed and resolved by a third reviewer if necessary. A total of 24 eligible articles were included in the review after removing duplicates and screening. General study characteristics, population characteristics, and NPS data were recorded (Table 1).

### Quality Assessment

The included studies were subject to quality assessment using the MMAT and JBI checklists (Hong et al., 2018; The Joanna Briggs Institute, 2017). No articles were excluded.

### Data Synthesis

A narrative synthesis was conducted using a deductive approach to address the research questions. The synthesis describes the study and population characteristics (Table 1), as well as exploring motivations of individuals to self-medicate with NPS and outcomes of use.

## Results

### Study Characteristics

The literature search yielded a total of 3563 articles and six were identified manually (Fig. 1). After excluding duplicates and screening, 24 were included. These represented a diverse array of research designs, including thirteen case reports, five surveys, four content analyses, and two interviews. Study demographics were international, with data collected from the USA, UK, Poland, Canada, France, Italy, Australia, and Sweden. The study period was from 2002 to 2022.

**Table 1** Characteristics and key findings of included studies ($n = 24$)

| Ref. | Study design (country) | Population | Mean age (YRS + SD) | Gender | Disorder self-medicated | NPS used | JBI/MMAT score | Notes |
|---|---|---|---|---|---|---|---|---|
| Case reports | | | | | | | | |
| Bailey et al. (2015) | Case report (UK) | $n = 1$ | 21 | Male | Paranoia<br>Substance-induced anxiety | Etizolam | 100% | Individual experiencing anxiety due to ethylphenidate use, took 3 mg of etizolam |
| Samokhvalov et al. (2013) | Case report (Canada) | $n = 1$ | 35 | Male | Anxiety<br>Depression<br>Dysphoria<br>Alcohol cravings | Phenibut<br>Phenazepam | 100% | Patient treated with 10 mg of baclofen for each gram of Phenibut |
| Menard et al. (2018) | Case report (France) | $n = 1$ | 33 | Male | ADHD | 3–4-CTMP | 89% | Patient experienced side effects of anxiety and agitation. Treated with methylphenidate |
| Maskell et al. (2016) | Case report (US) | $n = 1$ | 29 | Male | Chronic foot pain | Methoxetamine | 89% | Individual had ingested 5–10 mg every four hours for 5 days |
| Striebel et al. (2017) | Case report (US) | $n = 1$ | 29 | Male | Anxiety<br>Substance withdrawal | Methoxetamine | 100% | MXE used to promote feelings of calm and help him deal with the PTSD stressors, preferred to illicit ketamine |

**Table 1** (continued)

| Ref. | Study design (country) | Population | Mean age (YRS + SD) | Gender | Disorder self-medicated | NPS used | JBI/MMAT score | Notes |
|---|---|---|---|---|---|---|---|---|
| Pendkar et al. (2019) | Case report (US) | $n = 1$ | 31 | Male | Anxiety | Etizolam | 67% | Individual had a seizure after stopping etizolam use for 1 week when worried about dependence |
| Peterkin et al. (2022) | Case report (US) | $n = 1$ | 38 | Female | Anxiety<br>Opioid withdrawal<br>Benzodiazepine withdrawal | Phenibut<br>Gabapentin | 100% | Notes COVID-19 as a motivation for deciding to self-treat |
| Sommerfeld-Klatta et al. (2020) | Case report (Poland) | $n = 1$ | 26 | Female | Insomnia | Clonazolam | 100% | Likely given the NPS by her boyfriend |
| Pope et al. (2018) | Case report (Australia) | $n = 1$ | 32 | Male | Opioid withdrawal | Clonazolam<br>Flubromazolam | 100% | History of multiple sclerosis, substance use and bipolar disorder. Substances purchased through the internet |
| Giampreti et al. (2022) | Case report (Italy) | $n = 1$ | 17 | Male | Anxiety | Clonazolam | 100% | Used a self-made solution of 250 mg clonazolam (darknet) and 250 ml propyl glycerol (amazon), using information on the internet |

**Table 1** (continued)

| Ref. | Study design (country) | Population | Mean age (YRS + SD) | Gender | Disorder self-medicated | NPS used | JBI/MMAT score | Notes |
|---|---|---|---|---|---|---|---|---|
| Rod et al. (2018) | Case report (US) | $n = 1$ | 47 | Male | Alcoholism | Phenibut | 78% | History of polysubstance abuse (alcohol, benzodiazepines), seizures, anxiety, and depression. Presented to the emergency department (ED) after drinking a quart of vodka the previous night |
| Basile et al. (2022) | Case report (US) | $n = 1$ | 38 | Male | ADHD | N-methyl-cyclazodone | 78% | Purchased 'pure' powder online and had consumed a total of ~ 5 g mixed in water. He also had prescriptions for fluoxetine and aripiprazole for bipolar disorder. Sought evaluation for uncontrollable body movements |

**Table 1** (continued)

| Ref. | Study design (country) | Population | Mean age (YRS + SD) | Gender | Disorder self-medicated | NPS used | JBI/MMAT score | Notes |
|---|---|---|---|---|---|---|---|---|
| Ghani et al. (2021) | Case report (US) | $n = 1$ | 32 | Male | Anxiety | Phenibut Etizolam | 78% | Started on Depakote for agitation, a Valium taper for suspected benzodiazepine withdrawal and prevention of seizures, Seroquel for delirium, and baclofen for suspected GABAergic withdrawal symptoms |
| Surveys/questionnaires | | | | | | | | |
| Mason & Kuypers (2018) | Online Questionnaire (International) | $n = 1967$ | 25.9 | Males (79%) Female (20%) Other (1%) | Depressive disorders (31.8%) Anxiety disorders (21.1%) ADHD/ADD (6.2%) | Hallucinogens (34.7%) Cathinones (13.5%) Cannabinoids (8.0%) | 100% | *No data for link between which specific NPS used and which disorder self-medicated in overall sample |

**Table 1** (continued)

| Ref. | Study design (country) | Population | Mean age (YRS + SD) | Gender | Disorder self-medicated | NPS used | JBI/MMAT score | Notes |
|---|---|---|---|---|---|---|---|---|
| Hutten et al. (2019) | Online Questionnaire (International) | $n = 1062$* *diagnoses | 28.9 (SD = 10.1) | Male (74.6%) Female (25.4%) | Depressive disorders (72.7%) Anxiety disorders (55.6%) ADHD/ADD (37.2%) | 1P-LSD (13.1% of those who self-medicated $N = 68$) | 100% | Psychedelics were used to self-medicate by 520 (57.7%) of those with a mental diagnosis |
| Soussan & Kjellgren (2016) | Online survey (International) | $n = 619$ | 26.7 (SD = 9.47) | Males (82.7%) Females (17.3%) | 'Coping with life problems: Pain, boredom, emotions, anxiety, sleep' | NPS hallucinogens (25%) NPS stimulants (36%) NPS dissociative (50%) NPS GABA (78%) Synthetic cannabinoids (48%) NPS opioids (69%) | 80% | Methoxetamine most used with 73% planning to reuse *Details of self-medication elicited in Soussan et al, 2018a, 2018b |
| Soussan et al. (2018a) | Online survey (International) | $n = 613$ | Males 27.2 (SD = 9.3) Females 29.8 (SD = 10.1) | Male 512 (83.5%) Females 101 (16.5%) | Anxiety Depression Pain Migraine ADHD | NPS stimulants for ADHD Benzodiazepines for pain/stress 4-Aco-DMT for severe migraine Novel psychedelics for depression/migraine | 100% | *Specific drugs used not mentioned for some instances |
| Di Lorenzo et al. (2016) | Questionnaire (International) | $n = 54$ | N/A | Males 35 (64.8%) Females 19 (35.2%) | Cluster headaches | LSA (d-lysergic acid amide) 12/54 | 100% | 75% of those choosing to use LSA described the self-treatment as effective |

**Table 1** (continued)

| Ref. | Study design (country) | Population | Mean age (YRS + SD) | Gender | Disorder self-medicated | NPS used | JBI/MMAT score | Notes |
|---|---|---|---|---|---|---|---|---|
| Interviews | | | | | | | | |
| Gittins et al. (2018) | Qualitative interviews (UK) | $n = 12$ | 37 (SD = 9) | Male (100%) | Leg pain (P12) | Synthetic cannabinoids | 100% | *Several indications of NPS being used to cope, however not included as self-medication examples |
| Johnstad (2018) | Qualitative interviews (International) | $n = 21$ | Median age early 30s | Male (100%) | Depression<br>Social anxiety<br>Manic bipolar<br>Suicidal ideations | 2,5-dimethoxy-4-methylamphetamine (DOM) (microdose study) | 100% | *Specific experiences with DOM not mentioned. *Some issues with dosages |
| Content analysis | | | | | | | | |
| Abouchedid et al. (2018) | Internet snapshot (International) | $n = 333$ (*forum posts*) | N/A | Non-specified | Anxiety (134 mentions) | Diclazepam (23.9%)<br>Pyrazolam (53.0%)<br>Flubromazepam (10.2%) | 100% | Other uses include management of stimulant withdrawal (diclazepam, 16.1%; pyrazolam, 10.1%; flubromazepam, 9.2%) |

**Table 1** (continued)

| Ref. | Study design (country) | Population | Mean age (YRS + SD) | Gender | Disorder self-medicated | NPS used | JBI/MMAT score | Notes |
|---|---|---|---|---|---|---|---|---|
| Anderssson et al. (2017b) | Forum discussion analysis (International) | *n* = 32 *(topics)* | N/A | N/A | Migraine and cluster headaches | 1P-LSD<br>AL-LAD<br>4-AcO-MET<br>4-AcO-DMT<br>4-HO-MiPT<br>4-HO-MET<br>4-HO-DMT<br>5-MeO-DALT<br>5-MeO-MiPT | 100% | No severe adverse effects were reported, but there were some accounts of discomfort and some possible cases of remaining anxiety |
| Andersson & Kjellgren (2017) | Forum discussion analysis (Sweden) | *n* = 122 *(users)* | N/A | N/A | Insomnia<br>Anxiety | Flubromazolam | 100% | N/A |
| Andersson & Kjellgren 2019) | YouTube analysis (International) | *n* = 34 | N/A | Males 24 (70.6%)<br>Females 10 (29.4%) | Depression<br>PTSD<br>ADHD/ASD<br>Bi-polar<br>Anxiety<br>Problematic stuttering<br>Dyspraxia<br>Cluster headaches | 1P-LSD<br>4-Aco-DMT<br>5-MeO-DALT | 100% | *Microdose study. Issues with dosage being too high and complex relationship with anxiety |

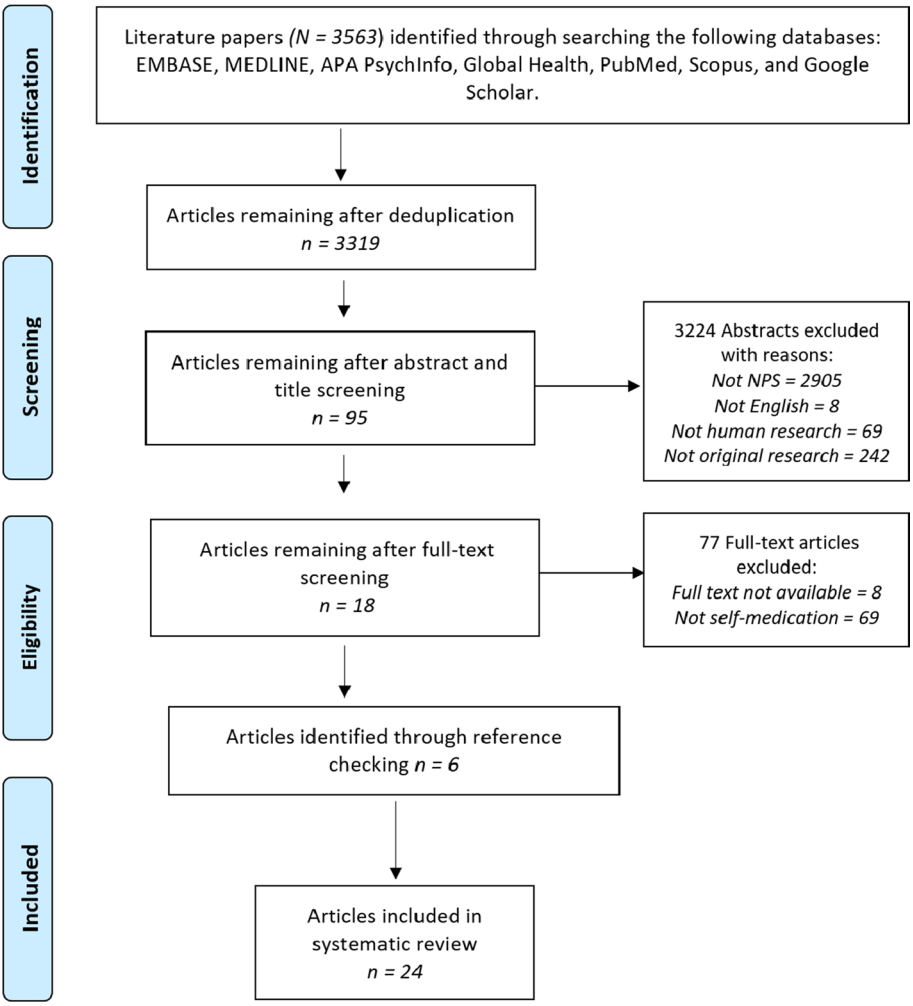


**Fig. 1** PRISMA flow diagram

## Substances Identified

The study highlighted a range of novel psychedelics including 1P-LSD, d-lysergic acid amide (LSA), AL-LAD, 4-AcO-DMT, 4-AcO-MET, 4-HO-MiPT, 4-HO-MET, psilocin, 5-MeO-DALT, 5-MeO-MiPT, and DOM. Novel benzodiazepines discussed for self-medication included clonazolam, etizolam, phenazepam, diclazepam, pyrazolam, flubromazepam, and flubromazolam. Methoxetamine was the only novel dissociative identified. Finally, we highlight the novel stimulants 3,4-CTMP and n-methyl-cyclazodone, as well as the GABAergic substance Phenibut.

### Demographics

Considering the case report data, the population of individuals self-medicating with NPS had an average age of 31 years old and was predominately male (85%). Survey data showed, on average, that males constituted 78% and females 22% of the population. The included interview studies had a 100% male population. No comparison was possible for content analysis.

### Disorders Represented

The majority of the studies (15) suggested NPS being used for the self-medication of anxiety-related disorders, followed by depressive disorders (6), ADHD/ASD (6), substance use disorders (4), chronic pain (3), migraines/cluster headaches (3), and PTSD (1). Other disorders represented in self-medication included insomnia (2), paranoid delusions, dyspraxia, and stuttering (1).

## Which NPS Are Being Used for Self-medication?

### Novel Psychedelics

Articles identified suggested that novel psychedelics were used predominately for the treatment of severe migraines or cluster headaches (CH), with many demonstrating potentially positive effects (Andersson & Kjellgren, 2019; Andersson et al., 2017a; di Lorenzo et al., 2016; Soussan et al., 2018a, 2018b). Andersson et al. (2017a) highlight the use of tryptamines such as 4-HO-MET, 4-AcO-DMT, 4-HO-MiPT, and 5-Meo-MiPT for the treatment of CH attacks, with AL-LAD also mentioned as an effective treatment option. Some data suggested that tryptamines were especially effective in stopping the recurrence of cluster cycles. Specifically, the use of psilocybin analogues 4-AcO-DMT and 4-AcO-MET demonstrated acute efficacy in aborting CH attacks in as little as 30 min. For some, synthetic tryptamines were preferred over organic substances, as their effects were considered less 'chaotic', and easier to deal with.

Further, Andersson et al. (2017a) provide evidence for the use of LSA seeds, found in plants like *Rivea corymbosa*, *Argyreia nervosa*, and *Ipomoea tricolor*, for the treatment of CH. Fifty seeds were recommended for a full preventative dose or less than 25 with more frequent dosing. Seeds were typically ingested whole, but there were reports of individuals extracting the active substances. LSA seeds were seen to be less efficacious than LSD or psilocybin. Potency variability and ineffective extraction were issues, as well as a tendency to underdose. *Rivea corymbosa* seeds were considered the most effective of the four varieties studied.

Evidence from Di Lorenzo et al. (2016) corroborates the use of novel psychedelics in the treatment of CH. In this sample, 29 of 54 suffered chronic and treatment-resistant cluster headaches. Twelve reported the use of LSA seeds. Although efficacy data is limited, the study indicated prophylactic effects from a variety of psychedelic substances, even with doses often sub-hallucinogenic and infrequent (three times a year).

Several novel psychedelics were also discussed in relation to depression. In research by Mason & Kuypers (2018), half of respondents (900) declared to have or have suffered

from a mental health disorder, with 77% (698) of them diagnosed by a professional. This represented 31.8% (625) of the total sample indicating a depressive disorder. In 81% of total diagnosed cases (436), individuals attempted to treat symptoms with psychedelics and 34.7% (682) declared the use of a psychedelic NPS.

### Novel Stimulants

Findings from the review suggest the use of novel stimulants predominately to self-medicate Attention Deficit Hyperactivity Disorder (ADHD). Menard et al. (2018) document a 33-year-old male with a history of cocaine dependence who discontinued his prescribed medication and instead used the novel stimulant 3,4-CTMP to alleviate symptoms of ADHD, which he obtained from the dark web. This resulted in the development of anxiety and agitation, leading to the individual's psychiatrist re-prescribing methylphenidate. Similarly, a case study by Basile et al. (2022) reports the hospitalization of a 38-year-old man who self-treated his ADHD with the novel stimulant n-methyl-cyclazodone, resulting in uncontrollable palpitations. Soussan et al., (2018a, 2018b) also documented similar practices of self-medication with stimulants, although the specific examples were not available.

### Novel Benzodiazepines

Seven case studies involving novel benzodiazepines were included, consisting of three for etizolam, three for clonazolam, and one for phenazepam. Sommerfeld-Klatta et al. (2020) report the case of a young female (55 kg) ingesting 10 mg (powder) of clonazolam acquired from her boyfriend to help with insomnia, following her suffering with acute bronchitis. After presenting to the hospital deeply unconscious, the woman was treated and released after 8 days. Giampreti et al. (2022) then describe clonazolam use in a younger individual. They report a 17-year-old patient with a past history of self-medicating anxiety with alprazolam. The individual was using a clonazolam solution created using 250 mg clonazolam (purchased on the darkweb) and 250 mL propyl glycol (bought on Amazon). At admission, he was heavily sedated. He was discharged 24 h after treatment. Further, Pendkar et al. (2019) present an individual self-medicating with etizolam for social anxiety before discontinuing use and experiencing a tonic–clonic seizure. In instances, novel benzodiazepines were used to reduce substance-induced anxiety experienced by stimulant use (Bailey et al., 2015). The use of novel benzodiazepines for anxiety was common and Ghani et al. (2021) describe a 32-year-old male self-medicating anxiety with tianeptine, etizolam, and phenibut. After presenting to the emergency department he stabilised. During his stay, he was agitated, delirious, and experienced visual hallucinations. He was discharged after 10 days. In some cases, the NPS substance is not known by the individual self-medicating. Pope et al. (2018) report the case of a 32-year-old who was admitted with a Glasgow Coma Score of 10 after taking three 'PEZ-like pills' to help cut down on his methadone use. These were later determined to be clonazolam and flubromazolam.

Finally, our review included two content analyses exploring novel benzodiazepine use. Abouchedid et al. (2018) highlight the use of diclazepam, pyrazolam, and flubromazepam for anxiolysis. Most (87.1%) of the subjects used benzodiazepines to self-treat anxiety symptoms, with pyrazolam being the most popular (53%). The use of flubromazolam was also evident with Andersson & Kjellgren (2017) analysing the internet discussion from 122 internet users and discussing its use for anxiety and insomnia.

### Novel Dissociatives

The current review identified two case reports involving self-medication with the novel dissociative methoxetamine (MXE) (Maskell et al., 2016; Striebel et al., 2017). Maskell et al. (2016) discuss the use of MXE by a 29-year-old male brought to the emergency department for altered mental status. After recovering, the patient admitted to sampling a new bag of MXE by dipping his finger in, prior to onset of symptoms. Further, he reported using MXE for its analgesic effects to treat chronic foot pain from a previous surgery. He had ingested 5–10 mg every 4 h for 5 days prior to presentation. In addition, Striebel et al. (2017) describe the case of a 29-year-old US veteran with chronic PTSD (service-connected) and a history of heavy polysubstance use. Four years after enrolling on the opioid therapy program (OTP), he disclosed that for the last year, he had been injecting MXE obtained from an online source, progressing up to using 50–70 mg daily. He believed that the MXE relieved the distress and dysphoria of withdrawal. The authors propose that he sought out the MXE to reduce the fear and anxiety associated with PTSD and psychosis.

### Phenibut

Four studies indicated the use of gamma-aminobutyric acid (GABA) analogue phenibut. Uses for phenibut included self-treating anxiety (Ghani et al., 2021) and the management of withdrawal symptoms from opioid, benzodiazepine (Peterkin et al., 2022), and alcohol use (Rod et al., 2018; Samokhvalov et al., 2013). Polydrug use was evident in most cases. Individuals using phenibut appeared older (32–47) and usually presented with withdrawal symptoms from phenibut after using for a prolonged period.

## Motivations

The motivations for using NPS were influenced by various factors. Reasons cited for self-treating included ease of acquisition with many purchasing online, abundant availability, low prices, a replacement for an unavailable substance, and lower perceived risk. In some cases, individuals were not aware they were using an NPS.

Several studies have documented the ease in purchasing NPS online, through both the clear web and dark web (Menard et al., 2018). This has offered individuals benefits such as the ability to 'dose accurately', as buying from online vendors allows for defined amounts. However, not all substances purchased may be what is being advertised. Additionally, identifying the substance purchased can be a challenge, with some users only able to provide generic labels (e.g. spice). Research has suggested NPS substances to match user expectation in around 63% of cases (Simonis et al., 2020), but as demonstrated in this review, NPS users may not be aware of what they are taking (Pope et al., 2018), posing significant risks.

Whilst legality was a motivator for some, many individuals with treatment-resistant disorders such as depression or CH likely disregarded the legal status of NPS, reaching out to NPS as a last resort effort. For example, one individual noted, *I have tried everything with no success, including ergot derivatives, opiates, anticonvulsants, NSAIDs…* (Andersson et al., 2017b). Others may choose NPS due to dissatisfaction with conventional treatments (Simonis et al., 2020.), whilst underestimating the legal consequences and overestimating the safety of NPS (Di Lorenzo et al., 2016).

### Outcomes

The outcomes of individuals who chose to self-medicate with NPS varied based on the pharmacological category of the substance used. For example, benzodiazepines were more strongly associated with withdrawal and dependence (Pendkar et al., 2019), although outcomes were seen to be dose-dependent (Andersson & Kjellgren 2017). Comparatively, psychedelic NPS were well tolerated and had low levels of perceived adverse effects. Mason & Kuypers (2018) found that 81% of individuals found psychedelic self-treatment to be effective, compared to 49% for clinical treatment. Evidence for the efficacy of psychedelics in the treatment of depression and CH was relatively strong, with some individuals describing relief for the first time in a prolong period (Andersson et al., 2017b). However, results for the treatment of anxiety with psychedelics were mixed, with instances of increased anxiety (Andersson & Kjellgren 2019).

## Discussion

### Key Findings

To the best of our understanding, this is the first article reviewing the use of NPS to self-medicate a multitude of disorders. It focuses on evidence from case reports, surveys, and content analysis, with the majority highlighting novel psychedelics.

We explored the use of 22 NPS for a multitude of disorders. The self-medication of anxiety, depression, and ADHD was most frequent and may reflect rapidly rising rates of depression and anxiety across Western countries (Bell & Blanchflower 2019; Kessler et al., 2012). Prevalence rates are increasing (Liu et al., 2020) and ethnic minorities and those of low income are over-represented (Miranda et al., 2008). Many individuals are experiencing treatment-resistant disorders and unmet needs are outpacing available care (Hoge et al., 2018). A lack of treatment is resulting in an increasing burden of preventable health issues (Figueroa et al., 2020). In lieu of treatment, our data suggests a subset of individuals may consider self-treatment with alternative substances.

Whilst unable to give a mean age for the total sample given the heterogeneity of data, the average mean age of participants included within case reports was 31 years. This is somewhat in line with research suggesting the typical NPS user to be younger (Vardakou et al., 2011; Werse & Morgenstern 2012). Additionally, several studies indicated a population with a middle-income background. This resonates with the behavioural economic theory of self-medication (Pagán et al., 2006), suggesting more affluent individuals may supplement their healthcare with self-medication. However, given the small sample size, we cannot make any definitive statements from the current review.

Several novel psychedelics were highlighted in the current review and appeared to be well tolerated with issues mainly surrounding incorrect dosages. Whilst psychedelic use has remained stable over time (Faden 2006), recent data suggests that the adolescent use of substances like LSD and ketamine is rising (Palamar et al., 2021; Yockey et al., 2020). For individuals suffering from treatment-resistant disorders, there may be an increasing willingness to experiment with novel psychedelics such as 1P-LSD, which are commonly perceived as legal alternatives.

Some individuals described the potentially beneficial effects of novel psychedelics in self-treating depression and CH, notably allowing individuals with CH to break the cluster

cycle after a prolonged period. Experiences with anxiety were more mixed, mirroring findings in the literature (dos Santos et al., 2018; Muttoni et al., 2019; Schimmel et al., 2022). Therapeutic options should be explored further, and data here suggests that LSA, 1P-LSD, and 4-AcO-DMT may have a good safety profile, with minimal dosing required. Online users encouraged others to find a specific substance that worked for them, suggesting variation in individual efficacy (Andersson et al., 2017a).

Some research focused on microdosing (Johnstad 2018). When considering dose, differences in NPS used were apparent (Hutten et al., 2019) with 1P-LSD commonly used for microdosing, but not for a macro dose. Possibly, the NPS nature of 1P-LSD lends itself to microdosing, with individuals being able to purchase microdose tabs via the dark web and clear websites (Dutchcitysales 2023), and for some, it may be seen as a legal alternative to LSD. Overall, psychedelic NPS might provide some therapeutic value; however, no definitive remarks can be made from the heterogenous sample of this review. Despite this, the discussion around the treatment of CH appears compelling. As psychedelic treatment and microdosing become more mainstream, individuals may look towards NPS alternatives to established psychedelics and this should be monitored. Care should be taken in extrapolating findings further, given the largely unstudied pharmacological effects of many of these substances.

Comparatively, novel benzodiazepine use demonstrated potential significant adverse effects. Whilst long-term benzodiazepine use for the treatment of anxiety is not clinically recommended, research has demonstrated that benzodiazepine use appears to be prevalent in the real-world treatment of anxiety-related disorders across the globe (Cunningham et al., 2010; Huerta et al., 2016; Moylan et al., 2012; Takeshima et al., 2016). The current review highlights concerning trends within the NPS benzodiazepine market, including evidence of them being used as adulterants due to their inexpensive nature, which has been documented in the toxicological literature (Laing et al., 2021; Lucie 2022). Additionally, the case report by Giampreti et al. (2022) provides particular concern given the young age of the individual and the observed ease of access. These apprehensions are echoed by others with benzodiazepine use increasing in young people (Vice 2023), exemplified by the recent death of a 14-year-old who thought he was using Xanax but was in fact ingesting clonazolam (Moore 2022). Further, Sommerfeld-Klatta et al. (2020) illustrate how NPS may be spreading to those with less pharmacological knowledge. In this case report, the individual had no prior experience with novel substances and was likely given the clonazolam powder by her boyfriend. This appears particularly dangerous when one considers the low active dose and the large amount of powdered clonazolam in the hands of someone pharmacologically naive. Potent novel benzodiazepines could pose a significant risk of overdose in those with less knowledge and could have significant detrimental health consequences. This issue should be closely monitored.

Finally, the novel benzodiazepine class is pharmacologically varied, with doses and half-life durations varying dramatically (Abouchedid et al., 2018), compounding the dangers of self-medication, particularly if an individual is mis-sold a substance. Novel benzodiazepines also demonstrate issues surrounding dependence, withdrawal, and toxicity when considering polydrug use. Within 25 instances in the UK where a novel benzodiazepine was implicated in the cause of death between 2013 and 2016, all were in conjunction with other drugs, over half of these being detectable opiates (Advisory Council on the Misuse of Drugs, 2016). In comparison to other NPS, benzodiazepines display a high propensity for abuse (Soussan and Kjellgren 2016).

Despite the recent popularity of dissociatives such as ketamine for the treatment of depression (Bahji et al., 2021; Krystal et al., 2019), our review included only two examples

of novel dissociative use for self-medication. Both involved the use of MXE, one for the treatment of PTSD-related anxiety (Striebel et al., 2017) and one for the treatment of chronic foot pain (Maskell et al., 2016). Examples in the literature of evidence regarding the anxiolytic effects of MXE are sparse. With increasing interest in MXE for its antidepressant effects (Botanas et al., 2017), we could possibly see an increase in research relating to its anxiolytic effects. Interestingly, whilst undertaking the review, there were instances of ketamine being used to self-medicate (Rolando & Beccaria 2019; Simonis et al., 2020; Ozgen & van den Brink 2021). Some discussions online indicate that individuals may be trying to emulate research protocols, using ketamine to self-treat depression (Anonymous, 2017), and this requires deeper investigation. We also outline the potential for dosing errors and the dangers of non-standardised designer drug manufacturing (Maskell et al., 2016). Incorrect dosages remain a danger for self-medication, especially considering that several substances have active effects in the microgram range.

The use of the novel stimulants 3,4-CTMP and N-methyl-cyclazodone was highlighted for the self-treatment of ADHD (Basile et al., 2022; Menard et al., 2018). Currently, there is a paucity of research investigating 3,4-CTMP; however, an effort has been made to characterise it pharmacologically (Davidson et al., 2018) and there is evidence of its use for 'chemsex' (Marillier et al., 2017). Reports suggest it to be more 'cocaine-like' than 'amphetamine-like', increasing dopamine levels more potently than methylphenidate (Davidson et al., 2018) and suggesting a high potential for abuse. This case report demonstrates the willingness of individuals to self-medicate despite having access to a healthcare professional. Similarly, there is scarce data surrounding the human use of N-methyl-cyclazodone. Only two studies demonstrate stimulant use in our review; however, in an observation of the subreddit 'r/researchchemicals', stimulants such as 2-FMA and 4F-MPH are frequently mentioned for self-medicating ADHD ("https://www.reddit.com/r/researchchemicals"), representing a gap in the literature.

Some have suggested that a blurring of drug categories has occurred over the last decade, with many prescription drugs used recreationally and prohibited substances being investigated for their therapeutic uses (Davidson & Schifano, 2016). This review supports that notion and suggests that a subset of individuals may be taking medication regimes into their own hands, and this may be linked to a dissatisfaction of conventional treatments. The pharmacology of many substances discussed is poorly understood making their use precarious. A better understanding of NPS is required by healthcare professionals and care should be taken to appropriately identify any substances an individual may be using.

## Limitations

This review is not without limitations. One major limitation relates to the fluidity of the NPS category, which constantly evolves and encompasses a wide range of substances, presenting challenges in accurately identifying and categorising NPS. New NPS may also have street names which make them difficult to identify (Simonis et al., 2020) and many surveys often use composite categories such as 'synthetic cathinones' or 'synthetic cannabinoids' (Mason & Kuypers 2018), making evaluation difficult. Attempting to overcome this in the current review, our search strategy included a near-comprehensive list of NPS (Appendix 1), and for inclusion, we adopted a relatively broad definition of NPS including phenibut and LSA seeds.

Additionally, there is a lack of consistency in the definition of 'self-medication' across studies. We utilise the following definition: 'using a substance to treat self-diagnosed or professionally diagnosed symptoms and diseases without consulting a doctor';

however, we excluded individuals from homeless or prison populations and excluded studies focusing on neuroenhancement. We believe that NPS use in these populations often represents a 'coping' strategy rather than an effort at self-medication and allows for a more streamlined discussion. Finally, the distinction between self-medication and neuroenhancement is not well established in the literature (Maier et al. 2013) and further clarity would aid research.

The current review also encompasses a diverse range of study methodologies, including case reports, surveys, content analyses, and interviews. The heterogenous nature of methodology and high proportion of case reports (50%) among the studies may limit the generalizability of the findings. As a result, firm conclusions cannot be drawn from this review. Lastly, the lack of substance verification is a limitation of qualitative data, as substances used may not be what the individual believes they are.

## Recommendations for Future Research

The current study provides insights into the phenomenon of self-medication using NPS; however, there is a need for additional research to expand our understanding in this area. There is a clear gap between NPS self-medication literature and what can be observed; therefore, future studies should aim to comprehensively identify the range of NPS being used, with a particular focus on dissociative and stimulant NPS that were not addressed in this review, but for which discussion is evident. Large-scale surveys and in-depth interviews could provide valuable information on self-medication practices with NPS.

Additionally, whilst the current study provides a foundation for further inquiry, many questions remain unanswered due to the limited information available on study methodology. Conducting primary research is necessary to address these gaps in our understanding and to fully explore the complex phenomenon of self-medication using NPS.

## Conclusions

This systematic review provides evidence of the phenomenon of self-medication with 22 NPS, primarily for the treatment of anxiety, depression, and ADHD. The findings indicate that the potential efficacy and safety profiles of NPS vary by category, with novel benzodiazepines posing the greatest risk. Currently, how many individuals self-medicate with NPS is unknown and caution must be exercised in generalising these results to the broader population. Further research is needed to fully understand the extent and implications of this phenomenon.

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**Data Availability** The data that support the findings of this study are available from the corresponding author, T.H, upon request.

## Declarations

**Competing Interest** The authors declare no competing interests.



## References

Abouchedid, R., Gilks, T., Dargan, P. I., Archer, J. R. H., & Wood, D. M. (2018). Assessment of the availability, cost, and motivations for use over time of the new psychoactive substances-benzodiazepines diclazepam, flubromazepam, and pyrazolam-in the UK. *Journal of Medical Toxicology, 14*(2), 134–143. https://doi.org/10.1007/s13181-018-0659-3

Advisory Council on the Misuse of Drugs (ACMD). (2016). Part of: Drug misuse and dependency Advice on U-47,700, etizolam and other designer benzodiazepines. https://assets.publishing.service.gov.uk/media/5a7f499640f0b62305b8639c/ACMD_TCDO_Report_U47700_and_Etizolam_and_designer_benzodiazepines.pdf

Andersson, M., & Kjellgren, A. (2017). The slippery slope of flubromazolam: Experiences of a novel psychoactive benzodiazepine as discussed on a Swedish online forum. *Nordisk alkohol- & narkotikatidskrift : NAT, 34*(3), 217–229. https://doi.org/10.1177/1455072517706304

Andersson, M., Persson, M., & Kjellgren, A. (2017b). Psychoactive substances as a last resort-a qualitative study of self-treatment of migraine and cluster headaches. *Harm Reduction Journal, 14*(1), 60. https://doi.org/10.1186/s12954-017-0186-6

Andersson, M., & Kjellgren, A. (2019). Twenty percent better with 20 micrograms? A qualitative study of psychedelic microdosing self-rapports and discussions on YouTube. *Harm Reduction Journal, 16*(1), 1–12. https://doi.org/10.1186/s12954-019-0333-3

Andersson, M., Persson, M., & Kjellgren, A. (2017a). Psychoactive substances as a last resort-a qualitative study of self-treatment of migraine and cluster headaches. *Harm Reduction Journal*, *14*(1). https://doi.org/10.1186/s12954-017-0186-6

Anonymous. (2017). Best functional dissociative for depression. Reddit. https://www.reddit.com/r/researchchemicals/comments/5why21/best_functional_dissociative_for_depression/. Accessed 1 June 2023.

Anonymous. (2022). Has anyone here actually used pyros functionally? Reddit. https://www.reddit.com/r/researchchemicals/comments/w8630j/has_anyone_here_actually_used_pyros_functionally/. Accessed 8 Aug 2022.

Anonymous. (2023). Is using 4fmph everyday dangerous? Reddit. https://www.reddit.com/r/researchchemicals/comments/zy3mw8/is_using_4fmph_every_day_dangerous/. Accessed 15 May 2023.

Bahji, A., Vazquez, G. H., & Zarate, C. A. (2021). Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. *Journal of Affective Disorders*. https://doi.org/10.1016/j.jad.2020.09.071

Bailey, G. P., Ho, J. H., Hudson, S., Archer, J. R. H., Dargan, P. I., & Wood, D. M. (2015). Nopaine No Gain: a case of recreational ethylphenidate toxicity. *Clinical Toxicology, 53*(4), 358–359. https://doi.org/10.3109/15563650.2015.1024953

Basile, J., N, J., Krotulski, A., & Osterhoudt, K. (2022). Toxicity from the NPS N-methyl-cyclazodone with laboratory confirmation-a dance befitting St. Vitus. *Clincal Toxicology, 60*, 117–118.

Baumeister, D., Tojo, L. M., & Tracy, D. K. (2015). Legal highs: Staying on top of the flood of novel psychoactive substances. *Therapeutic Advances in Psychopharmacology*. https://doi.org/10.1177/2045125314559539

Bell, D. N. F., & Blanchflower, D. G. (2019). The well-being of the overemployed and the underemployed and the rise in depression in the UK. *Journal of Economic Behavior and Organization*, *161*. https://doi.org/10.1016/j.jebo.2019.03.018

Bennadi, D. (2013). Self-medication: A current challenge. *Journal of Basic and Clinical Pharmacy, 5*(1), 19–23. https://doi.org/10.4103/0976-0105.128253

Bluelight. (2023). https://bluelight.org/xf/. Accessed 12 Jan 2023.

Bolton, J., Sareen, J., Cox, B. J., & Robinson, J. (2009). Self-medication of anxiety disorders with alcohol and drugs: Results from a nationally representative sample. *Journal of anxiety disorders, 23*(1), 38–45. https://doi.org/10.1016/j.janxdis.2008.03.013

Botanas, C. J., de la Peña, J. B., Custodio, R. J., & dela Peña IJ, Kim M, Woo T, Kim HJ, Kim HI, Cho MC, Lee YS, Cheong JH. (2017). Methoxetamine produces rapid and sustained antidepressant effects probably via glutamatergic and serotonergic mechanisms. *Neuropharmacology, 126*, 121–127. https://doi.org/10.1016/j.neuropharm.2017.08.038

Cunningham, C. M., Hanley, G. E., & Morgan, S. (2010). Patterns in the use of benzodiazepines in British Columbia: examining the impact of increasing research and guideline cautions against long-term use. *Health policy (Amsterdam, Netherlands), 97*(2–3), 122–129. https://doi.org/10.1016/j.healthpol.2010.03.008

Davidson, C., Raby, C. A. R., Barrese, V., & Ramsey, J. (2018). In Vitro Neurochemical Assessment of Methylphenidate and Its "Legal High" Analogs 3,4-CTMP and Ethylphenidate in Rat Nucleus Accumbens and Bed Nucleus of the Stria Terminalis. *Frontiers in Psychiatry, 9*, 149. https://doi.org/10.3389/fpsyt.2018.00149

Davidson, C., & Schifano, F. (2016). The potential utility of some legal highs in CNS disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. https://doi.org/10.1016/j.pnpbp.2015.07.010

Deen, A. A., Claridge, H., Treble, R. D., Hamnett, H. J., & Copeland, C. S. (2021). Deaths from novel psychoactive substances in England, Wales and Northern Ireland: Evaluating the impact of the UK psychoactive substances act 2016. *Journal of Psychopharmacology, 35*(11), 1315–1323. https://doi.org/10.1177/02698811211026645

Deligianni, E., Daniel, O. J., Corkery, J. M., Schifano, F., & Lione, L. A. (2020). Impact of the UK Psychoactive Substances Act on awareness, use, experiences and knowledge of potential associated health risks of novel psychoactive substances. *British Journal of Clinical Pharmacology, 86*(3), 505–516. https://doi.org/10.1111/bcp.14123

Di Lorenzo, C., Coppola, G., Di Lorenzo, G., Bracaglia, M., Rossi, P., & Pierelli, F. (2016). The use of illicit drugs as self-medication in the treatment of cluster headache: Results from an Italian online survey. *Cephalalgia, 36*(2), 194–198. https://doi.org/10.1177/0333102415583145

dos Santos, R. G., Bouso, J. C., Alcázar-Córcoles, M. Á., & Hallak, J. E. C. (2018). Efficacy, tolerability, and safety of serotonergic psychedelics for the management of mood, anxiety, and substance-use disorders: A systematic review of systematic reviews. *Expert Review of Clinical Pharmacology*. https://doi.org/10.1080/17512433.2018.1511424

Dutchcitysales. (2023). https://www.dutchcitysales.net/. Accessed 12 Jan 2023.

European Monitoring Centre for Drugs and Drug Addiction. (2022). European Drug Report 2022: Trends and Developments, Publications Office of the European Union, Luxembourg.

Faden, V. B. (2006). Trends in initiation of alcohol use in the United States 1975 to 2003. *Alcoholism, Clinical and Experimental Research, 30*(6), 1011–1022. https://doi.org/10.1111/j.1530-0277.2006.00115.x

Fetensa, G., Tolossa, T., Etafa, W., & Fekadu, G. (2021). Prevalence and predictors of self-medication among university students in Ethiopia: A systematic review and meta-analysis. *Journal of Pharmaceutical Policy and Practice*. https://doi.org/10.1186/s40545-021-00391-y

Figueroa, J. F., Phelan, J., Orav, E. J., Patel, V., & Jha, A. K. (2020). Association of Mental Health Disorders With Health Care Spending in the Medicare Population. *JAMA network open, 3*(3),e201210. https://doi.org/10.1001/jamanetworkopen.2020.1210

Ghani, S., Taylor, E., & Gopalakrishnan, S. (2021). Is this Withdrawal or Intoxication? Case Report Regarding Complications of Unregulated Use of Tianeptine, Etizolam, and Phenibut in the USA. *CNS Spectrums, 26*(2), 169–169. https://doi.org/10.1017/S1092852920002734

Giampreti, A., Valli, A., Gallo, M., Eleftheriou, G., Faraoni, L., Cirronis, M., & Bacis, G. (2022). Designer benzodiazepine as self-medication for anxiety: central nervous system depression in a 17-year-old patient after liquid clonazolam use. *Clincal Toxicology, 60*, 7–8.

Gittins, R., Guirguis, A., Schifano, F., & Maidment, I. (2018). Exploration of the Use of New Psychoactive Substances by Individuals in Treatment for Substance Misuse in the UK. *Brain Sciences, 8*(4), 58. https://doi.org/10.3390/brainsci8040058

Harris, K. M., & Edlund, M. J. (2005). Self-medication of mental health problems: New evidence from a National Survey. *Health Services Research*. https://doi.org/10.1111/j.1475-6773.2005.00345.x

Hill, R. G. (2020). Understanding the UK psychoactive substances Act. *British Journal of Clinical Pharmacology*. https://doi.org/10.1111/bcp.14168

Hoge, M. A., Stuart, G. W., Morris, J. A., Huey, L. Y., Flaherty, M. T., & Paris, M., Jr. (2018). Behavioral health workforce development in the United States. *In Substance Abuse and Addiction*. https://doi.org/10.4018/978-1-5225-7666-2.ch023

Høiseth, G., Tuv, S. S., & Karinen, R. (2016). Blood concentrations of new designer benzodiazepines in forensic cases. *Forensic Science International, 268*, 35–38. https://doi.org/10.1016/j.forsciint.2016.09.006

Hong, Q. N., Fàbregues, S., Bartlett, G., Boardman, F., Cargo, M., Dagenais, P., et al. (2018). The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. *Education for Information, 34*(4). https://doi.org/10.3233/EFI-180221

Huerta, C., Abbing-Karahagopian, V., Requena, G., Oliva, B., Alvarez, Y., Gardarsdottir, H., Miret, M., Schneider, C., Gil, M., Souverein, P. C., De Bruin, M. L., Slattery, J., De Groot, M. C., Hesse, U., Rottenkolber, M., Schmiedl, S., Montero, D., Bate, A., Ruigomez, A., … de Abajo, F. J. (2016). Exposure to benzodiazepines (anxiolytics, hypnotics and related drugs) in seven European electronic healthcare databases: a cross-national descriptive study from the PROTECT-EU Project. *Pharmacoepidemiology and drug safety, 25*(Suppl 1), 56–65. https://doi.org/10.1002/pds.3825

Humphries, C. (2022). The United Kingdom's Psychoactive Substances Act 2016. Where are we now? *Drug Science, Policy and Law*.

Hutten, N. R. P. W., Mason, N. L., Dolder, P. C., & Kuypers, K. P. C. (2019). Self-Rated Effectiveness of Microdosing With Psychedelics for Mental and Physical Health Problems Among Microdosers. *Frontiers in psychiatry, 10*, 672. https://doi.org/10.3389/fpsyt.2019.00672

Johnstad, P. G. (2018). Powerful substances in tiny amounts: An interview study of psychedelic microdosing. *NAD Nordic Studies on Alcohol and Drugs, 35*(1), 39–51. https://doi.org/10.1177/1455072517753339

Jolliff, H. A. (2020). Clonazolam abuse: A report of two cases. *In Toxicology Cases for the Clinical and Forensic Laboratory*. https://doi.org/10.1016/B978-0-12-815846-3.00067-3

Jones, W. R., Masood, M., Huke, V., Reid, F., Roche, J., Patel, M., & Morgan, J. F. (2016). Novel psychoactive substance use and internet drug purchasing in eating disorders. *Research and Advances in Psychiatry, 3*(2), 33–43.

Kessler, R. C., Petukhova, M., Sampson, N. A., Zaslavsky, A. M., & Wittchen, H.-U. (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *International Journal of Methods in Psychiatric Research, 21*(3), 169–184. https://doi.org/10.1002/mpr.1359

Khantzian, E. J. (1985). The self medication hypothesis of addictive disorders: Focus on heroin and cocaine dependence. *American Journal of Psychiatry*. https://doi.org/10.1176/ajp.142.11.1259

Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. *Harvard Review of Psychiatry*. https://doi.org/10.3109/10673229709030550

Khantzian, E. J. (2003). The self-medication hypothesis revisited: The dually diagnosed patient. *Primary Psychiatry., 10*, 53–54.

Krystal, J. H., Abdallah, C. G., Sanacora, G., Charney, D. S., & Duman, R. S. (2019). Ketamine: A paradigm shift for depression research and treatment. *Neuron*. https://doi.org/10.1016/j.neuron.2019.02.005

Laing, M. K., Ti, L., Marmel, A., Tobias, S., Shapiro, A. M., Laing, R., Lysyshyn, M., & Socías, M. E. (2021). An outbreak of novel psychoactive substance benzodiazepines in the unregulated drug supply: Preliminary results from a community drug checking program using point-of-care and confirmatory methods. *THe International Journal on Drug Policy, 93*, 103169. https://doi.org/10.1016/j.drugpo.2021.103169

Liu, Q., He, H., Yang, J., Feng, X., Zhao, F., & Lyu, J. (2020). Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study. *Journal of Psychiatric Research, 126*, 134–140. https://doi.org/10.1016/j.jpsychires.2019.08.002

Lucie, J., Jurasek, B., Kohout, M., Cihlarova, P., Vagnerova, M., & Kuchar, M. (2022). Counterfeits of Xanax – combination of designer benzodiazepines clonazolam and flualprazolam. *Toxicologie Analytique et Clinique, 34*, S122. https://doi.org/10.1016/j.toxac.2022.06.198

Maier, L. J., Liechti, M. E., Herzig, F., & Schaub, M. P. (2013). To dope or not to dope: neuroenhancement with prescription drugs and drugs of abuse among swiss university students. *PLoS ONE, 8*(11), e77967. https://doi.org/10.1371/journal.pone.0077967

Marillier, M., Batisse, A., Richeval, C., Labrouve, V., Martinez, M., Allorge, D., et al. (2017). CHEMSEX, NPS & risk reduction management: Preliminary results of a pilot study. *Toxicologie Analytique et Clinique, 29*. https://doi.org/10.1016/j.toxac.2016.12.003

Martin, A., & Anette, K. (2016). Aspects of Substance Displacement - From Illicit Drugs to Novel Psychoactive Substances. *Journal of Addiction Research & Therapy, 7*. https://doi.org/10.4172/2155-6105.1000283

Martinotti, G., Lupi, M., Acciavatti, T., Cinosi, E., Santacroce, R., Signorelli, M. S., Bandini, L., Lisi, G., Quattrone, D., Ciambrone, P., Aguglia, A., Pinna, F., Calò, S., Janiri, L., & di Giannantonio, M. (2014). Novel psychoactive substances in young adults with and without psychiatric comorbidities. *BioMed research international, 2014*, 815424. https://doi.org/10.1155/2014/815424

Maskell, K. F., Bailey, M. L., & Rose, S. R. (2016). Self medication with methoxetamine as an analgesic resulting in significant Toxicity. *Pain Medicine, 17*(9), 1773–1775. https://doi.org/10.1093/pm/pnw041

Mason, N. L., & Kuypers, K. P. C. (2018). Mental health of a self-selected sample of psychedelic users and self-medication practices with psychedelics. *Journal of Psychedelic Studies*, *2*(1), 45–52. Accessed 25 April 2022.

Menard, O., Deheul, S., Carton, L., Gauthier, S., Cottencin, O., & Bordet, R. (2018). Self medication by NPS in a patient with adult ADHD. *Fundamental and Clinical Pharmacology, 32*(Supplement 1), 86. https://doi.org/10.1111/fcp.12371

Miranda, J., McGuire, T. G., Williams, D. R., & Wang, P. (2008). Mental health in the context of health disparities. *American Journal of Psychiatry*. https://doi.org/10.1176/appi.ajp.2008.08030333

Moore, C. M. H. J. D. M. P. P. (2022). Clonazolam Intoxication case report danger of designer benzodiazepines. *The American Journal of Forensic Medicine and Pathology, 43*, 372–375.

Moosmann, B., King, L. A., & Auwärter, V. (2015). Designer benzodiazepines: A new challenge. *World Psychiatry*. https://doi.org/10.1002/wps.20236

Moylan, S., Giorlando, F., Nordfjærn, T., & Berk, M. (2012). The role of alprazolam for the treatment of panic disorder in Australia. *Australian and New Zealand Journal of Psychiatry*. https://doi.org/10.1177/0004867411432074

Muttoni, S., Ardissino, M., & John, C. (2019). Classical psychedelics for the treatment of depression and anxiety: A systematic review. *Journal of Affective Disorders*. https://doi.org/10.1016/j.jad.2019.07.076

Neicun, J., Steenhuizen, M., van Kessel, R., Yang, J. C., Negri, A., Czabanowska, K., Corazza, O., & Roman-Urrestarazu, A. (2019). Mapping novel psychoactive substances policy in the EU: The case of Portugal, the Netherlands, Czech Republic, Poland, the United Kingdom and Sweden. *PloS one, 14*(6), e0218011. https://doi.org/10.1371/journal.pone.0218011

Neicun, J., Yang, J. C., Shih, H., Nadella, P., van Kessel, R., Negri, A., et al. (2021). Erratum: lifetime prevalence of novel psychoactive substances use among adults in the USA: Sociodemographic, mental health and illicit drug use correlates. Evidence from a population-based survey 2007–2014 (PLoS ONE (2020) 15:10 (e0241056) DOI: https://doi.org/10.1371/journal.pone.0241056). *PLoS ONE*. https://doi.org/10.1371/journal.pone.0251006

Özgen, M. H., & van den Brink, W. (2021). Ketamine als zelfmedicatie bij patiënt met autismespectrumstoornis en therapieresistente depressie [Ketamine self-medication in a patient with autism spectrum disorder and comorbid treatment-resistant depression]. *Tijdschrift Voor Psychiatrie, 63*(12), 890–894.

Pagán, J. A., Ross, S., Yau, J., & Polsky, D. (2006). Self-medication and health insurance coverage in Mexico. *Health Policy (Amsterdam, Netherlands), 75*(2), 170–177. https://doi.org/10.1016/j.healthpol.2005.03.007

Palamar, J. J., Martins, S. S., Su, M. K., & Ompad, D. C. (2015). Self-reported use of novel psychoactive substances in a US nationally representative survey: Prevalence, correlates, and a call for new survey methods to prevent underreporting. *Drug and Alcohol Dependence, 156*, 112–119. https://doi.org/10.1016/j.drugalcdep.2015.08.028

Palamar, J. J., Rutherford, C., & Keyes, K. M. (2021). Trends in Ketamine Use, Exposures, and Seizures in the United States up to 2019. *American Journal of Public Health, 111*(11), 2046–2049. https://doi.org/10.2105/AJPH.2021.306486

Peacock, A., Bruno, R., Gisev, N., Degenhardt, L., Hall, W., Sedefov, R., et al. (2019). New psychoactive substances: Challenges for drug surveillance, control, and public health responses. *The Lancet*. https://doi.org/10.1016/S0140-6736(19)32231-7

Pendkar, C., Karnik, S., Shamian, B., Shankar, S., Nasreen, S., Kupfer, Y., & Kamholz, S. (2019). 706: ETIZOLAM WITHDRAWAL. *Critical Care Medicine, 47*, 333. https://doi.org/10.1097/01.ccm.0000551457.28929.1f

Peterkin, A. F., Abraham, R., & Harris, M. T. H. (2022). A Case of Phenibut Directed Detoxification Leading to Toxicity During the COVID-19 Pandemic. *Journal of Addiction Medicine, 16*(5), 602–605. https://doi.org/10.1097/ADM.0000000000000966

Pope, J. D., Weng Choy, K., Drummer, O. H., & Schneider, H. G. (2018). Novel Benzodiazepines (Clonazolam and Flubromazolam) Identified in Candy-Like Pills. *The Journal of Applied Laboratory Medicine, 3*(1), 48–55. https://doi.org/10.1373/jalm.2017.025387

Porteous, T., Bond, C., Hannaford, P., & Sinclair, H. (2005). How and why are non-prescription analgesics used in Scotland? *Family Practice, 22*(1), 78–85. https://doi.org/10.1093/fampra/cmh719

Potter, G., & Chatwin, C. (2017). Not particularly special: critiquing 'NPS' as a category of drugs. Drugs: Education. *Prevention and Policy, 25*, 1–8. https://doi.org/10.1080/09687637.2017.1411885

Reddit. (2023). https://www.reddit.com/. Accessed 12 Jan 2023.

Reuter, P., & Pardo, B. (2017). Can new psychoactive substances be regulated effectively? An assessment of the British Psychoactive Substances Bill. *Addiction (Abingdon, England), 112*(1), 25–31. https://doi.org/10.1111/add.13439

Robinson, J. A., Sareen, J., Cox, B. J., & Bolton, J. M. (2009a). Correlates of self-medication for anxiety disorders: results from the National Epidemiolgic Survey on Alcohol and Related Conditions. *THe Journal of Nervous and Mental Disease, 197*(12), 873–878. https://doi.org/10.1097/NMD.0b013e3181c299c2

Robinson, J., Sareen, J., Cox, B. J., & Bolton, J. (2009b). Self-medication of anxiety disorders with alcohol and drugs: Results from a nationally representative sample. *Journal of Anxiety Disorders, 23*(1), 38–45. https://doi.org/10.1016/j.janxdis.2008.03.013

Rod, W., Kudryk, A., Brunetti, L., Sun, N., & Nguyen, M. (2018). 935: Phenibut withdrawal management in the setting of concomitant kratom and alcohol dependence. *Critical Care Medicine., 46*, 451. https://doi.org/10.1097/01.ccm.0000528942.37373.7a

Rolando, S., & Beccaria, F. (2019). "The junkie abuses, the psychonaut learns": A qualitative analysis of an online drug forum community. *Drugs and Alcohol Today, 19*(4), 282–294. https://doi.org/10.1108/DAT-10-2018-0052

Samokhvalov, A. V., Paton-Gay, C. L., Balchand, K., & Rehm, J. (2013). Phenibut dependence. *BMJ Case Reports, 2013*, bcr2012008381. https://doi.org/10.1136/bcr-2012-008381

Schimmel, N., Breeksema, J. J., Smith-Apeldoorn, S. Y., Veraart, J., van den Brink, W., & Schoevers, R. A. (2022). Psychedelics for the treatment of depression, anxiety, and existential distress in patients with a terminal illness: A systematic review. *Psychopharmacology (Berl)*. https://doi.org/10.1007/s00213-021-06027-y

Seddon, T. (2014). Drug policy and global regulatory capitalism: the case of new psychoactive substances (NPS). *The International Journal on Drug Policy, 25*(5), 1019–1024. https://doi.org/10.1016/j.drugpo.2014.03.009

Sedefov, R., Gallegos, A., Mounteney, J., & Kenny, P. (2013). Monitoring novel psychoactive substances. a global perspective. *In Novel Psychoactive Substances: Classification, Pharmacology and Toxicology*. https://doi.org/10.1016/B978-0-12-415816-0.00002-X

Shafi, A., Berry, A. J., Sumnall, H., Wood, D. M., & Tracy, D. K. (2020). New psychoactive substances: a review and updates. *Therapeutic Advances in Psychopharmacology, 10*, 2045125320967197. https://doi.org/10.1177/2045125320967197

Shehnaz, S. I., Agarwal, A. K., & Khan, N. (2014). A systematic review of self-medication practices among adolescents. *Journal of Adolescent Health*. https://doi.org/10.1016/j.jadohealth.2014.07.001

Simonis, S., Canfyn, M., Van Dijck, A., Van Havere, T., Deconinck, E., Blanckaert, P., & Gremeaux, L. (2020). Awareness of users and motivational factors for using new psychoactive substances in Belgium. *Harm Reduction Journal, 17*(1), 52.

Smith, K. E., Rogers, J. M., Schriefer, D., & Grundmann, O. (2021). Therapeutic benefit with caveats?: analyzing social media data to understand the complexities of kratom use. *Drug and Alcohol Dependence, 226*, 108879. https://doi.org/10.1016/j.drugalcdep.2021.108879

Sommerfeld-Klatta, K., Łukasik-Głębocka, M., Teżyk, A., Panieński, P., Żaba, C., & Zielińska-Psuja, B. (2020). Clonazolam a new designer benzodiazepine intoxication confirmed by blood concentration. *Forensic Science International., 310*, 110237. https://doi.org/10.1016/j.forsciint.2020.110237

Soussan, C., Andersson, M., & Kjellgren, A. (2018a). The diverse reasons for using Novel Psychoactive Substances - a qualitative study of the users' own perspectives. *International Journal of Drug Policy, 52*, 71–78. https://doi.org/10.1016/j.drugpo.2017.11.003

Soussan, C., & Kjellgren, A. (2016). The users of Novel Psychoactive Substances: Online survey about their characteristics, attitudes and motivations. *The International Journal on Drug Policy, 32*, 77–84. https://doi.org/10.1016/j.drugpo.2016.03.007

Soussan, C., Andersson, M., & Kjellgren, A. (2018b). The diverse reasons for using Novel Psychoactive Substances - A qualitative study of the users' own perspectives. *The International Journal on Drug Policy, 52*, 71–78. https://doi.org/10.1016/j.drugpo.2017.11.003

Striebel, J. M., Nelson, E. E., & Kalapatapu, R. K. (2017). "Being with a Buddha": A case report of methoxetamine use in a United States veteran with PTSD. *Case Reports in Psychiatry, 2017*, 1–4. https://doi.org/10.1155/2017/2319094

Takeshima, N., Ogawa, Y., Hayasaka, Y., & Furukawa, T. A. (2016). Continuation and discontinuation of benzodiazepine prescriptions: A cohort study based on a large claims database in Japan. *Psychiatry Research, 237*, 201–207. https://doi.org/10.1016/j.psychres.2016.01.040

The Joanna Briggs Institute. (2017). Checklist for qualitative research. *The Joanna Briggs Institute*. https://joannabriggs.org/ebp/critical_appraisal_tools

Tong, A., Flemming, K., McInnes, E., Oliver, S., & Craig, J. (2012). Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. *BMC Medical Research Methodology, 12*, 181. https://doi.org/10.1186/1471-2288-12-181

United Nations Office On Drugs And Crime. (2013). World Drug report. *UNODC. United Nations Office on Drugs and Crime, 2013*. https://www.unodc.org/unodc/secured/wdr/wdr2013/World_Drug_Report_2013.pdf

Vardakou, I., Pistos, C., & Spiliopoulou, C. (2011). Drugs for youth via Internet and the example of mephedrone. *Toxicology Letters*. https://doi.org/10.1016/j.toxlet.2010.12.014

Vice. (2023). What you said about your Xanax use. Vice. https://www.vice.com/en/article/bjpn7q/what-you-said-about-your-xanax-use. Accessed 12 Jan 2023.

Webb, N. E., Wood, D. M., Greene, S. L., Hunter, L. J., Archer, J. R. H., Dines, A. M., & Dargan, P. I. (2019). Change in the new psychoactive substances associated with Emergency Department acute toxicity presentations associated with the introduction of the UK 2016 Psychoactive Substances Act. *Clinical Toxicology (Philadelphia, Pa.), 57*(1), 36–41. https://doi.org/10.1080/15563650.2018.1494277

Werse, B., & Morgenstern, C. (2012). How to handle legal highs? Findings from a German online survey and considerations on drug policy issues. *Drugs and Alcohol Today, 12*. https://doi.org/10.1108/17459261211286636

Yockey, R. A., Vidourek, R. A., & King, K. A. (2020). Trends in LSD use among US adults: 2015–2018. *Drug and Alcohol Dependence, 212*, 108071. https://doi.org/10.1016/j.drugalcdep.2020.108071