NEW TRENDS OF SUBSTANCE ABUSE: LOOKING FOR NEW PSYCHOTROPIC EFFECTS OF CHEM SEX DRUGS, COGNITIVE ENHANCERS, AND NEW PSYCHOACTIVE SUBSTANCES

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PUBLISHED IN: Frontiers in Psychiatry

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88966-366-8
DOI 10.3389/978-2-88966-366-8

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Citation: Zaami, S., Pichini, S., Torrens, M., Scherbaum, N. L., eds. (2021). New Trends of Substance Abuse: Looking for New Psychotropic Effects of Chem Sex Drugs, Cognitive Enhancers, and New Psychoactive Substances. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88966-366-8

Table of Contents

frontiers in Psychiatry

EDITORIAL
published: 23 November 2020
doi: 10.3389/fpsyt.2020.612192

Editorial: New Trends of Substance Abuse: Looking for New Psychotropic Effects of Chem Sex Drugs, Cognitive Enhancers, and New Psychoactive Substances

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Keywords: chem sex drugs, cognitive enhancers, psychoactive substances, psychotropic effects, new trend of substance abuse

Editorial on the Research Topic

New Trends of Substance Abuse: Looking for New Psychotropic Effects of Chem Sex Drugs, Cognitive Enhancers, and New Psychoactive Substances

In the last few years, a wide range of pharmacologically active substances entered the legal and illegal market of abused compounds creating new challenges for health professionals dealing with users and their health threats (1–6). Among the increasing number of abused substances, we can include not only new psychoactive substances (NPS), but also chemsex drugs, and cognitive enhancers (7–10).

Chemsex drugs are a group of psychoactive substances (e.g., cocaine, methamphetamine, synthetic cathinones, and synthetic cannabinoids and gamma hydroxybutyric acid, GHB, GBL) and non-psychoactive drugs (e.g., erectile dysfunction agents and alkyl nitrites) intentionally or non-intentionally used in the context of sexual intercourses, most commonly among gay and bisexual men (7, 8). The reported simultaneous use of more than one substance at a time has been reported to entail medical and psychiatric complications, such as psychosis, aggressive behavior, and suicidal ideation.

Similarly, cognitive enhancers are used in medical practice as medication to treat specific cognition deficits in mental diseases, such as attention deficit hyperactivity disorder and Alzheimer's disease. In contrast, their non-medical use has been spreading worldwide due to their alleged capability to increase mental alertness and concentration, as well as to boost memory and energy levels. Although the psychostimulant effects of these substances are necessary to treat cognitive impairment, the psychiatric/psychotropic effects of their misuse, and the consequences for mental health, are poorly described (9, 10).

Generally speaking, unlike what happened in the past century, every year a non-negligible number of new psychoactive substances appear in the illegal market. Their permanence both on the market and on web-based channels only depends on "consumers' satisfaction": a balance between number and length of positive subjective effects vs. acute side effects (11). Whereas, both outcomes

OPEN ACCESS

Edited and reviewed by:
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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *30 September 2020*
Accepted: *13 October 2020*
Published: *23 November 2020*

Citation:
Pichini S, Di Trana A, Torrens M, Scherbaum N and Zaami S (2020) Editorial: New Trends of Substance Abuse: Looking for New Psychotropic Effects of Chem Sex Drugs, Cognitive Enhancers, and New Psychoactive Substances. Front. Psychiatry 11:612192. doi: 10.3389/fpsyt.2020.612192

can be reported by the same users, e.g., in web forums, short- and long-term psychiatric effects cannot be specifically identified and described due to the speed at which such substances enter and leave traffic channels.

This Research Topic seeks to provide updated studies, reviews, mini reviews, opinion papers, perspective articles, and case reports on psychiatric and psychotropic effects of chemsex drugs, cognitive enhancers, and more generally on new psychoactive substances. This collection aims to shed light on this incoming hazard to scientists and health professionals operating in the field of psychiatric damages caused by drug abuse.

As above reported, evidence on the Chemsex drugs' influence on mental health were provided by Bohn et al.. The research group administered to volunteers from the German MSM community a survey concerning recreational substance use, substance use in a sexual setting, mental health, adverse consequences of Chemsex behavior, and others. They concluded that the consumers of methamphetamine, mephedrone, GHB and or ketamine in sexual settings presented several more symptoms of depression, anxiety and somatization than the non-chemsex abusers and German general population.

Besides, Pereira et al. investigated the effects of regular GHB consumption and GHB-induced comas on the human brain structure and impulsivity. The study showed that only multiple GHB-induced comas could affect the microstructural tissue in the white matter, that is alleged to be the cause of the higher self-reported impulsivity.

An emerging phenomenon associated to Chemsex is the so-called "slam," being the practice of injecting drugs in Chemsex contests. A study on the cathinones injection in slam context was presented by Schreck et al. with the aim to evaluate the presence of the cathinone use disorder. Based on 39 "slam" notifications, Cathinone related disorder appeared particularly important in this population of users due to the negative consequences of slam practice.

The problem of stigmatization of drug addiction and the consequent social exclusion is discussed by Brown. After an historical overview of main drug related social issues, the author identified in the emerging phenomenon of Chemsex the chance to do better, preventing the dehumanization of the MSM communities which could feed the drug abuse among MSM communities.

The marked increase of the prescription of substances like methylphenidate has recently raised concerns, suggesting a possible misuse of these substances to obtain mind-booster effects and create new niches in the NPS market (8). In fact, Napoletano et al. outlined the online availability of cognitive enhancers, comparing the information on online fora and the EMCDDA and UNODC NPS databases. Through the website NPSfinder®, 142 cognitive enhancers not reported in the official databases were individuated.

Besides recreational consumption, cocaine is also abused for social or cognitive enhancement. The motivation pushing people to take cocaine to self-medicate deficits in cognitive abilities was assessed by Kexel et al. in a sample of 42 cocaine users, divided into a non-social motive group and a social motive group. Then, the social motive group was compared to a control group to assess their cognitive functioning through a comprehensive neuropsychological test. The study confirmed that people who use cocaine as a cognitive enhancer have considerable deficits in cognitive empathy and working memory. Currently, different treatments for cocaine addiction have been proposed in the literature. The long-term outcomes of an alternative approach were evaluated by Madeo et al. in their retrospective observational study. A large cohort of cocaine addicts who underwent repetitive transcranial magnetic stimulation (rTMS) for 3 months were observed and regular toxicological analysis of urine were conducted. As already observed in smaller samples, the rTMS shows promising results in the treatment of cocaine addiction.

The ethical implications of cognitive enhancers prescription were discussed by Zaami, Tagliabracci et al. and Ricci, who both focused their attention on the effectiveness of cosmetic neurology and the possible misuse to obtain "super-human" performances in healthy subjects. Although several opinions have been expressed by the international bioethical committee, the issue is still controversial and official guidelines are required by physicians. On the other hand, Schleim proposed a different approach to the cognitive enhancers issue, defining it as instrumental drug use. To this purpose, a brief discussion on the most relevant research and anecdotal evidence was reported by the author to corroborate his thesis.

The NPS issue is an everchanging reality, always posing new challenges to the scientific community and professionals working against this phenomenon. Investigating the NPS and other drugs use among patients in detoxification treatment in Germany, Specka et al. showed that polydrug consumption was common in that population, especially in opiate abusers, but NPS use in particular was infrequent and only short-term. The most commonly used NPS class in this population were synthetic cannabinoids. It is interesting to note that the most frequent reason for NPS use according to the participants, was that NPS were not included in the usual toxicological tests. Although this study shows that the NPS consumption is not so common. Giorgetti et al. drawn the attention toward the fact that a concerning number of NPS related deaths are reported in the literature. The research group focused on the post-mortem toxicology of synthetic cannabinoids-related fatalities. According to their research, the 26 cases reported are not sufficient to identify a typical toxic range for this class of substances and further analysis of post-mortem findings should be conducted to elucidate the toxicological profile of synthetic cannabinoids.

Corazza et al. conducted a phenomenological qualitative study to investigate the experiences of prisoners and professionals on "spice" consumption in prison, with the aims to elucidate the impact of NPS abuse on workers and people in custodial settings. Due to the frequent violent events experienced, the professionals involved in this study suggested to improve detection and treatment and support services in prisons together with enhanced training and education to face the problem.

Also, the psychiatric disorders caused by NPS abuse were investigated by Martinotti et al., who administered a questionnaire to a sample of inpatients hospitalized in Psychiatric Ward in Ibiza confirmed to have recently abused substances by

toxicological analysis. According to their research, stimulants and psychodyspleptics drugs are the most popular club drugs and the polydrug consumption is a common practice of party goers. It is interesting to notice that the largest part of the considered population has already had a Bipolar Disorder diagnosis.

Nagy et al. assessed intake patterns of the cathinone alpha-pyrrolidinopropriophenone (a-PPP) in condition of prolonged free access to the drug, in an animal model. The authors concluded that a-PPP shows a limited abuse potential and/or support only recreational use patterns in rats.

On the other hand, NPS are also studied as safer alternatives to current therapies, such as in the case of mytraginine studied by Hassan et al. to treat morphine withdrawal symptoms in rats. After inducing morphine abstinence in the animals, the rats that showed withdrawal syndrome were treated with buprenorphine, methadone, or mytraginine and the effects were monitored and measured for 28 days. Although a high intraperitoneal dose of mytraginine was required (3–50 mg/kg), the substance showed a good potential as opiate withdrawal treatment compared to medication usually used in detoxification treatment.

Since the beginning of 2020, the COVID-19 pandemic has been changing the habits of the global population at every level. Zaami, Marinelli et al. analyzed the possible consequences of this unprecedent situation on the abusers' health, concluding by drawing the attention of the scientific community toward the importance of the psychiatric and psychological assistance to this fragile part of population.

In conclusion, this Research Topic is providing updated studies and reviews concerning the psychiatric and psychological implications of Chemsex drugs, cognitive enhancers and NPS abuse, highlighting the importance to continuously investigate this still unclear field by the scientific community and health professionals.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

The Topic Editors express their gratitude to all the contributors for submitting their work to this Research Topic, to the Review Editors and external Reviewers who participated in the review process, and to the Editorial and Production teams of Frontiers for their valuable assistance through the various stages of the publication process. The work was supported by the Presidency of the Ministers Council, Department of Antidrug Policies, in Italy.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

OPINION
published: 23 January 2020
doi: 10.3389/fpsyt.2019.01006

Use of Methylphenidate Analogues as Cognitive Enhancers: The Prelude to Cosmetic Neurology and an Ethical Issue

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Keywords: cognitive enhancers, mental health, alterations, medical ethics, cosmetic neurology

OPEN ACCESS

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *11 October 2019*
Accepted: *20 December 2019*
Published: *23 January 2020*

Citation:
Zaami S, Tagliabracci A, Berretta P, Busardò FP and Marinelli E (2020) Use of Methylphenidate Analogues as Cognitive Enhancers: The Prelude to Cosmetic Neurology and an Ethical Issue. Front. Psychiatry 10:1006. doi: 10.3389/fpsyt.2019.01006

INTRODUCTION

Drugs involved in the treatment of Alzheimer's disease and other cognitive deficits such as attention deficit hyperactivity disorder (ADHD), strokes, schizophrenia, and aging are medically defined as cognitive enhancers (1). Amphetamines were the first drugs used to stimulate memory consolidation and improve concentration, and were followed by non-amphetaminic central nervous system (CNS) stimulants modafinil and armodafinil, which are largely prescribed for the treatment of narcolepsy and ADHD, although their mechanism of action is not entirely understood. Atomoxetine, a selective nor-adrenaline reuptake inhibitor, has been used in children with medication-resistant ADHD or undergoing side effects related to other drugs, while donepezil, a second-generation acetylcholinesterase inhibitor, has been employed for the treatment of mild-to-moderately-severe symptoms of Alzheimer-related dementia (2).

Nevertheless, methylphenidate is undoubtedly the most prescribed cognitive enhancer. It is also the most misused. Indeed, the non-medical use of methylphenidate and cognitive enhancers in an attempt to improve memory, increase mental concentration, control anxiety, and stimulate motivation and creativity is a rising worldwide phenomenon (2, 3). Due to methylphenidate being a prescription drug with medical restrictions in several countries, many illegal analogues have emerged on the internet and darknet drug markets during the last few years (3).

The misuse of cognitive enhancers in adults and young healthy individuals with the aim of increasing neurological functions is part of a phenomenon defined as "cosmetic neurology" (2). In addition, psychedelic microdosing using small doses of psychedelic substances, such as LSD and psilocybin is becoming more common (4). However, this cognitive enhancement comes with mental and ethical costs.

Risks for Physical and Mental Health of Cognitive Enhancers

The physical and mental health risks associated with the use of methylphenidate analogues such as ethylphenidate, 3,4-dichloromethylphenidate, 3,4-dichloroethylphenidate, 4-fluoromethylphenidate, 4-fluoroethylphenidate, methylnaphthidate, ethylnaphthidate, isopropylphenidate, propylphenidate, 4-methylmethylphenidate, and N-benzylethylphenidate

were recently reviewed and several severe intoxications and fatalities were reported (5). Moreover, the neurological and psychiatric consequences due to the misuse of methylphenidate analogues have been carefully evaluated. Psychiatric manifestations such as impulsive behavior, verbal, visual and memory impairment, gambling, compulsive shopping, and hypersexuality have been demonstrated, especially in younger users, due to excessive dopaminergic stimulation (2, 6). Furthermore, "psychostimulants" also alter the glutamatergic system, which can result in the impairment of behavioral flexibility and lead to the development and/or potentiation of addictive behaviors. Methylphenidate was proven to lower drug abuse liability in patients with ADHD. Still, it may also lead to similar behavioral rigidity and increase the risk for addictive or obsessive-compulsive behaviors, since the drug impacts glutamatergic signalling (3, 5).

Ethical issues raised by cognitive enhancement have been debated for over a decade (7): foremost experts have identified multiple ethical concerns including risks to mental and health safety. In 2015, the US Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) released a report on the issue of cognitive enhancement, reporting findings, and establishing recommendations for the scientific community (8). A major issue is the current medical acceptance, or even endorsement, of interventions intended to restore or sustain "normality." Both explicitly and implicitly, such a stance arguably adheres to the idea of a set of essential sociocultural requirements to function "normally", considering abnormal or antisocial any deviation from established standards (3).

Remarks from the Australian Alcohol and Drug Foundation (9) have cast doubts on the actual cognitive benefits of most enhancers, indicating that scientific studies showed only little to no benefits for cognitive enhancement in healthy individuals, while the associated side effects do pose health risks (10). Furthermore, granted that the use of cognitive enhancers may somehow help in masking fatigue, boredom or procrastination, there is no evidence to suggest that they can actually make people smarter. Moreover, their effects are apparently temporary, lasting until their metabolization and elimination (11). Some of these drugs can cause dependence and have a wide range of side effects. They can be particularly harmful to young people as brains are not fully developed until the age 25.

Medical Ethics

In 2014, the Italian Code of Medical Ethics included for the first time a new article defining human enhancement and related medical practices (12). The article was meant to reflect the relationship between this new field of medical practice and professional ethics. The article allowed for medical treatments going beyond conventional therapeutic goals, as long as several ethical and clinical criteria were met. Nonetheless, the problematic application of these criteria to human enhancement generated issues warranting an in-depth reflection.

DISCUSSION

The 2014 article of the Italian Code of Medical Ethics was replaced in 2017 by two new articles (76 and 76 –BIS), which are currently enforced (13). The new articles focus on medical enhancement and cosmetic medicine, stating that medical doctors being asked to provide or prescribe cognitive enhancers must always act in adherence to the highest standards of respect and protection for human dignity, human identity and integrity, and the inherent genetic traits in accordance with the principles of proportionality and precaution.

Nevertheless, it was shown that off-label use of cognitive enhancers can be efficacious in the treatment of postoperative cognitive dysfunction after major surgery in elderly patients, significantly decreasing the incidence of neurocognitive deficits (14). Other neuroscientists reported benefits for jobs requiring adaptive learning or attention shifting under pressure and recommend further research on the safety and efficacy of cognitive enhancers (15).

In the meantime, more reliable means to enhance cognitive functions should be promoted and prioritized: education, constant intellectual exercise and learning, a rewarding social life, interaction, a stimulating and healthy lifestyle. Such an approach is certainly more demanding and time-consuming than taking a supposedly "enhancing" drug, but it is much better for the individual in terms of personal identity development, creation of satisfactory interrelationships, self-esteem, and self-fulfilment.

AUTHOR CONTRIBUTIONS

SZ and FB provided initial idea and construct of the opinion. PB, AT, and EM co-authored and edited the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 17 February 2020
doi: 10.3389/fpsyt.2020.00053

Pharmacological Human Enhancement: An Overview of the Looming Bioethical and Regulatory Challenges

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OPEN ACCESS

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *21 December 2019*
Accepted: *21 January 2020*
Published: *17 February 2020*

Citation:
Ricci G (2020) Pharmacological Human Enhancement: An Overview of the Looming Bioethical and Regulatory Challenges. Front. Psychiatry 11:53. doi: 10.3389/fpsyt.2020.00053

Cognitive enhancement, a rather broad-ranging principle, can be achieved in various ways: healthy eating and consistent physical exercise can lead to long-term improvements in many cognitive domains; commonplace stimulants such as caffeine, on the other hand, temporarily raise levels of alertness, attentiveness, and concentration; sedative substances are also used as an indirect form of enhancement to relax before an exam or an important meeting. Such approaches raise no ethical issue. Nonetheless, clinical research has led to the off-label use of drugs called nootropics or "smart drugs", which can, under certain conditions, elicit some degree of cognition-improving effects: methylphenidate and modafinil can enhance working memory and concentration in healthy individuals, although the significance and effectiveness of such applications are dubious. Such "cognitive enhancement" methods, however, do raise multiple ethical issues, and their contentious nature has caused bioethical authorities to lay out opinions and recommendations meant to regulate their use. Most notably, the Italian Committee on Bioethics has extensively dealt with the spread of nootropics, which resulted in the Italian Code of Medical Ethics including "cognitive enhancement" drugs and their prescription by doctors as critical points, along with cosmetic surgery (the latest version of the Code, updated in December 2017, deals with the two separately, in Article 76 and 76 BIS). The United States Presidential Commission for the Study of Bioethical Issues broadened the scope of cognitive enhancement techniques so as to include neural modifiers, i.e. mechanisms of brain and nervous system change: a much wider array of interventions, technologies, behaviors, and environmental conditions that may potentially affect several aspects of the human brain and nervous system. The potential of neuroscience to profoundly reshape society is nothing short of mind-blowing.

Keywords: cognitive enhancement, human enhancement, smart drugs, nootropics, bioethics

INTRODUCTION

The ever-growing use of nootropics—also known as "smart drugs"—such as modafinil, piracetam, and methylphenidate by healthy users seeking to enhance their cognitive capabilities has led to widespread social alarm. Although currently-available nootropics offer only modest improvements in terms of cognitive performance, more effective compounds are likely to be developed in the near future, and the off-label use of such substances will probably rise as well. According to recent surveys, the use of such drugs by healthy scholars or by professionals in the ever more competitive labor markets may become commonplace in the short term (1, 2). Methylphenidate, modafinil, amphetamine, and dextroamphetamine are stimulants that inhibit dopamine and norepinephrine reuptake in the brain, affecting cognition and pleasure (3), and have gained popularity as "study drugs". In 2011 in Germany, Franke et al. reported a prevalence of 1.55% pharmaceutical cognitive enhancer users in a sample of 1,035 pupils from vocational and grammar schools, and a prevalence of 0.78% users in 512 students in medicine, pharmacy, and economics (4). In 2015 in the Swiss canton of Zurich, Liakoni et al. reported a prevalence of 54.5% users among 1,139 students from vocational schools and upper secondary schools (9.2% of prescription drug users, 44% of which used methylphenidate) (5). The same year in the Netherlands, Schelle et al. reported a prevalence of 1.7% prescription drug users for cognitive enhancement in a sample of 1,572 university students (methylphenidate or beta-blockers) (6). In 2016 in Germany, Dietz et al. reported a prevalence of 19% prescription and illicit drug users for cognitive enhancement among 1,021 people working in the field of economics; methylphenidate, amphetamine, and modafinil were the most commonly used prescription drugs (7).

The use of cognitive enhancement has raised ethical concerns. Additionally, while their effects on cognitive enhancement is arguable, the use of methylphenidate, modafinil, amphetamine, and other prescription drugs involves health risks, including dependence, tolerance, and cardiovascular, neurologic, and psychological disorders (8). To deal with these ethical and health issues, international laws are adapting. The author aimed to provide an overview of the situation regarding the ethical and regulatory implications of nootropic use by focusing on the Italian Code of Medical Ethics and drawing a comparison with the international regulations.

COGNITIVE ENHANCEMENT: THE ITALIAN CODE OF MEDICAL ETHICS AND THE ITALIAN COMMITTEE FOR BIOETHICS OFFER VALUABLE PERSPECTIVES

In 2014, the article 76 of the Italian Code of Medical Ethics first attempted to define human enhancement and medical practices and treatments associated (9, 10). Article 76 was meant to clarify the relation between this new field of medical practice and professional ethics. Indeed, the inclusion of medical/pharmacological enhancement practices in the Italian Code allowed medical treatments going beyond conventional therapeutic goals, as long as ethical and clinical criteria are met. Still, the problematic application of those criteria to treatments aiming at human enhancement generated various issues warranting an in-depth reflection. The indisputable importance of the newly-available and ever-evolving human enhancement techniques is addressed in the new version of the article of the Italian Code of Medical Ethics [articles 76 and 76 bis (11), released by the National Federation of Physicians' and Dentists' Orders on the 15th of December 2017] which further clarified the ethical and professional standards that health care professionals should meet when evaluating pharmacological enhancement through nootropics. Cognitive/physical enhancement and aesthetic medicine are addressed separately in the new version of the article (articles 76 and 76 bis, respectively). The new article 76 states that medical doctors being asked to provide or prescribe non-therapeutic treatments aiming at achieving cognitive/physical enhancement should always be guided by the highest standards of respect and protection for human dignity, identity, and integrity, and operate in accordance with the principles of proportionality and precaution.

Information also has become essential: medical doctors are required to obtain written informed consent, after explaining all possible risks arising from the proposed treatment, and should turn down any request for treatment or prescription that they consider disproportionate or unacceptably risky due to their invasive or irreversible nature. In order to fully understand the evolution of the concept of health, it is necessary to explore the changes that have occurred over time, taking into account several Italian constitutional precepts and opinions by the Italian Bioethics Committee. The new concept of the right to enjoy good health has apparently been broadened to include the right to become "better", i.e. more performant or better-looking. A new meaning of "health" was introduced, unrelated to the concept of "care" and inspired by a peculiar concept of "happiness", a principle not found in the Italian Constitution. The relation between this new field of medical practice and professional ethics is quite complex. Article 76 of the Italian Code of Medical Ethics allows medical treatments beyond the usual therapeutic goals. However, extreme caution is needed due to uncertain and insufficient evidence regarding the safety of most nootropics: in a 2013 opinion, the Italian Committee for Bioethics argued that more comprehensive research is necessary to outline the benefits and risks of nootropics, upon which experts did not reach consensus. In the meantime, more reliable means to enhance cognitive functions should be promoted and prioritized: education, constant intellectual exercise and learning, a rewarding social life and interactions, and a stimulating and healthy lifestyle. As discussed by the Committee, such an approach is certainly more demanding and time-consuming than taking a supposedly "enhancing" drug, but it is much better in terms of development of personal identity, establishment of satisfactory interrelationships, self-esteem, and self-fulfillment (12). Such remarks and concerns seem to have been specifically addressed in the updated article 76 of the Italian Code of Medical Ethics, and most notably by the United States

Presidential Commission for the Study of Bioethical Issues, among others.

As Nootropics use Becomes Rife, Ethical Doubts Linger

In April 2015, in the United States (13), a controversy arose around the growing use of Adderall®, a combination of amphetamines, in young adults without therapeutic purpose. Amphetamines and other stimulants are used off label by individuals seeking to heighten their competitive advantage by working longer and with a greater degree of attentiveness while sleeping less (14). Similarly, an 'epidemic' of amphetamine use by students seeking top grades and better test scores (15) was reported. These psychoactive drugs may alter the perception of reality of users, including their own actions and subsequent consequences (16). Such cognitive enhancement methods are still being explored: it is unclear whether enhancers are actually effective or have the potential to alter and manipulate memories, moral autonomy, and personality. It may arguably be appropriate to draw distinctions among different tools and methods to achieve enhancement, based on their risk-benefit ratios. It is worth noting that certain techniques are more risky, and others are more likely to succeed. For instance, pharmaceutical enhancers are currently considered the method most likely to succeed in achieving a reasonable level of cognitive improvement, in safe enough a manner (17). Greater risk is entailed by brain manipulation and stimulation; nonetheless, it is not clear yet whether those risks should be considered so high that competent individuals are not allowed to consent to them in light of different risks that individuals are legally allowed to take [for cosmetic improvements for example (18)]. The fundamental question is: do enhancers conflict with societal ethical values? According to some, performance-enhancing drugs should be banned, since they might create unfair competition. Moreover, mainstream use might indirectly pressure non-users to take nootropics, in the attempt to remain competitive. Is it conceivable, however, to restrict the freedom and autonomy of everyone out of fear that it may influence someone else's choices? The use of nootropics is often viewed as unjustifiable; yet, libertarian approaches tend to advocate for the individual right to determine whether such risks are worth taking (19).

WHAT ETHICAL BOUNDARIES SHOULD BE OUTLINED?

Where should an "ethical line" be drawn, if at all, between merely treating or preventing disorders and deficiencies in order to achieve 'normal' functioning, and resorting to drugs or devices for improvement or "enhancement", maybe to the point of becoming 'super-human'? Should resources be spent trying to turn average people into smarter and/or better performing versions of themselves? Even though the use of nootropics for the purpose of cognitive enhancement has been getting more and more widespread over the past years and such drugs are broadly perceived to somehow improve academic and professional performances, not enough empirical evidence supports the assumption that these drugs indeed give rise to substantial enhancement in healthy users. In that respect, a 2017 survey of 898 undergraduates, who were not diagnosed with attention deficit hyperactivity disorder (ADHD), reported that the use of cognitive enhancers did not result in an increase in the grade point average or an advantage of any sort over non-users (20). That is further confirmation that research on nootropics still appears to be inconclusive in terms of clarifying and defining how such drugs act as mind stimulants (21). Remarks from the Australian Alcohol and Drug Foundation (22) have cast doubt on the actual cognitive benefits of most nootropics, underlining that scientific studies showed only little to no benefits for cognitive enhancement in healthy individuals, while the associated side effects do pose health risks (23). Furthermore, granted that the use of nootropics may somehow help to bear fatigue, boredom, or procrastination, there is no evidence suggesting that they can actually make people smarter. Besides, their effects are apparently temporary, lasting until their metabolization and elimination (24). Some of these drugs can be addictive and have a range of side effects particularly harmful to young people, as their brains continue to develop into their mid-twenties. Medical associations and institutions should urgently devise clear guidelines in order to help medical doctors and health care institutions to face the issue of cognitive enhancement in healthy individuals.

Substances interacting with the mediators of memory and learning circuits such as glutamate, dopamine, and norepinephrine can potentially improve brain function in healthy users, even to the point of improving their baseline levels of functioning. That is already happening: non-medical use of prescription stimulants such as methylphenidate and the illicit use of psychostimulants for cognitive enhancement have risen among adolescents and young adults in schools and college campuses (8, 25, 26). However, there may be health and ethical costs. For instance, an alteration of the glutamatergic system caused by the intake of psychostimulants may impair behavioral flexibility, leading to the development and/or potentiation of addictive behaviors. Methylphenidate may lower drug abuse liability in ADHD patients, but it may also lead to similar behavioral rigidity and increase the risk for addictive or obsessive-compulsive behaviors by affecting glutamatergic signaling (27, 28). Another example of nootropic that has been under great scrutiny in the scientific community is modafinil, a compound structurally similar to methylphenidate and currently approved by the US Food and Drug Administration (FDA) for the treatment of narcolepsy, obstructive sleep apnea, excessive daytime sleepiness in adults and children (29), and shift-work disorder. The effects of modafinil on alertness and wakefulness in healthy individuals who are not sleep-deprived, and its military applications (30), has led to its use as a cognitive enhancer. Still, it has been observed that modafinil at certain doses can cause a reduction in *N*-methyl-D-aspartate (NMDA) receptor levels, impairments in short-term and long-term brain plasticity, which was also observed with methylphenidate (31). With such a record, still under-documented and indicating potential health

hazards, it is of paramount importance to be able to rely on unequivocal standards, recommendations, and guidelines from scientific institutions in order to regulate and govern the growing diffusion of nootropics. Most academic institutions, companies, and business associations have not taken a definite stance yet, either in favor or opposed to their use; such ambiguity leaves the issue of cognitive enhancement in a sort of a limbo: it is criticized when openly addressed, yet the cultural environments of business and academia, which are highly competitive settings, somehow support the use of these drugs in private. Two main arguments are frequently expressed by ethicists opposed to cognitive enhancement: firstly, it runs counter to the absolute value of authenticity and secondly, it is tantamount to a form of unfairness and cheating. Still, in the view of the author, both those arguments fail to thoroughly account for the individual and social factors that may get people to use or oppose the use of nootropics. The intuition that the use of cognitive enhancement by healthy people is unfair can be explained both philosophically and psychologically (32). As mentioned above, the ethical and philosophical ramifications of cognitive enhancers are somewhat complex, and lend themselves to multiple reflections and interpretations.

US PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES: NEURAL MODIFICATION HAS THE POTENTIAL TO RESHAPE SOCIETY

In 2015, the US Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) released a Report (33) on the issue of cognitive enhancement, and laid out its findings and recommendations for the scientific community. The Committee widened the scope of the debate by including all forms of neural modification. The relevance of future research developments on the matter is nothing less than mind-blowing: it has the potential to profoundly reshape society in the years to come. "Gray Matters" (34) attempted to answer some of those thorny questions, and outline a tenable path for informed, sensible, and productive exchanges in order to start a public discussion centered on cognitive enhancement. A related issue is the current medical acceptance, or even endorsement, of interventions intended to restore or sustain "normality." Such a stance apparently adheres to the idea of a set of socio-cultural requirements to function "normally", considering abnormal or anti-social any deviation from established standards. What posture should be taken up when some people strive for a level of "optimal functioning", seeking what they personally view as the nadir of the good life and what about society setting requirements that individuals in special positions and professions (e.g. police officers, doctors, pilots, or military personnel) are supposed to meet so as to achieve an "acceptable" level of optimal functioning? Medicine's essential, commendable function in service of achieving a good, healthy life is not to be considered as automatically extendable to living a "great" life, or to attaining above average, excellent performances in a socially-sanctioned function or service (34). Hence, justifications for specialized enhancements meant to achieve extraordinary lifestyles or performances will not necessarily be obtained starting from and according to medical principles (35). Furthermore, as we argued before, cognitive enhancement is not the end of the line, far from it: unremitting scientific progress and advancements make it essential to move beyond it and toward a broader array of interventions, technologies, behaviors and environmental conditions that can affect many aspects of the human brain and nervous system. The expression 'neural modifiers' is frequently used to refer to this wider pool of brain mechanisms and nervous system variations. Three general categories of neural modifiers can be identified: those meant to keep, or even strengthen, neural health but only within its normal boundaries; those for the purpose of treating an illness or a disorder; and lastly, the most controversial type: those conceived to improve or enhance one's capabilities beyond their normal, average function (36, 37). No category of neural modifiers—even those that make us better than 'normal'—is in the author's estimation inherently ethical or unethical. Instead, each form of neural modifier should be assessed on its own terms and merits, on a case-by-case basis, so as to best determine whether its use is ethical in a given context. Stakeholders and members of the public need to ask questions to make this ethical assessment, such as: what is the method and ultimate goal of the neural modifier? Is it safe and effective for that purpose? Who is choosing the modifier, and is that choice free of coercion and pressure? And the list goes on.

Neuroscience research holds tremendous promise, but it is also the subject of excessive media hyperbole. It is also worth noting that neurotechniques have wide-ranging applications in the legal realm as well: namely, the identification of biomarkers for anxiety-related conditions such as post-traumatic stress disorder, which may result in better therapeutic options and more accurate evaluations of psychological disorders; the implications in tort as well as in criminal law, e.g. for the calculation of compensatory damages, will be remarkable (38, 39). Still, the Bioethics Commission cautions against unrealistic claims and exaggeration. Conversations about neural modification, and cognitive enhancement in particular, generate hype among scholars, journalists, and the public. For example, the potentially enhancing effects of drugs such as methylphenidate and amphetamines, which are normally used to treat patients suffering from ADHD have often been overstated by the media (40). Furthermore, according to the Commission, existing, low-tech strategies ought to be prioritized by scholars in terms of new research and its funding, rather than highly technological methodologies and neural modifiers, which are frequently costly, and whose benefits many believe to be dubious or minimal (41, 42). Moreover, research aimed at treating neurological disorders, promoting mental health, and ending suffering should be at the forefront. The committee also advocates for research on the prevalence, possible benefits, and risks of new neural modifiers for the development of neural functions, and stresses equality of opportunities as an added

value: access to neural enhancers that are proven to be beneficial, effective, harmless, and morally acceptable should be ensured for anyone (43, 44). Nonetheless, in light of the innovative nature of those tools, solid guidance about the use of neural modifiers needs to be provided for all those involved: patients, parents, employers, specialists, and educators; the potential risks and benefits must be further researched and disclosed. Neurologically sound minors and adolescents should not be prescribed drugs with uncertain or unverified benefits. Such decisions have in fact a higher degree of ethical complexity when they affect children, since minors lack the legal and ethical capacity to consent to treatment and are more vulnerable to external influences and even coercion (45).

CONCLUSIONS

It is safe to assume that the lack of clear guidance for physicians has been causing inequality in patient access. Some healthy patients have been legitimately prescribed nootropics by doctors in favor of cognitive enhancers; is it not unfair that others have been breaking the law in order to gain access to the same drugs? It is the medical community's duty to evaluate the risk-benefit ratio of neural modifiers for cognitive enhancement in the healthy. More research is needed to figure out the possible hazards entailed by the use of nootropics. If a thorough review of the evidence confirms that a certain medicine has a benefit/harm profile that warrants its use by healthy patients, appropriate steps should be taken by the medical community in order to ensure that patients have been informed of their options. Conversely, if the potential harms of cognitive enhancement for the healthy are deemed to be too great, doctors should strive to educate their patients and the public at large as to the potential hazards of nootropic use. According to Roache and Savulescu, nobody can know for sure how to use these drugs safely and effectively (46); in fact, there is a dearth of scientific evidence as to the large-scale use of nootropics [or other techniques such as transcranial electrical stimulation (47)] aimed at human enhancement. As pointed out by the British Medical Association in 2015, it is difficult to improve the cognitive capabilities of healthy individuals already functioning at an optimum level (48). Currently available evidence suggests that healthy individuals seeking to preserve or enhance their cognitive capabilities should avoid pharmacological cognitive enhancers and focus instead on a healthy and rewarding lifestyle; that is in our opinion a sensible and well-balanced approach. More thorough research is undeniably necessary, if we are to ever dispel the lingering doubts about cognitive enhancement: medical professional organizations will then be able to outline evidence-based professional criteria, recommendations, and guidelines for large-scale cognitive enhancement for healthy users. Ultimately, in the view of the author, the fundamental standard to be met is safety: given the scarcity of scientific evidence as to the actual enhancing capabilities of nootropics and their potential for unwanted harmful side-effects, recommendations from international health care bodies should be quite strict and essentially against their use. After all, there are several instances of protective/restrictive measures and approaches that are dictated by the prioritization of safety, when it comes to techniques and drugs aimed at improving performance rather than treating diseases: the use of performance-enhancing drugs in sports certainly falls within that category. Erythropoietin abuse among cyclists has been tackled and harshly punished in the name of safety for athletes, and an approach along those lines, the author believe, could also be adopted toward nootropics use in society at large.

AUTHOR CONTRIBUTIONS

The author designed, drafted, and wrote the review paper.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

BRIEF RESEARCH REPORT
published: 28 February 2020
doi: 10.3389/fpsyt.2020.00158

Long-Term Outcome of Repetitive Transcranial Magnetic Stimulation in a Large Cohort of Patients With Cocaine-Use Disorder: An Observational Study

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: 05 December 2019
Accepted: 19 February 2020
Published: 28 February 2020

Citation:
Madeo G, Terraneo A, Cardullo S, Gómez Pérez LJ, Cellini N, Sarlo M, Bonci A and Gallimberti L (2020) Long-Term Outcome of Repetitive Transcranial Magnetic Stimulation in a Large Cohort of Patients With Cocaine-Use Disorder: An Observational Study. Front. Psychiatry 11:158. doi: 10.3389/fpsyt.2020.00158

Background: Cocaine is a psychostimulant drug used as performance enhancer throughout history. The prolonged use of cocaine is associated with addiction and a broad range of cognitive deficits. Currently, there are no medications proven to be effective for cocaine-use disorder (CocUD). Previous preliminary clinical work suggests some benefit from repetitive transcranial magnetic stimulation (rTMS) stimulating the prefrontal cortex (PFC), involved in inhibitory cognitive control, decision-making and attention. All published studies to date have been limited by small sample sizes and short follow-up times.

Methods: This is a retrospective observational study of 284 outpatients (of whom 268 were men) meeting DSM-5 criteria for CocUD. At treatment entry, most were using cocaine every day or several times per week. All patients underwent 3 months of rTMS and were followed for up to 2 years, 8 months. Self-report, reports by family or significant others and regular urine screens were used to assess drug use.

Results: Median time to the first lapse (resumption of cocaine use) since the beginning of treatment was 91 days. For most patients, TMS was re-administered weekly, then monthly, throughout follow-up. The decrease in frequency of rTMS sessions was not accompanied by an increase in lapses to cocaine use. Mean frequency of cocaine use was <1·0 day/month (median 0), while serious rTMS-related adverse events were infrequent, consistent with published reports from smaller studies.

Conclusions: This is the first follow-up study to show that rTMS treatment is accompanied by long-lasting reductions in cocaine use in a large cohort.

Keywords: cocaine use disorder (CocUD), transcranial magnetic stimulation (TMS), left dorsolateral prefrontal cortex (l-DLPFC), long-term follow up, addiction

INTRODUCTION

Cocaine is a psychostimulant drug generally used as enhancer of cognitive performances, confidence, sociability, energy, and wakefulness. However, cocaine has been a focus of attention on a global scale for the serious harms related to its use, including addiction and cognitive dysfunctions. Currently, no medications have been proven to be effective for cocaine use disorder (CocUD). The traditional strategy has been to develop medications or psychological interventions to attenuate drug reward, which is mainly mediated by the dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens. This approach has not resulted in effective therapeutic interventions for cocaine addiction. Recently, repetitive transcranial magnetic stimulation (rTMS) has received increasing attention as a potential treatment for CocUD (1). As we and others have suggested, rTMS of left dorsolateral prefrontal cortex (l-DLPFC) may represent a human translation of preclinical findings that cocaine-seeking is attenuated by optogenetic activation of specific prefrontal circuits (2, 3). Both preclinical and clinical findings suggest that DLPFC has a key role in top-down modulation of emotional and behavioral processes relevant to addiction (4, 5). Thus, exogenously increasing the neuronal excitability of DLPFC via high-frequency rTMS might help reduce craving and prevent lapse[*1] to cocaine use.

Clinical confirmation that rTMS is effective for CocUD awaits results from randomized controlled trials that are now in progress. Studies published to date are limited by small sample sizes and short duration of follow-up. In almost half the published studies using rTMS or a similar intervention for CocUD, there was, strictly speaking, no follow-up: responses (e.g., cocaine craving) were assessed only within the laboratory on the day of stimulation (6–9). In 6 studies that assessed real-world outcomes, follow-up durations ranged from 5 days to 6 months (median 39 days), and the number of cocaine users receiving stimulation ranged from 6 to 36 (median 14) (10–15).

Here we report results from a cohort of 284 cocaine users who received rTMS and were then followed for up to 2 years, 8 months (median 164 days). This is a retrospective chart review, with all the attendant limitations thereof. However, it is also unprecedented in its size and duration. Until there are results from large randomized trials, the data we report here provide the strongest evidence to date that rTMS is well-tolerated and possibly effective in people with CocUD.

METHODS

Study Design and Participants

Patients signed informed consent on the day of clinic intake and agreed that their data could be used for research. Patients were informed that the data collected would be processed in accordance with the law on privacy and in compliance with Legislative Decree No. 196 of June 30, 2003, "Personal Data Protection Code," ensuring anonymity. The data were extracted from patient clinical records and anonymized for analysis. All subjects gave their informed consent for inclusion before they participated in the study. This was a retrospective chart review of data from 284 men and women who were treated from 2013 to 2017 and followed for at least 12 weeks after the first week of rTMS sessions. The protocol, limited to the retrospective chart review, was approved by the Ethical Committee for the Psychological Research, Departments of Psychology, University of Padua (Protocol 2551) and the study was conducted in accordance with the Declaration of Helsinki. The total of 284 includes 58 patients who were lost to follow-up within the first 12 weeks (i.e., this was an intent-to-treat sample) but excludes 44 patients for whom 12 weeks had not yet elapsed when data analysis started. All patients voluntarily underwent treatment for CocUD in an rTMS protocol at a clinic center for addiction treatment in Padua, Italy. At intake, each patient was assessed by a psychiatrist and a psychologist with expertise in the treatment of addiction. A complete family, physiological, remote pathological and near pathological history was collected, in addition to a detailed psychiatric, toxicological and clinical history. Patients were between 18 and 70 years of age and met DSM-5 criteria for CocUD. A published screening form was administered to all the patients to exclude contraindications to rTMS (16). Each patient underwent rTMS using a medical device (MagPro R30) targeting the l-DLPFC. The stimulation parameters, in accord with international recommendations for patient safety and ethics (16), were: frequency 15 Hz, intensity 100% of the motor threshold, 60 impulses per stimulation train, inter-train interval 15 s, and 40 total trains, for a session duration of 13 min. For the first 5 days, patients received two rTMS sessions per day (on either an inpatient or outpatient basis, reflecting the patient's needs). rTMS was then administered on an outpatient basis at weekly intervals (twice per day on each session day) for 11 consecutive weeks, as in our published pilot study (15). rTMS was re-administered throughout follow-up on an individualized basis to patients who reported lapses to cocaine use, and to patients whose clinical evaluations showed ongoing cocaine craving, including stress-induced craving.

Measures

The primary outcome measure was lapse to cocaine use during follow-up. Cocaine use was assessed through a combination of urine screening, self-report, and reports by collateral informants (typically family members). As in our published pilot study (15), the "zero" day for follow-up monitoring was set at 8 days after the initial 5-day course of rTMS (for consistency in outcome analysis, this was done regardless of whether the initial sessions were inpatient or outpatient.) After that 8-day grace period (during which only 29 of 284 patients tested positive for cocaine), any indications of cocaine use (whether by urine or by report) was coded as a lapse. Of the 284 patients,

[1]The terms *lapse* and *relapse* each refer to a resumption of drug use during some period of deliberate abstinence. A lapse is *any* such resumption of drug use, however brief; a relapse is a resumption that is prolonged and problematic. Neither term has a standardized operational definition. In this paper, we refer to any resumption of cocaine use as a lapse. Thus, some of the lapses in our participants could probably be characterized as relapses.

147 maintained regular contact with the clinic through follow-up visits and phone calls, allowing us to reliably trace their precise patterns of cocaine use and abstinence during follow-up. For the other 137 patients, we have reliable data only on the date of initial lapse to cocaine use (if any) or loss to follow-up.

Statistical Analysis

Because this is a retrospective chart review, results are presented descriptively. For the sample as a whole, we used Kaplan-Meier survival analysis (SAS Proc Lifetest) to calculate the median number of days until the first lapse to cocaine use. Data were coded as right-censored for patients who were still abstinent at the end of monitoring (∼44% of censored cases) or with whom the clinic lost contact (∼56% of censored cases). To help contextualize the "first lapse" findings, we display them together with historical control data from an outpatient cohort of 173 cocaine users in the US who were undergoing group and/or individual psychotherapy after discharge from inpatient treatment (17, 18)[2]. The two samples are not intended to be directly comparable, but they share important characteristics: both had just been discharged from an inpatient stay, and both continued to receive treatment as needed during a lengthy outpatient follow-up. For the subset of our 147 patients who were regularly followed, we created a case-by-case display of the relationship between booster sessions of rTMS and stretches of abstinence from cocaine. We know of no published data set to which this can be compared.

Role of the Funding Source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the anonymized data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Patient Characteristics

Demographic and drug-use data are shown in **Table 1**. Most patients were male and were using cocaine at least weekly (typically by nasal insufflation, though in some cases by smoking) before initiation of rTMS.

TABLE 1 | Sample characteristics.

	Total sample ($n = 284$)	Closely followed subsample ($n = 147$)
Age (mean, SD)	38.3 (8.4)	36.6 (7.7)
Sex		
Male	268 (94%)	139 (95%)
Female	16 (6%)	8 (5%)
Cocaine use before treatment entry*		
Daily	45%	30%
Weekly or more (not daily)	45%	51%
Monthly or more (not weekly)	2%	5%
Less than monthly	7%	14%
Cocaine route of administration*		
Snorting	90%	86%
Smoking	9%	11%
Both	1%	3%

Cocaine-use data were available for 126 participants, 43 of whom were in the closely followed subsample; these are the denominators for the percentages. Some percentages add up to slightly <100 due to rounding error.

First Lapse to Cocaine Use in the Sample as a Whole

For the 284 patients in the whole sample, the duration of follow-up ranged from 4 to 989 days (2 years, 8 months); median was 164 days (just over 5 months). Time to the first lapse is shown in **Figure 1**. Median time to the first use of cocaine was 91 days (95% confidence interval 70–109 days). Of the patients who had at least 12 months of follow-up, 10 out of 55 (18%) maintained abstinence throughout. Of the patients who had at least 18 months of follow-up, 2 out of 6 (33%) maintained abstinence throughout. In a separate cohort of "treatment as usual" outpatients, median time to the first use of cocaine was 51 days (95% confidence interval 39-78 days). The difference between "treatment as usual" patients and rTMS patients seemed to emerge most clearly around 80 days after discharge from inpatient treatment.

Patterns of Cocaine Use and Abstinence in the Closely Followed Subsample

In the 147 closely followed patients, the duration of follow-up ranged from 84 days (12 weeks) to 974 days (2 years, 8 months); median was 217 days (just over 7 months). Time courses of rTMS and cocaine use are shown in **Figure 2**. For most patients, rTMS (light rectangles) was re-administered weekly, then monthly. Lapses to cocaine use (black circles) tended to occur every month or so for most patients, but there were long stretches of abstinence between lapses. This is shown in collapsed form in **Figure 3**, which illustrates more clearly that the gradual decrease in re-administration of rTMS (green circles) did not leave patients more vulnerable to lapses to cocaine use (red rectangles). The mean number of cocaine uses per patient was <1·0 day/month (median 0). Self-reported use of other drugs, including alcohol, gave no indication that patients were substituting other drugs for cocaine (data not shown).

Adverse Events

Adverse events (AEs) were reported by 41 of the 284 patients. No patient reported more than one. AEs reported were: headache

[2]The results from the comparison cohort were collected ∼15 years ago as part of a larger data set. The authors who graciously allowed us to use the lapse results were unable to retrieve raw data such as the demographics of the cocaine-using subgroup. In the full comparison sample ($n = 827$), which included people in treatment for dependence on alcohol, marijuana, and heroin, 24% were women, and race/ethnicity were more heterogeneous than in our patients: 47% were European American, 40% were African American, another 12% were classified as Hispanic, and the race of the remaining 1% was classified as "other." Their mean age was 30. For more information, see Dodge et al. (17).

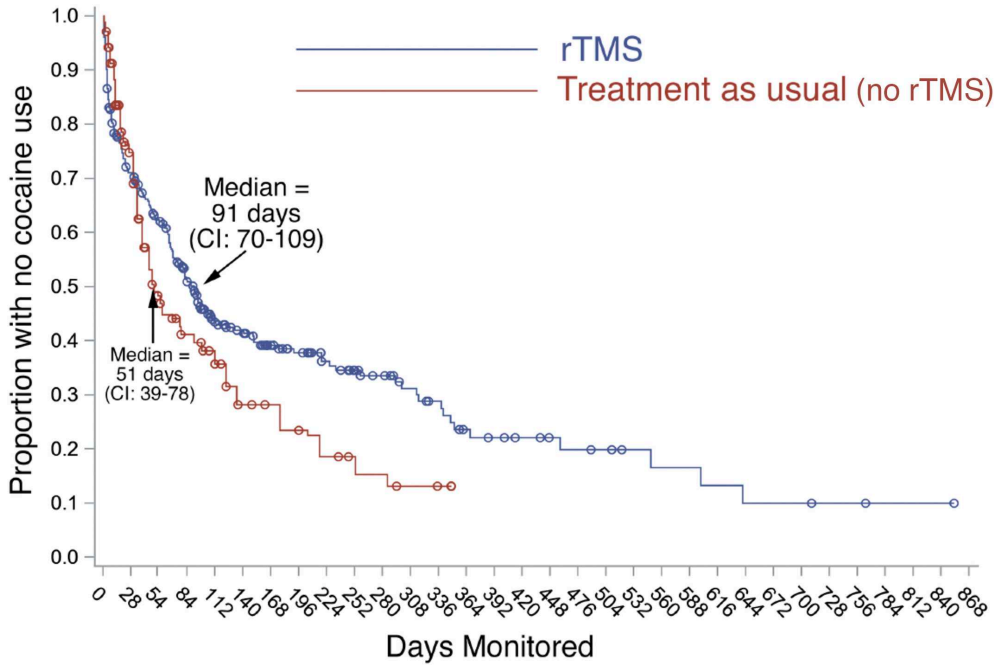

FIGURE 1 | Time to first resumption of cocaine use in full sample and comparison cohort. Blue line: Proportion of our patients ($n = 284$) remaining abstinent from cocaine after the first course of rTMS, monitored by urine screening, self-report, and family corroboration. Day 0 is 8 days after the initial course of rTMS. rTMS continued during follow-up (not shown in this figure). Red line: Proportion of patients in a separate cohort of 173 "treatment as usual (no-rTMS)" outpatients in New Haven, CT (17). Like our rTMS patients, they achieved initial abstinence and were followed up during ongoing treatment (group and individual psychotherapy) for cocaine-use disorder.

($n = 23$), hypomania ($n = 4$), anxiety ($n = 2$) irritability ($n = 2$), dental pain ($n = 2$), scalp discomfort during the first 2 weeks of sessions ($n = 1$), angioedema and urticaria ($n = 1$), distractibility ($n = 1$), dizziness ($n = 1$), nausea ($n = 1$), nausea and numbness ($n = 1$), seizure ($n = 1$), and a hypomanic episode ($n = 1$). The seizure occurred in a 27-year-old woman 66 days after her first rTMS session. She has used cocaine shortly before; she had not recently undergone rTMS. The hypomanic episode occurred in a 37-year-old man, just under 90 days after his first rTMS session. His family reported that he had begun speaking aloud to himself without realizing it. rTMS was suspended for medical examinations, which did not show any abnormalities. Other AEs were transient and resolved spontaneously or with over-the-counter medications.

DISCUSSION

This large set of outcome data adds to the evidence that rTMS can be used to treat CocUD. Our data have all the limitations inherent in retrospective chart review, but one conclusion we can draw confidently is that rTMS for CocUD, at least as administered here, can be considered a long-term rather than only an acute treatment. Several published discussions have stated or implied that rTMS might be a time-limited treatment with lifelong "normalizing" effects on addiction to cocaine or other drugs (19–21). Our findings do not rule that out; we tested only one brain site (left DLPFC) and only one set of stimulation parameters. But at that site, using those parameters, it was feasible, acceptable, and often seemingly necessary to continue treatment sessions p.r.n. for months or years, with adverse events generally few and transient. A similar long-term role has been proposed for rTMS in treatment of mood disorders (22–24). Therefore, rTMS for CocUD may find its place as an additional tool in settings where psychotherapeutic or behavioral treatments are administered. Meta-analyses have repeatedly shown that the most effective known treatments for CocUD are behavioral ones incorporating both tangible incentives for abstinence and social reinforcement of abstinence (25). rTMS could readily be integrated into those behavioral approaches, to be given as needed. Although our data do not permit strong conclusions about the effectiveness of rTMS, it is intriguing to see our outcomes side by side with outcomes in the most comparable cohort we could find. Both cohorts were receiving ongoing care as needed after becoming abstinent from cocaine. The survival curves for resumption of cocaine use indicate a considerably longer duration of abstinence in our rTMS-treated cohort than in the cohort that received "treatment as usual (no-rTMS)" in the form of individual and group psychotherapy.

To our knowledge, there are no available studies in the literature analyzing the lapse rates related to other conventional forms of treatment (pharmacological, pharmaco-,

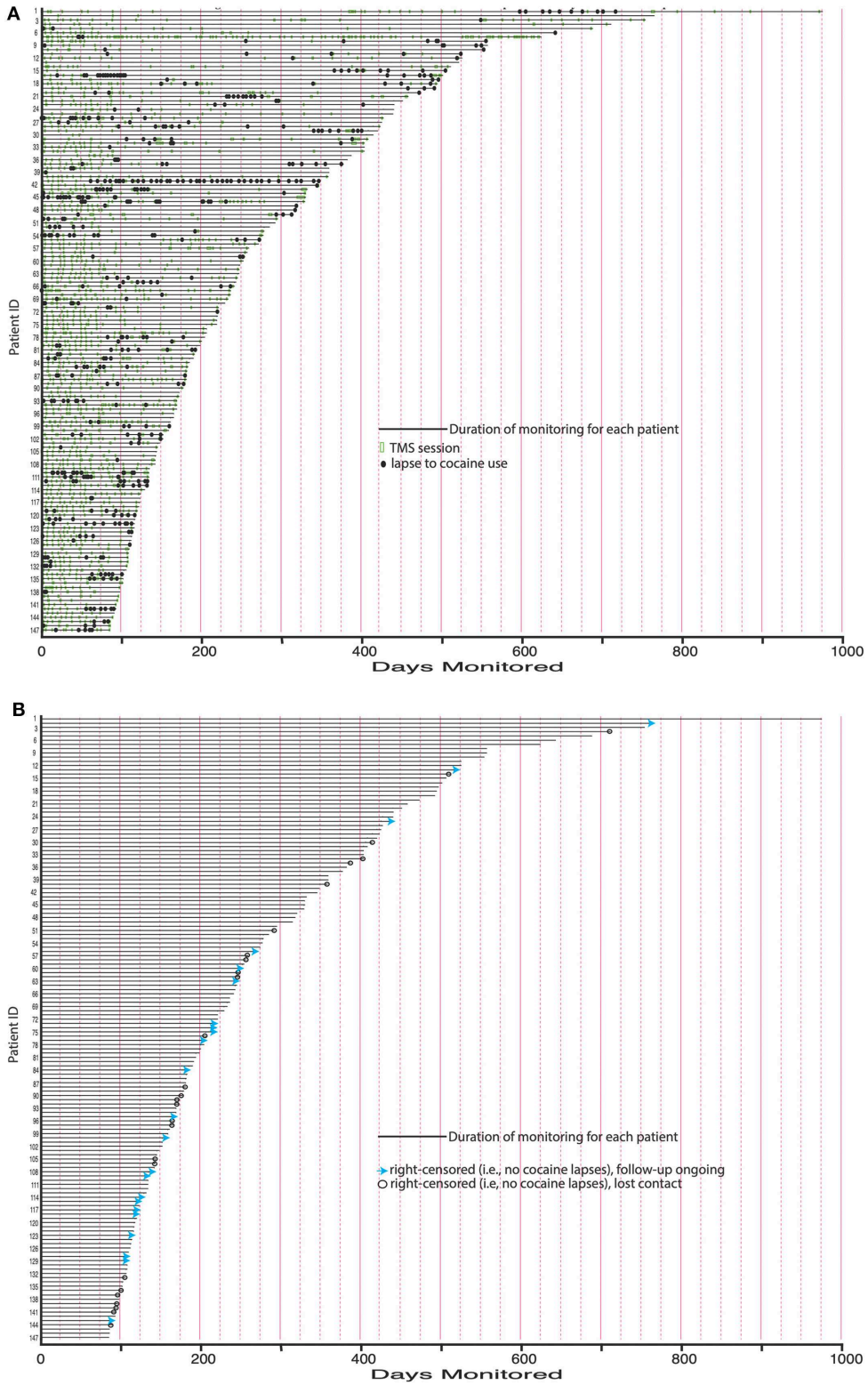

FIGURE 2 | (A) Maintenance rTMS sessions and time between lapses for closely followed subsample. Green rectangles: Maintenance rTMS sessions after the initial 8-day course of rTMS. For most patients, rTMS was readministered weekly, then monthly. This was done in response to lapses and in anticipation of lapses. Black circles: Lapses to cocaine use. Lapses tended to occur approximately every month for most patients, but with long stretches of abstinence separating them. **(B)** Causes of censoring in closely followed subsample. Blue arrows: Continuously abstinent patients for whom follow-up is ongoing. Open black circles: Continuously abstinent patients who were lost to further follow-up.

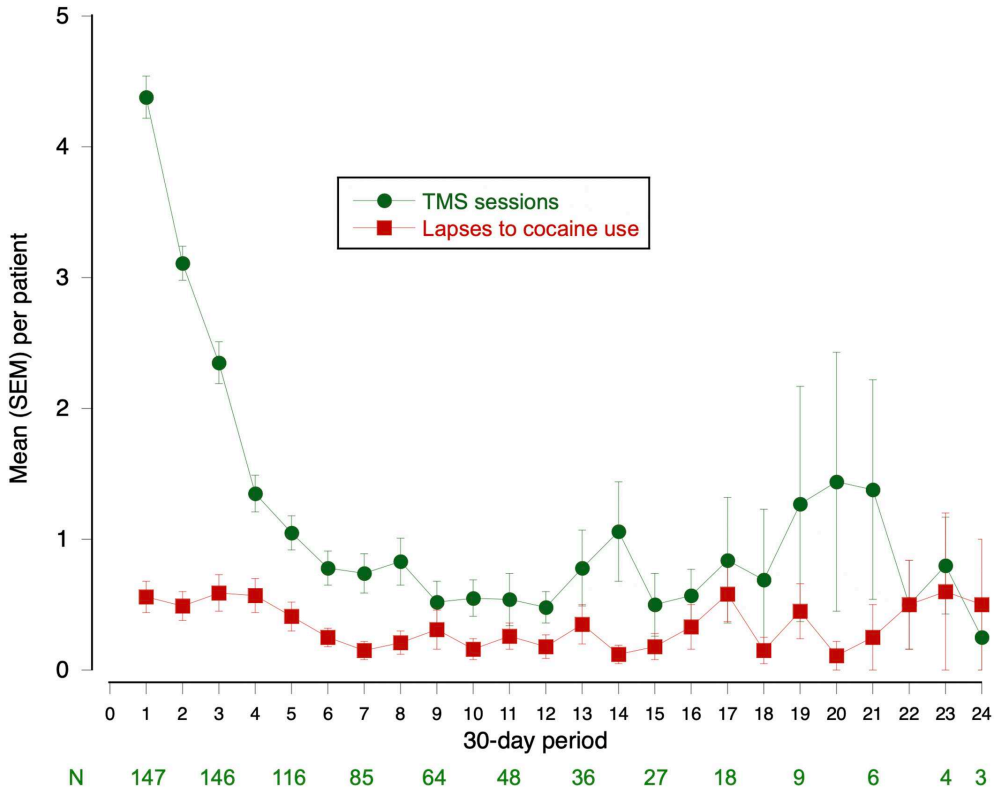

FIGURE 3 | Maintenance rTMS sessions and lapses in closely followed subsample, month by month. This is a collapsed view of data from **Figure 2**. Green line: Mean (SEM) number of rTMS sessions per patient. Red line: Mean (SEM) number of cocaine lapses per patient.

or psychotherapy) for cocaine addiction, especially when considering large cohorts of patients and long period of observation. Nevertheless, we can argue that clinical outcomes, including lapse rate, may show a significant difference compared to conventional treatment for addiction. Compelling evidence from preclinical and clinical studies indicates that rTMS influences neural activity in the short and long term by mechanisms involving neuroplasticity and resulting in substantial behavioral changes (2, 3, 26, 27). These rTMS mediated effects have offered a neural circuit-based treatment for cocaine addiction. Indeed, the long-term neurophysiological changes induced by rTMS on frontal brain regions have the potential to affect behaviors related to drug craving, intake, and relapse and have been proposed as a significant biomarker for predicting treatment outcome.

Human laboratory studies with rTMS suggest that the site we stimulated, left DLPFC, might also be an appropriate target for people with addictions to heroin (28), methamphetamine (29, 30), nicotine (31), or cannabis (32).

In conclusion, rTMS continues to show promise as the first neurobiological treatment for CocUD. Our data add appreciably to the number of patients tested and the length of follow-up. The crucial next step, already under way (e.g., ClinicalTrials.gov identifiers NCT03607591, NCT03333460, and NCT02986438), is represented by sham-controlled randomized trials with sufficient sample size and follow-up duration (33).

DATA AVAILABILITY STATEMENT

The datasets for this article are not publicly available to protect proprietary information. Requests to access the datasets should be directed to LGa (luigigallimberti.novellafronda@gmail.com).

ETHICS STATEMENT

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Local Ethics Committee of University of Padua (Protocol 2551, number code: A0A52E7461375325ABBC1C2D9C54F844). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AT and LGa: conceptualization. GM, SC, and LGó: data curation. SC: formal analysis. SC, GM, and LGó: methodology. AT: project administration. LGa: supervision. GM, AT, SC, LGó, NC, MS, and

LGa: validation. GM, SC, LGó, NC, MS, and LGa: visualization. GM: writing—original draft. GM, AT, SC, LGó, NC, MS, AB, and LGa: writing—review and editing.

FUNDING

This article was funded by the Novella Fronda Foundation, Human and Neuroscience Research, Padua, Italy. Novella Fronda Foundation had no role in data collection, data analysis, data interpretation, or writing of the report. LGa had full access to all the anonymized data in the study and had final responsibility for the decision to submit for publication.

ACKNOWLEDGMENTS

We acknowledge the donors who made liberal donations to support this study. Also, the authors would like to thank the Zardi-Gori Foundation for the fellowship bursary.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 02 April 2020
doi: 10.3389/fpsyt.2020.00166

Effects of Recreational GHB Use and Multiple GHB-Induced Comas on Brain Structure and Impulsivity

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OPEN ACCESS

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: 30 November 2019
Accepted: 21 February 2020
Published: 02 April 2020

Citation:
Raposo Pereira F, McMaster MTB, Schellekens A, Polderman N, de Vries YDAT, van den Brink W and van Wingen GA (2020) Effects of Recreational GHB Use and Multiple GHB-Induced Comas on Brain Structure and Impulsivity. Front. Psychiatry 11:166. doi: 10.3389/fpsyt.2020.00166

Background and Aims: The regular use of gamma-hydroxybutyrate acid (GHB) can induce GHB-induced comas. Other substance use disorders are associated with alterations in brain structure and impulsivity. Here we aim to investigate if these are also modulated by either regular GHB use or GHB-induced comas.

Methods: In a sample of human males, structural and diffusion neuroimaging data were collected for 27 GHB users with ≥4 GHB-induced comas (GHB-Coma), 27 GHB users without GHB-induced comas (GHB-NoComa), and 27 polydrug users who never used GHB (No-GHB). The structural brain parameters were analyzed macroscopically using voxel-based morphometry and microscopically using tract-based spatial statistics (TBSS) and tractography. Impulsivity was assessed with the Barrat Impulsivity Scale.

Results: In comparison to the other two groups, the GHB-Coma group showed a higher fractional anisotropy in the body of the corpus callosum and a lower mean diffusivity in the forceps minor (*i.e.*, whole-brain TBSS analysis). No macrostructural differences nor microstructural differences, as assessed with tractography, were observed. The GHB-Coma group also reported higher impulsivity, which was more strongly associated with white matter volume and fractional anisotropy in tracts involved in impulse control (post-hoc analysis). GHB use per se was associated neither with differences in brain structure nor with impulsivity.

Conclusions: The results suggest that multiple GHB-induced comas, but not GHB use per se, are associated with microstructural alterations in white matter and with higher self-reported impulsivity, which in turn was associated with white matter tracts involved in impulse control.

Keywords: gamma-hydroxybutyric acid, gamma-hydroxybutyric acid-induced comas, neuroimaging, substance use disorders, diffusion imaging, rape drug, impulsivity, corpus callosum

INTRODUCTION

Since it was first synthesized in the 1960s, gamma-hydroxybutyrate acid (GHB) has been regularly used for different therapeutic purposes (1–4). Over the last three decades, however, the unique profile of GHB, combining stimulant and sedative effects, has contributed to its appeal as a recreational drug (1, 3, 4). The appealing effects of the drug start with euphoria, relaxation, and sexual arousal, readily evolving into a state of sedation and altered consciousness when higher doses are used (1–6). This intangible stimulant–sedative shift is dangerously associated with poor control of dosage and effect duration, which creates a high risk for overdosing (including GHB-induced coma), and can lead to tolerance and addiction (2–5). Despite the low prevalence of GHB use (last year's prevalence was 0.1–13% worldwide), the number of GHB users seeking treatment for drug withdrawal and GHB addiction is rising, and GHB overdose ranks as the fourth most common drug related overdose in European emergency rooms (2, 4, 6–8).

GHB-induced comas are among the most common manifestations of GHB overdose, with many chronic heavy users experiencing on average more than 10 lifetime episodes (1–5). These are transient but deep comas that often reach Glasgow Coma Scale scores as low as 3 (totally unresponsive) (1, 2, 4, 5). Regardless, the absence of "hangover" after recovery of consciousness contributes to the erroneous idea among recreational users that GHB use is safe and harmless (1, 2, 4, 5). However, we recently showed that heavy GHB use with multiple GHB-induced comas is associated with differences in cognition and affect, which were linked to the abnormal activation of the prefrontal cortex (PFC) and the limbic regions (*e.g.*, the hippocampus), and their functional connectivity with the temporal–parietal lobe regions involved in perception and attention (9–11). To a smaller extent, GHB use itself was also associated with altered resting state functional connectivity between the executive and the default mode networks (12).

Despite the above evidence, nothing is known about the effects of recreational GHB use and multiple GHB-induced comas on brain structure. On succinic semialdehyde dehydrogenase (SSADH) deficiency, a condition known to induce an abnormal accumulation of GABA and GHB in the brain, gray matter atrophy and white matter myelin alterations in the PFC, insula, limbic system (*e.g.*, hippocampus), and the parietal-occipital cortex have been observed (13, 14). These are brain regions rich in GHB-binding sites and particularly sensitive to GHB-induced neurotoxicity, as shown studies on rodents (15–18). Furthermore, substance use disorders and in particular alcohol-use dependence (another GABAergic dependence), have been associated with substantial alterations in gray matter regions that are often linked to impulse control (*i.e.*, orbital-frontal cortex, anterior cingulate cortex, medial frontal gyrus, and insula) (19–23). Moreover, alterations in white matter tracts implicated in reward processing and inhibitory control have been observed in both substance use disorders and conditions involving altered states of consciousness (*i.e.*, inferior frontal-occipital fasciculus, IFOF; inferior longitudinal fasciculus, ILF; uncinate fasciculus, UF; cortical spinal tract, CST; internal capsule, corona radiate, superior longitudinal fasciculus, SLF; cingulum; or corpus callosum, CC) (19, 20, 22–29). Such alterations might be the structural correlate underlying the high levels of impulsivity that are often comorbid with these conditions (2, 19, 20, 22–25, 30).

This study aimed to investigate the effects of recreational GHB use and multiple GHB-induced comas on impulse control and brain structure. Self-reported impulsivity was measured with the Barratt Impulsivity Scale (BIS). The macrostructural differences were assessed with voxel-based morphometry analysis (VBM) of structural magnetic resonance imaging (sMRI) data, and diffusion-weighted imaging (DWI) data were investigated with a univariate whole-brain level tract-based spatial statistical analysis (TBSS) or with a region-of-interest (ROI) probabilistic tractography analysis (TrackVis), focused on the ILF, IFOF, and UF, for the assessment of microstructural differences. To distinguish between the effects of recreational GHB use as such and multiple GHB-induced comas, three different groups of participants were recruited: (1) GHB users who had ≥4 GHB-induced comas, (2) GHB users who never had a GHB-induced coma, and (3) polydrug users who never used GHB. We tested the following hypotheses:

a. Regular recreational users of GHB who had multiple GHB-induced comas show higher impulsivity and macrostructural and microstructural brain alterations when compared to GHB users who never had a GHB-induced coma and to polydrug users who never used GHB.
b. Regular recreational users of GHB who never had a GHB-induced coma show higher impulsivity and macrostructural and microstructural brain alterations when compared to polydrug users who never used GHB.

Abbreviations: ANOVA, analysis of variance; AD, axial diffusivity; BIS, Barrat Impulsivity Scale; BET, brain extraction tool; CBT, cognitive behavioral therapy; CAT12, Computational Anatomy Toolbox 12; CC, corpus callosum; CST, cortical spinal tract; DWI, diffusion-weighted imaging; FWE, family-wise-error; FOV, field of view; FA, fractional anisotropy; FWHM, full-width half-maximum; fMRI, functional magnetic resonance imaging; GHB, gamma-hydroxybutyrate acid; IFOF, inferior frontal-occipital fasciculus; ILF, inferior longitudinal fasciculus; IQ, intelligence quotient; MPRAGE, magnetization-prepared rapid gradient echo; MD, mean diffusivity; MNI, Montreal Neurologic Institute; MET, motivation enhancement therapy; PFC, prefrontal cortex; RD, radial diffusivity; SPM, Statistical Parametric Mapping software; sMRI, structural magnetic resonance imaging; SSADH, succinic semialdehyde dehydrogenase; SLF, superior longitudinal fasciculus; TFCE, threshold-free cluster-enhancement permutation tests; TIV, total intracranial volume; TBSS, tract-based spatial statistics; UF, uncinate fasciculus; VBM, voxel-based morphometry.

MATERIALS AND METHODS

Participants

The participants (n = 81) were recruited for this cross-sectional study through addiction centers in The Netherlands, flyers, internet advertisements, and snowball sampling. Three different groups of male participants, matched on age and

education level, were included: 27 GHB users with ≥4 GHB-induced comas (GHB-Coma), 27 GHB users without GHB-induced comas (GHB-NoComa), and 27 polydrug users who never used GHB (No-GHB). The criteria considered in this study were a result of self-reported parameters and urine tests. The inclusion criterion for the GHB-Coma group was >4 GHB-induced comas (to increase the contrast with GHB-NoComa group). The inclusion criterion for the GHB groups was the use of GHB ≥25 times within the 2 years preceding this assessment. The overall inclusion criteria were age (between 18 and 40 years), native Dutch speaker, and male gender (since the majority of GHB users are males) (4, 5, 9). The polydrug use criteria consisted in the co-use of alcohol, nicotine, cannabis, cocaine, any other stimulants (amphetamines, khat, and methylphenidate), ecstasy, ketamine, and/or sedatives (benzodiazepines). Abstinence from recreational drugs for at least 24 h preceding the initiation of this study was required from all of the participants. The overall exclusion criteria were a history of epilepsy, general anesthesia within the 2 years preceding the study, a contra-indication for functional magnetic resonance imaging (fMRI) scanning (*e.g.*, metal objects in the body or head injury), any coma unrelated to GHB use, and currently under treatment for narcolepsy with cataplexy (since the treatment may involve the use of medication based on GHB). The participants excluded due to low-quality scans were two GHB-Coma and two no GHB cases, respectively. The study procedures were explained prior to the assessments and written consent was obtained from the participants. This study was performed in accordance with the Helsinki Declaration principles (7th revision, 2013) and the Medical Research Involving Human Subjects Act (WMO, 1998) and approved by the Medical Ethics Review Committee of the Academic Medical Centre (ethical protocol number: METC 2014_172) (31).

Procedure

The data herein presented were part of a study assessing the effects of chronic GHB use and GHB-induced comas in the human brain. It entailed a urine test, self-reporting questionnaires (*i.e.*, substance use habits, negative affect, and impulsivity), and structural and functional imaging scans collected as follows: sMRI, resting state (fMRI), episodic memory (fMRI), DWI, working-memory (fMRI), and emotion identification (fMRI). Outside the scanner, the participants performed digitized neuropsychological tests concerning verbal memory, spatial memory, intra-/extra-dimensional set shifting, and probabilistic reversal learning. In this report, we will only present data on impulsivity and brain structure. Other findings have been presented elsewhere (9–12).

Questionnaires and Cognitive Testing

To assess the use of recreational drugs other than GHB, the participants completed the MATE 2:1 substance use questionnaire (32). The Dutch version of the adult reading test was used to assess premorbid intellectual functioning, considered a proxy for intelligence quotient (IQ) (33). Individual differences in impulsivity were assessed with the self-reported BIS (34, 35). This scale consists of six first-order factors (attention, cognitive instability, motor, perseverance, self-control, and cognitive complexity), each comprising three to seven items presented in random order. Each item is scored from 1 to 4, from never to always feeling a certain way, respectively (35). The scores of all items are then summed up per factor, where higher scores indicate higher impulsivity levels and lower scores indicate lower impulsivity levels (35).

Statistical Analysis of Demographic and Clinical Data

Demographic and clinical data were analyzed with the SPSS24 software (IBM Software Analytics, New York, USA). Normally distributed data were evaluated through ANOVA. If not normally distributed, the data were transformed in order to obtain a normal distribution or were evaluated with non-parametric tests (**Tables 1** and **2**). The GHB use groups were tested for differences in daily dose (ml/day), days of using GHB in the preceding month, months of daily use, and total exposure as defined by years of use × daily dose. All of the groups were tested for differences in co-use of alcohol, nicotine, cannabis, cocaine, stimulants (amphetamines, khat, methylphenidate), ecstasy, ketamine, and sedatives (benzodiazepines). This was performed by assessing the self-reported measures of drug use considered in the MATE 2:1 questionnaire and represented here by a computed variable of total exposure to each substance (*i.e.*, years of weekly use × daily dose; **Table 2**). The study groups were assessed for differences in impulsivity (BIS subscale; **Table 1**) (35).

TABLE 1 | Demographic and behavioral data.

	GHB-Coma (*N* = 27)		GHB-NoComa (*N* = 27)		No-GHB (*N* = 27)		Difference
	Mean	± SD	Mean	± SD	Mean	± SD	*P**
Age	25.60	5.43	26.22	4.58	27.76	9.31	0.506[a]
Educational level	6.56	1.61	6.81	1.18	6.64	1.41	0.799[a]
Premorbid IQ	90.20	10.30	97.63	7.52	93.88	8.32	0.027c,b[1,*]
Daily dose of GHB (ml/day)	48.16	41.09	17.87	11.17	–	–	< 0.001[b,*]
Days of GHB use last 30 days	12.96	13.23	2.85	2.16	–	–	0.039[b,*]
Months of daily GHB use	24.64	43.69	0.12	0.37	–	–	0.001[b]
BIS attention	12.72	2.46	10.96	2.55	11.92	2.55	0.049
BIS cognitive instability	7.68	2.01	6.59	2.00	6.04	1.74	0.013
BIS motor impulsivity	16.48	3.44	15.07	3.64	15.07	3.64	0.129
BIS perseverance	7.56	1.69	7.85	1.46	8.16	1.40	0.376
BIS self-control	14.80	2.58	12.59	3.17	12.56	1.94	0.005 b,c,2,3,*
BIS cognitive complexity	12.84	2.90	11.48	2.28	11.81	2.55	0.103

SD, standard deviation; a, ANOVA; b, Mann–Whitney U; c, Kruskal–Wallis. [1]Post-hoc Mann–Whitney U: premorbid IQ_GHB-Coma < GHB-NoComa, p = 0.008. [2]Post-hoc Mann–Whitney U: self-control_GHB-Coma > GHB-NoComa, p = 0.012. [3]Post-hoc Mann–Whitney U: self-control_GHB-Coma > No-GHB, p = 0.002.

TABLE 2 | Exposure to recreational drugs (MATE2.1).

Exposure to recreational drugs							
	GHB-Coma (*N* = 27)		GHB-NoComa (*N* = 27)		No-GHB (*N* = 27)		Difference
	Mean	SD	Mean	SD	Mean	SD	*p*[a]
Alcohol	4.98	11.89	11.94	23.76	12.57	35.55	0.258
Nicotine	105.35	137.90	40.31	61.70	42.13	86.48	0.082
Cannabis	5.09	9.00	3.36	5.45	3.68	6.13	0.876
Cocaine	1.84	5.24	0.20	0.50	0.03	0.12	$0.045^{2,3,*}$
Stimulants	3.63	7.84	0.57	2.15	0.16	0.39	$0.003^{2,3,*}$
Ecstasy	2.10	5.00	0.09	0.32	0.41	1.38	$0.013^{1,*}$
Ketamine	0.17	0.47	0.22	0.87	0.06	0.20	0.519
Sedatives	1.65	7.78	0.16	0.80	0.00	0.00	$0.001^{1,2,*}$

*SD, standard deviation. a, Kruskal–Wallis. [1]Post-hoc analysis Mann–Whitney U: GHB-coma > GHB-NoComa; ecstasy, p = 0.005; sedatives, p = 0.010. [2]Post-hoc analysis Mann–Whitney U: GHB-Coma > No-GHB; cocaine, p = 0.014; stimulants, p = 0.002; sedatives, p = 0.001. [3]Post-hoc analysis Mann–Whitney U: GHB-NoComa > No-GHB; cocaine, p = 0.050; stimulants, p = 0.007. *p < 0.05.*

Image Acquisition

Diffusion-weighted and structural images were collected with a 3.0-T Ingenia scanner with a 32-channel head coil (Phillips Medical System, Best, The Netherlands). T1-weighted structural images (sagittal acquisition; voxel size: 1.0 × 1.0 × 1.0 mm^3; flip angle: 9°; field of view: 256 × 240 mm^2) were acquired with a magnetization-prepared rapid gradient echo sequence for spatial normalization purposes. Diffusion-weighted images were acquired in 32 isotropic directions in order to test white matter abnormalities. Each image consisted of 48 transverse slices (TE: 92 ms; voxel size: 2.5 × 2.5 × 2.5 mm^3; flip angle: 90°; matrix: 94 × 94; b-value= 1,000 s/mm; 30 diffusion-weighted directions).

Structural MRI Preprocessing and Analysis

Preprocessing of structural data was conducted using the Computational Anatomy Toolbox 12 (CAT12; v.1363, http://dbm.neuro.uni-jena.de/cat12/) as implemented on Statistical Parametric Mapping software (SPM12 v.7219, Welcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/software/spm12). Prior to preprocessing, the origin was manually set to the anterior commissure. T1-weighted images were segmented into gray matter, white matter, and cerebral spinal fluid after bias-field correction to remove non-uniformities in intensity, normalized into Montreal Neurologic Institute (MNI152) space, and smoothed using a Gaussian kernel of 8 mm at full-width half-maximum. In addition, total intracranial volume (TIV) was estimated to correct for differences in total brain size.

A voxel-based analysis of gray and white matter images thresholded at a tissue probability of 0.15 was performed to assess the macrostructural volume differences between groups. Since the differences between the groups were found in IQ and exposure to cocaine, stimulants, ecstasy, and sedatives, these were introduced as nuisance covariates in a general linear model (IQ as linear variable; co-exposure to the four substances as dummy variables). The number of variables representing co-exposure to other drugs in which group differences were observed was adapted to the sample size considered for each neuroimaging method of analysis. TIV was used to correct for differences in brain volume across subjects (36).

DTI Preprocessing

Preprocessing of DTI data was conducted with the FMRIB Software Library 5.0.10 (FSL; Analysis Group, FMRIB, Oxford, UK; www.fmrib.ox.ac.uk/fsl) (37). Pre-processing consisted in eddy-current correction of potential distortions induced by gradient coils and head motion artefacts, individual non-brain tissue removal with the brain extraction tool, estimation of the diffusion tensor model at each voxel with the DTIFit tool, generating fractional anisotropy (FA; degree of diffusion directionality), mean diffusivity (MD; average diffusivity rate), axial diffusivity (AD; diffusion rate along the main axis of the tensor), and radial diffusivity (RD; diffusion rate transverse to the main axis of the tensor) scalars (23–25, 38). The diffusion tensor was then assessed for voxel-wise microstructural differences in white matter, at whole-brain with TBSS, or at three *a priori* defined ROI (tracts) with streamline tractography analysis.

Whole-Brain TBSS Analysis

Whole-brain white matter differences were assessed with TBSS (FSL) as follows: (1) non-linear alignment of individual pre-processed FA images to a common FMRIB58 FA brain template (MNI152, 1 × 1 × 1 mm space), (2) averaging of aligned images into a mean FA map of all individual FA images, (3) creation of a mean FA skeleton map and a mean FA mask by computing a white matter tract skeleton into the mean FA map, and (4) creation of an all-skeletonized FA map (preserving only the central voxels of tracts common to all subjects) thresholding the mean FA skeleton map at 0.2 (39). All FA skeletonized data were submitted to voxel-wise statistical analyses. IQ, exposure to cocaine, stimulants, ecstasy, and sedatives were introduced as nuisance covariates as described previously. The same analysis was repeated for MD, AD, and RD scalars by projecting the aligned individual images of each participant into the created mean FA skeleton map.

Tractography ROI Analysis

Tractography was performed on the ILF, the IFOF, and the UF based on their involvement in impulse control and proximity to regions where functional alterations were associated with recreational GHB use (9–11, 19, 23, 24, 26). Integrity differences in these tracts were assessed with streamline tractography using the TrackVis software (v0.6.01;Wang R, Wedeen VJ, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, 2015, www.trackvis.org/download/). For compatibility reasons, data were transformed from nifti to dtk format, and the tensor orientation was flipped around the z-axis (diffusion toolkit; v0.6.4.1; Wang R, Wedeen VJ, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, 2016). 3D virtual dissections were performed per participant, per tract and per hemisphere, by manually delineating two ROIs per tract on the FA maps of each participant based on established references of regions crossed by specific tract bundles (40, 41).

An exclusion ROI was hand-drawn when needed for undesirable streamline elimination. The following ROIs were drawn on white matter: (a) ILF_ROI1: sagittal plane (first coronal slice, posterior edge of the cingulum), entire occipital area from the parietal–occipital sulcus medially to the temporal–occipital junction laterally; (b) ILF_ROI2: sagittal plane (most posterior slice, separation between the temporal and frontal lobes), entire ipsilateral–temporal lobe; (c) IFOF_ROI1: sagittal plane (first coronal slice between the posterior edge of the cingulum and of the parietal–occipital sulcus), entire occipital region posterior to the parietal–occipital sulcus and the temporal–occipital junction; (d) IFOF_ROI2: sagittal plane (first coronal slice, leveled at the anterior edge of the CC genu), entire external capsule; and (e) UF_ROI1: identical to IFOF_ROI2. UF_ROI2: sagittal plane (most posterior coronal slice, separation between the temporal and frontal lobes), entire anterior temporal lobe extending prior to the tract's u-shape section. When all tracts were identified, the mean FA, MD, AD, and RD data were extracted and assessed with Kruskal–Wallis non-parametric tests; family-wise-error (FWE) rate was corrected ($p_{FWE} < 0.05$) for multiple comparisons using a height threshold of $p < 0.001$ and a Bonferroni correction to account for the multiple ROIs tested.

Statistical Analysis of Voxel-Wise Neuroimaging Data

For VBM and TBSS analyses, multiple voxel-wise comparisons were corrected with threshold-free cluster enhancement permutation tests (TFCE; $p_{FWE} < 0.05$) (36). Two orthogonal planned contrasts were used to test our hypothesis considering GHB-induced coma (contrast a; GHB-Coma group vs. GHB-No Coma group and No-GHB group) or GHB use per se (contrast b; GHB-NoComa group vs. No-GHB group).

RESULTS

Demographic and Clinical Characteristics

There were no significant group differences in age (mean ± SD = 26.51 ± 6.90) and education level (mean ± SD = 6.67 ± 1.40; **Table 1**) in any of the different sample sizes that had to be considered for each neuroimaging method of analysis (due to the quality of data acquisition). However, premorbid IQ was significantly lower in the GHB-Coma than in the GHB-NoComa group ($p = 0.008$). On average, the GHB-Coma group used GHB in higher daily doses ($U = 139$, $p < 0.001$), more frequently in the preceding month ($U = 229$, $p = 0.018$), and daily during more months ($U = 192$, $p = 0.001$) when compared to the GHB-NoComa group. The co-use of recreational drugs was also significantly different between groups ($p_{FWE} < 0.05$; **Table 2**). Overall the GHB-Coma group used more ecstasy and sedatives than the GHB-NoComa group and more cocaine, other stimulants, and sedatives than the No-GHB group, while the GHB-NoComa group used more cocaine and other stimulants than the No-GHB group. Such differences were considered in our neuroimaging analysis by introducing them as nuisance covariates. Finally, the GHB-Coma group showed lower attention and self-control and higher cognitive instability than the other two groups. However, when the analysis was Bonferroni corrected for multiple comparisons ($\alpha = .05/6 = 0.008$), only self-control [higher impulsivity; $X^2(2) = 10.437$, $p = 0.005$] remained statistically lower in the GHB-Coma group compared to the GHB-NoComa group and the No-GHB group ($p = 0.012$ and $p = 0.002$, respectively).

Neuroimaging Data

When testing for the effect of GHB-induced coma, in comparison with the other two groups, the GHB-Coma group showed higher FA in the body of the CC and lower MD in the forceps minor (tracts identified with DTI-JHU atlas; **Table 3**; **Figure 1**) (40). No differences in the brain macrostructure nor in tractography were found. When testing for the effect of GHB use per se, no significant differences were observed. During the analysis of the neuroimaging data, the following participants were excluded per neuroimaging method due to excessive head movement inside the scanner or insufficient brain coverage: GHB-Coma group: three VBM, two TBSS, and two tractography; GHB-NoComa group: one VBM, two TBSS, and four tractography; No-GHB group: two VBM, four TBSS, and four tractography. These differences in the sample number were considered throughout the analysis of demographic and clinical data and values were adjusted whenever necessary. However, in **Table 1** and **Table 2**, the data presented concerns the totality of the study sample.

Correlations

In a *post hoc* analysis, we assessed whether group differences in impulsivity were associated with macrostructure or microstructure (DTI indices from TBSS or tractography analyses) data by using a group-by-impulsivity interaction controlled for IQ, cocaine, other stimulants, ecstasy, sedatives, and TIV (19, 22, 23). Macrostructurally (VBM), when compared with the other two groups, the GHB-Coma group showed a stronger correlation with white matter volume of the posterior SLF (**Table 4** and **Figure 2**). When the four DTI indices assessed with TBSS were considered, the same interaction analysis

TABLE 3 | White matter tracts where increased fractional anisotropy and decreased mean diffusivity were observed in the GHB-Coma group when compared with the GHB-NoComa group and the No-GHB group.

Microstructural differences in white matter integrity associated with multiple GHB-induced comas						
Regions	**L/R**	**MNI coordinates**				
		X	**Y**	**Z**	**Voxels**	***P***
Increased FA coma > others						
Body of corpus callosum	L	-14	2	32	369	0.042
Decreased MD coma > others						
Forceps minor	L	-17	40	-7	8,188	0.03

R, right; L, left; FA, fractional anisotropy; MD, mean diffusivity; MNI: Montreal Neurological Institute. Differences resulting from a tract-based spatial statistical (TBSS) analysis of white matter; family-wise-error (FWE; p < 0.05) corrected using threshold-free cluster enhancement (TFCE).

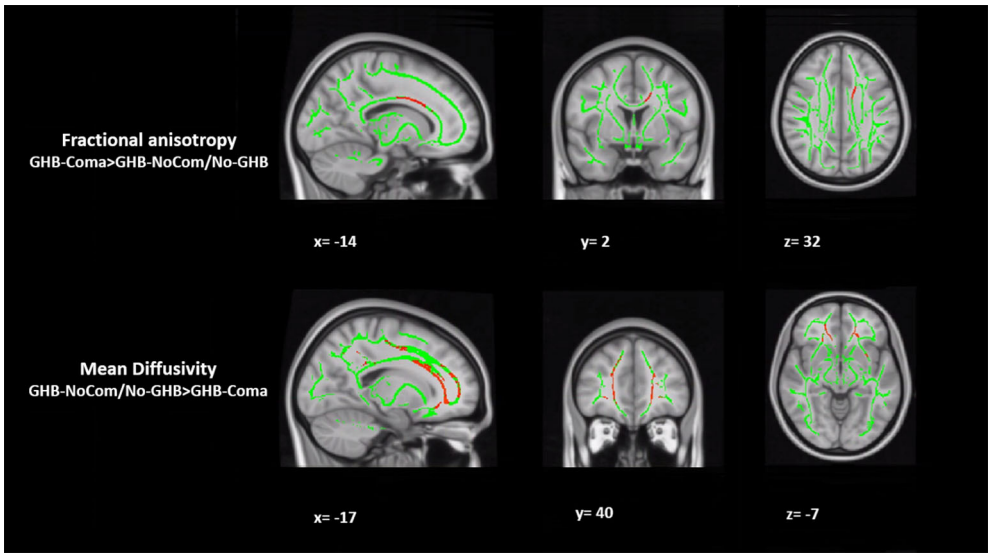

FIGURE 1 | Tract-based spatial statistical (TBSS) analysis of white matter. The figure represents the sagittal, coronal, and axial brain planes of white matter skeleton (in green), with representations of increased fractional anisotropy of the body of the corpus callosum and decreased mean diffusivity of the forceps minor in the GHB-coma group, when compared with the GHB-no coma group and the No-GHB group (in red). [family-wise-error (FWE; $p < 0.05$) corrected using the threshold-free cluster enhancement (TFCE)].

TABLE 4 | List of the white matter tracts resulting from a group-by-impulsivity interaction analysis (according to different neuroimaging techniques, *i.e.*, VBM, TBSS, and tractography) showing significant interactions with impulse control in the GHB-oma group when compared with the GHB-NoComa group and the No-GHB group.

White matter regions interacting with self-control (impulsivity) found in association with the effect of multiple GHB-induced comas						
Regions	**L/R**	**MNI coordinates**				
		X	**Y**	**Z**	**Voxels**	***P***
VBM						
White matter volume <-> impulsivity						
Superior longitudinal fasciculus (III)	L	-45	-33	1.5	425	0.034[a]
TBSS						
FA <-> impulsivity						
Body of corpus callosum	L	-16	-26	33	1,455	0.033[a]
Uncinate fasciculus	L	-26	30	10	1,228	0.037[a]
Tractography						
FA <-> impulsivity						
Uncinate fasciculus	L	–	–	–	$F = 3.528$	0.065[b]
Tractography						
AD <-> impulsivity						
Uncinate fasciculus	L	–	–	–	$F = 3.534$	0.065[b]

VBM, voxel-based morphometry; TBSS, tract-based spatial statistics; R, right; L, left; FA, fractional anisotropy; AD, axial diffusivity; MNI, Montreal Neurological Institute. [a]Analysis family-wise-error (FWE; $p < 0.05$) corrected using threshold-free cluster enhancement (TFCE). [b]Analysis FWE ($p < 0.05$) uncorrected for multiple comparisons

showed a stronger correlation between impulsivity and FA of the left cingulum and the left UF in the GHB-Coma group when compared with the other two groups (**Table 4**; **Figure 3**). Lastly, a similar interaction was assessed with an ANOVA on the four DTI indices (per tract and per hemisphere) obtained from tractography assessment. This showed similar tendencies for the FA and AD of the left UF, which did not survive correction for multiple comparisons (**Table 4**). No interaction effect was observed between gray matter and impulsivity.

DISCUSSION

GHB-induced comas seem to be associated with anatomical differences exclusively in the white matter at a microstructural level. Furthermore, the GHB-Coma group reported higher impulsivity than the other two groups, which strongly interacted with the FA of the left corpus callosum body and the left UF microstructurally and macrostructurally with the left SLF. No morphological brain differences were associated with GHB use per se, indicating that the structural brain abnormalities were primarily related to GHB-induced comas.

When compared with the other two groups, a voxel-wise TBSS analysis showed increased FA in the body of the CC and decreased MD in the forceps minor (part of the CC) of the GHB-Coma group. In contradiction of our first hypothesis, increased FA and decreased MD are general indicators of white matter integrity. This suggests that the anatomical alterations observed might have been present already before the occurrence of GHB-induced comas and represent a risk factor for the onset and development of heavy chronic use of GHB (22, 26, 42, 43). However, a similar directionality in FA and MD has been associated with different acute and subacute unconscious periods (hours to weeks) as a consequence of cytotoxic edema

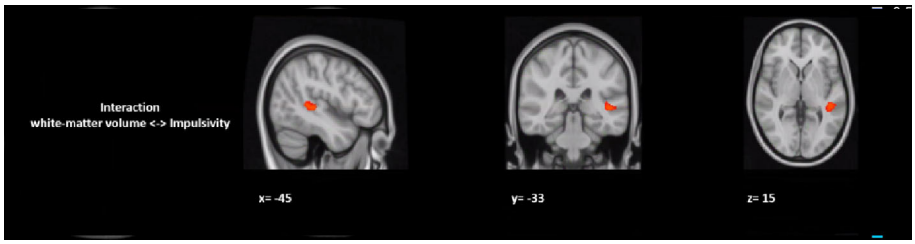

FIGURE 2 | Group by impulsivity interaction analysis between white matter volume (macrostructure) and self-control. The figure represents the sagittal, coronal, and axial brain representations of a white matter region in the superior longitudinal fasciculus, shown to strongly interact with the self-control levels of the GHB-coma group when compared to the GHB-no coma group and the no GHB groups. [family-wise-error (FWE; $p < 0.05$) corrected using the threshold-free cluster enhancement (TFCE)].

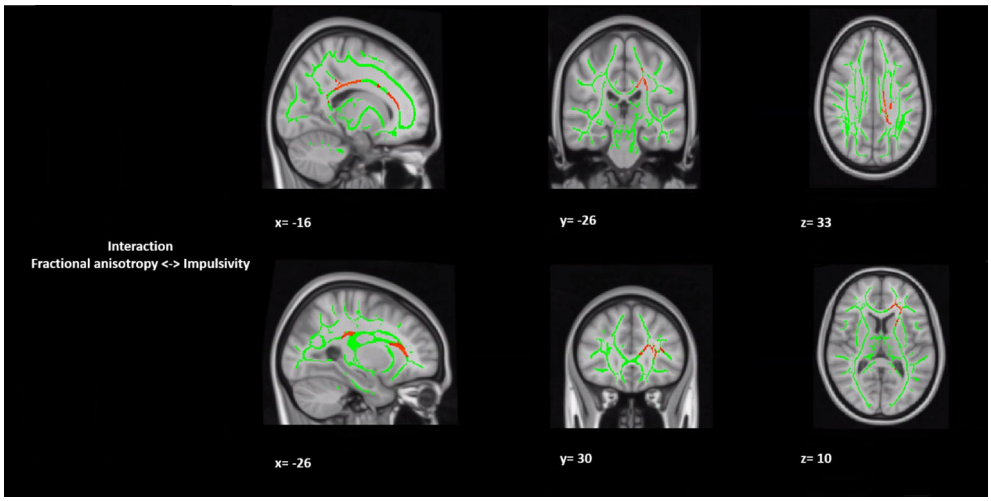

FIGURE 3 | Group by impulsivity interaction analysis between white matter integrity (microstructure) and selfcontrol. The figure represents sagittal, coronal, and axial brain representations of the body of the corpus callosum and the uncinate fasciculus, shown to strongly interact with the self-control levels of the GHB-coma group when compared to the GHB-no coma group and the no GHB group. In green, representation of the white matter skeleton; in red, regions where interaction was different between groups. [family-wise-error (FWE; $p < 0.05$) corrected using the threshold-free cluster enhancement (TFCE)].

(cellular swelling linked to hypoxia) that results from factors such as myelin injuries (42–46). In alcohol use disorders (another GABAergic drug of abuse), the same directionality has also been suggested to be a result of myelin dysregulation, which was correlated with severity of alcohol drinking (47). Together these findings suggest that both or either the number of GHB-induced comas or the heavy doses taken chronically by the GHB-Coma group contribute to the anatomical alterations observed. Nevertheless, only AD or RD are sensitive biomarkers to the axonal or myelin nature of white matter alterations (respectively) and these parameters were not associated with GHB-induced comas (42–46). Thus, the myelin nature of the observed white matter abnormalities remains hypothetical. Furthermore, the CC and the forceps minor (branch of the CC) are tracts responsible for inter-hemispheric communication. Disruption in their integrity has been linked to deficits in affect dysregulation, associative memory, goal-directed behavior, or impulse control (48–50). Interestingly, parts of these fasciculi parallel functional connectivity pathways where alterations were previously associated with the GHB-Coma group while performing similar cognitive processes, suggesting that the alterations found might represent a structural correlate to such functional deficits (9–12).

In contrast to these TBSS findings, no alterations in white matter integrity were found with tractography. However, TBSS assesses local integrity, whereas tractography assesses mean integrity along the entire tract, suggesting that in the GHB-Coma group, microstructural differences in white matter only occur at a more local level (19, 26, 51, 52). Moreover, transient unconsciousness is mostly associated with subtle injuries often observed only in white matter, of which relatively crude methods such as structural MRI lack the sensitivity to detect (23, 25, 26,

53, 54). This was also the case in this study where no macrostructural differences in gray or white matter were observed between the groups. Thus, the occurrence of macroanatomical differences is likely related to a more severe exposure to GHB and/or to multiple GHB-induced comas.

Lastly, since impulsivity is a common comorbidity of substance use disorders (particularly of alcohol use dependence) and a lasting effect of transient unconsciousness, we decided to compare the level of impulse control between the groups (19, 21–26, 29, 53). In the mentioned conditions, gray and white matter alterations have been observed in regions linked to inhibitory control (19, 21–26, 29, 53). Here, although no alterations were observed in gray matter, we found a strong interaction in the GHB-Coma group between self-control and the SLF (macrostructurally) and with the FA of the CC and the UF (microstructurally), tracts that are highly implicated in impulse control. Furthermore, considering the structural alterations observed in the CC of the GHB-Coma group, it is reasonable to assume the involvement of this brain region in self-control. The interaction between the CC and lower self-control in the GHB-Coma group might thus be a neural correlate of the increased impulsivity in this group. Nevertheless, no data are available of the period prior to this study. Hence, this cross-sectional study cannot distinguish between impulsivity as a consequence of heavy GHB use or repeated GHB-induced comas and impulsivity as a risk factor for heavy GHB use. The same stands for the lower IQ observed in the GHB-Coma group when compared with the other two groups. Despite the fact that all of the participants were matched for education level (median/high level), the lower IQ observed in the GHB-Coma group suggests this to be a result of heavy use of GHB and/or the number of GHB-induced comas of this group. However, the cross-sectional nature of this study does not allow us to establish a causal link.

Moreover, it is important to consider the fact that the prefrontal and limbic parts of the white matter tracts, where alterations were found in this study, are regions rich in GHB binding sites that have been shown to be highly sensitive to neurotoxicity induced by chronic GHB intake (as observed in animal studies) (19, 21–26, 29, 53). Moreover, GHB-induced comas have been compared to a state of pharmacological-induced unconsciousness and might also represent a source of neurotoxicity based on their capacity to induce hypoxia and consequent oxidative stress in such sensitive regions (4, 55, 56). The GHB-Coma group chronically used high concentrations of GHB and had multiple GHB-induced comas. Therefore, the observed outcomes might be partly explained by GHB-induced neurotoxicity resulting from either one or both of these factors, which in turn might potentiate the development of GHB use disorders. However, no structural scans or information on impulsivity was collected before the first GHB-induced coma had occurred and it cannot be excluded that anatomical and/or impulsivity differences were risk factors for the start of GHB use. Finally, the lack of structural group differences associated with GHB use per se might be related to the lack of a healthy control group and does not mean that differences with healthy (drug-naive) controls would not exist. Also, even the doses used by the GHB-NoComa group are still higher than the typical therapeutic doses used for narcolepsy and alcohol use disorders. Therefore, patients using medically prescribed GHB should not worry about neurotoxicity.

The multimodal assessment of brain structure was a particular strength of this study. It allowed the characterization of macrostructural and microstructural brain differences at the whole brain or at ROIs (23, 25, 26, 51, 52). The inclusion of two control groups is another strength that allowed us to distinguish between the effects of GHB use per se and GHB-induced comas. However, this study also has limitations. First, the exclusion of females does not allow the generalization of these results to female GHB users (4, 5). Second, premorbid IQ was lower in the GHB-Coma group when compared with the other two groups. This might have been an *a priori* trait that biased the motivational system of this group towards the immediate reward provided by GHB use. However, all groups were matched for education level and, therefore, the lower IQ in the GHB-Coma group is most likely a result from the repeated GHB-induced comas. Notwithstanding, IQ was used as a covariate in the analysis. Moreover, the last few years have witnessed an increase in the use of GBL (*i.e.*, pro-drug of GHB). However, the participants included in this study reported solely the use of GHB in its absolute form (57). Another limitation is the fact that the assessment of GHB use was based solely on self-reported data. However, objective markers of GHB in blood or urine are nearly impossible to obtain as the metabolization and excretion is rapid and no standardized procedures and cut-off points are currently available for hair analysis (57, 58). There were also significant differences in the co-use of recreational substances between the groups, and despite their introduction as nuisance covariates to control for their influence, residual confounding cannot be excluded. Finally, due to its cross-sectional nature, this study addresses neither causality nor directionality.

In conclusion, multiple GHB-induced comas, but not GHB use per se, are associated with microstructural alterations in parts of the corpus callosum linked to goal-directed behavior, associative memory, and affect regulation. In the GHB-Coma group, these alterations might be suggested as the structural basis for the brain activity differences observed during the processing of such cognitive control functions. Moreover, the GHB-Coma group reported low self-control, which was found to interact with regions responsible for impulse regulation. Hence, considering the increasing treatment demand for GHB use disorders, defining the neurobiological substrates of comorbid impulsivity becomes of fundamental importance for the development of interventions that can normalize or improve the current treatments. Besides, the chronic use of high-doses of GHB with multiple GHB-induced comas represents a serious risk for brain impairment, and maximum treatment efforts are required, including relapse prevention using a combination of psychotherapy (*e.g.*, MET/CBT) and pharmacotherapy (*e.g.*, baclofen) (59, 60). Finally, it is of primordial relevance to integrate such findings in current awareness campaigns in

order to change the common misleading perception among chronic users that GHB use is safe and that no harm is associated with GHB intoxication or GHB-induced comas.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Review Committee of the Academic Medical Centre. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM, WV, and GV designed the study. MM, NP, and YD collected the behavioral and neuroimaging data. AS contributed in the collection of the data. FR performed the neuroimaging and statistical analyses. FR and GV were responsible for the interpretation of the data. FR wrote the manuscript. FR, MM, WV, GV, YD, and AS have revised and approved the submission of the final manuscript.

FUNDING

This research was funded and supported by the Ministry of Health, Welfare, and Sport of The Netherlands.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Leonardo Cerliani and Luka Liebrand for kindly sharing their knowledge on the subject of this manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 07 May 2020
doi: 10.3389/fpsyt.2020.00411

Mitragynine Attenuates Morphine Withdrawal Effects in Rats—A Comparison With Methadone and Buprenorphine

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OPEN ACCESS

Edited by:
Simona Zaami, Sapienza University of Rome, Italy

Reviewed by:
Fabrizio Schifano, University of Hertfordshire, United Kingdom
Ornella Corazza, University of Hertfordshire, United Kingdom

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *06 December 2019*
Accepted: *22 April 2020*
Published: *07 May 2020*

Citation:
Hassan R, Pike See C, Sreenivasan S, Mansor SM, Müller CP and Hassan Z (2020) Mitragynine Attenuates Morphine Withdrawal Effects in Rats—A Comparison With Methadone and Buprenorphine. Front. Psychiatry 11:411. doi: 10.3389/fpsyt.2020.00411

Background: Opiate addiction is a major health problem in many countries. A crucial component of the medical treatment is the management of highly aversive opiate withdrawal signs, which may otherwise lead to resumption of drug taking. In a medication-assisted treatment (MAT), methadone and buprenorphine have been implemented as substitution drugs. Despite MAT effectiveness, there are still limitations and side effects of using methadone and buprenorphine. Thus, other alternative therapies with less side effects, overdosing, and co-morbidities are desired. One of the potential pharmacotherapies may involve kratom's major indole alkaloid, mitragynine, since kratom (*Mitragyna speciosa* Korth.) preparations have been reported to alleviate opiate withdrawal signs in self-treatment in Malaysian opiate addicts.

Methods: Based on the morphine withdrawal model, rats were morphine treated with increasing doses from 10 to 50 mg/kg twice daily over a period of 6 days. The treatment was discontinued on day 7 in order to induce a spontaneous morphine abstinence. The withdrawal signs were measured daily after 24 h of the last morphine administration over a period of 28 abstinence days. In rats that developed withdrawal signs, a drug replacement treatment was given using mitragynine, methadone, or buprenorphine and the global withdrawal score was evaluated.

Results: The morphine withdrawal model induced profound withdrawal signs for 16 days. Mitragynine (5–30 mg/kg; i.p.) was able to attenuate acute withdrawal signs in morphine dependent rats. On the other hand, smaller doses of methadone (0.5–2 mg/kg; i.p.) and buprenorphine (0.4–1.6 mg/kg; i.p.) were necessary to mitigate these effects.

Conclusions: These data suggest that mitragynine may be a potential drug candidate for opiate withdrawal treatment.

Keywords: mitragynine, kratom, morphine, withdrawal, substitution, methadone, buprenorphinel

INTRODUCTION

Abuse and addiction to opioids including prescription pain relievers, heroin, and synthetic opioids such as fentanyl caused a serious national crisis in the United States (US), that affects public health as well as social and economic welfare (1). According to Centers for Disease Control and Prevention (CDC), the opioid crisis has occurred in three waves. The first wave began in the 1990s with the rises of death cases related to overdose of prescription opioids. The second wave emerged in 2010 involving heroin overdoses. The third wave began in 2013 with the sharp rise of overdose death numbers involving synthetic opioids, particularly illicitly manufactured fentanyl (IMF). Fentanyl is 50–100 times more potent than morphine as an analgesic agent. In the US alone, more than 47,000 opioid-related overdose deaths occurred during 2017, which are closely related to synthetic opioids, especially fentanyl (2). At present, IMF still contributes greatly to overdose fatalities (3) in many states of the US and in Canada (4, 5). IMF fatalities are generally due to co-administration of other illicit drugs, such as cocaine, heroin, and methamphetamine (6, 7), which leads to overdose and consequently death.

As stated in the *World Drug Report 2019*, an estimated 271 million people worldwide used drugs and almost 13% are estimated to suffer from drug use disorder, to a point where they may experience dependence and/or require treatment (8). In Malaysia, opioid remains the main type of illicit substance, with estimated 187 771 opiate users. Mu-opioid receptor agonists are the mainstay in drug replacement therapy. Buprenorphine and methadone are recommended in pharmacotherapy of opioid use disorder based on their mechanisms of action in alleviating withdrawal signs (9). However, both have clinical limitations in their effectiveness and safety.

Typically, methadone therapy is considered as safe. It has a long half-life and makes outpatient management feasible. Nevertheless, several risk factors have been recognized, such as; i) drug–drug interaction with other drugs, ii) torsade de pointes, which elevated risk of some individuals, and iii) the inadequate or erroneous dose increase adjustment, specifically, when prescribing methadone for pain (10). Moreover, methadone efficacy shows high inter-individual variance due to pharmacokinetic and pharmacodynamic factors (11). The effective half-life of methadone for analgesia in many patients does not reflect the half-life for respiratory depression and cardiac side effects, making consistent and safe dosing difficult for methadone (12). This often leads to an overdose which is associated with serious side effects, including potentially lethal respiratory depression. Indeed, unintentional deaths are much more common after methadone administration than after any other opioid (13). Methadone fatality occurred not only among out-treatment patient but also for in-treatment patients. Fatality that occurred might be due to the methadone itself or due to drug–drug interactions. Caplehorn and Drummer identified 13 fatalities in methadone maintenance programs with 11 out of 13 cases related to methadone toxicity, one case of other drug toxicity and one case of other death causes in the first week. In the second week, 25 fatalities were reported with one case of methadone toxicity, 5 cases of other drug toxicity, and 19 cases of other death causes (14). Meanwhile, another study done by Kelty et al. demonstrated a high rate of mortality in methadone-treated patients during the first 28 days of treatment as compared to naltrexone-treated patients (15). Moreover, a study done by Bell et al. revealed 60 sudden deaths associated with methadone, where 19 out of 32 in-treatment cases and 24 out of 28 cases of out-treatment were linked to overdose (16). The autopsy results for all 43 methadone overdose positive deaths revealed at least one other drug was involved (16).

An alternative option to methadone is the buprenorphine replacement therapy. It acts as mu-partial agonist at mu opiate receptor (MOR) and has "ceiling effect" for respiratory depression. Thus, it offers advantages in terms of safety as compared to methadone. Buprenorphine has been approved in several countries as an efficient and safe maintenance therapy for heroin addiction which resulted in a salutary effect with a reduction in heroin overdose-related deaths in countries that implemented office-based buprenorphine maintenance. In France, however, several cases of asphyxia deaths were reported among addicts treated with buprenorphine concomitant with other drugs like benzodiazepines. Drug–drug interactions with buprenorphine may cause severe respiratory depression (17). Buprenorphine has been reported to cause seven fatality cases, four cases were associated with buprenorphine poisoning, followed by two suicidal cases and one undetermined case (18).

The kratom plant (*Mitragyna speciosa* Korth.) has been long used traditionally for its pharmacological effects and its narcotic action in Southeast Asian nations, especially Thailand and Malaysia. People use kratom plant preparations for their medicinal value in treating pain, mood swing, coughing, diarrhea, and intestinal infection (19, 20). Kratom is also used as a substitution of heroin and morphine when access to these drugs is prevented and as treatment for drug withdrawal signs (21, 22). Kratom leaves consist of over 25 alkaloids, where mitragynine is the main indole alkaloid (23).

Recent fatality reports by CDC revealed 152 deaths between July 2016 and December 2017, where multiple drugs were detected in almost every kratom-related death (24). Another study reported 156 death cases linked to kratom use, where 87% cases associated with polydrug use. Another 23% cases was due to kratom itself, with 6 cases found mitragynine in toxicology test (25). However, the claim that six fatalities was due to mitragynine alone does not mention the sources, thus, the truth on the claim was unclear. High post-mortem mitragynine concentration may not always reflect the direct involvement in a fatality (26). Gershman et al. reviewed the Colorado death certificates for any mentioning of kratom or mitragynine from 1999 through 2017. They found four death cases due to mitragynine. Further investigation on these four cases were performed through toxicology screening with high-performance liquid chromatography with tandem mass spectrometry using available residual blood. Result revealed that all these three death cases was indeed due to drug–drug interaction between mitragynine and other drugs instead of

mitragynine compound alone (27). Death resulting solely from ingestion of kratom appears as extremely rare (28).

Mitragynine acts as partial agonist on human μ opioid receptor (MOR) and δ opioid receptor (DOR) while it acts as a competitive antagonist on human κ opioid receptor (KOR) (29). In addition, *in vivo* test showed that antinociceptive effects of mitragynine are mediated by supraspinal MOR and DOR (30). Boyer et al. reported that although mitragynine works as an agonist at the MOR, respiratory depression, coma, pulmonary edema, and death have not been associated with human kratom ingestion (31). Mitragynine, therefore, may exert several pharmacological effects that could help attenuating opioid withdrawal signs. An *in vitro* study from Kruegel et al. reported that mitragynine is a G-protein-biased agonist of the MOR, which does not recruit ß-arrestin following receptor activation (29). In particular, some evidence indicates that those MOR agonists that are biased toward G protein signalling over ß-arrestin signalling induce less respiratory depression, tolerance development, and constipation, while remaining potent analgesics (32, 33). In the present study we tested the effectiveness of mitragynine to mitigate morphine withdrawal behavior in rats, in comparison with the established substitution drugs, methadone and buprenorphine. We further evaluated the effects of mitragynine on morphine-withdrawal induced changes in hematological, biochemical, and histopathological parameters.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats were purchased from Animal Research and Service Centre, Universiti Sains Malaysia, Penang, Malaysia, weighing 200–300 g at the beginning of the experiment. All 84 rats were naive and used in a single experiment only. They were socially housed in groups of six per cage under standard laboratory conditions, with temperature- controlled environment (24 ± 1°C). The room was maintained on a 12-h light/12-h dark normal cycle (lights on from 07:00 to 19:00 h). Animals were handled for one week prior to commencement of the experiments. Food and water were available *ad libitum*. The experimental procedures were reviewed and approved by the Animal Ethics Committee of Universiti Sains Malaysia [Reference number: USM/Animal Ethics Approval/2016/(716)].

Drug Preparation

Morphine hydrochloride, methadone hydrochloride, and buprenorphine hydrochloride were purchased from Sigma Chemicals Co. (USA). Mitragynine was extracted, isolated, and verified from fresh leaves of *M. speciosa* at the Centre for Drug Research, Universiti Sains Malaysia as described previously (34). Purified mitragynine was confirmed by high-performance liquid chromatography (HPLC) and proton nuclear magnetic resonance (1H-NMR) (400 MHz) analysis (35). Mitragynine obtained by this procedure was approximately 98% pure (36). Mitragynine was dissolved in 20% of Tween 80 as vehicle. Fresh stocks of morphine, methadone, buprenorphine, and mitragynine were prepared daily according to the weight of animals in the experimental design. They were dissolved in vehicle (20% Tween 80; Sigma Aldrich, UK) and injected intraperitoneally (i.p.).

Experimental Design

Experiment I: Morphine Withdrawal Model

In this experiment, a morphine withdrawal model was developed by measuring the severity and duration of withdrawal signs. Morphine was injected with the dose that was progressively increased from 10 to 50 mg/kg twice daily over a period of 6 days (**Supplementary Table 1**). The vehicle group received 20% Tween 80 twice daily for 6 days. Both treatments were disrupted on day 7 in order to induce a spontaneous opiate abstinence. The withdrawal syndrome was evaluated daily over a period of 28 days after the last dose of drug treatment.

Experiment II: Mitragynine Substitution Treatment in Morphine Withdrawn Rats

Based on the above findings, the severity of spontaneous morphine abstinence was first observed, 24 h after the last dose of morphine. Hence, the substitutive treatment of drugs, i.e. mitragynine, methadone, and buprenorphine were administered before 24 h to prevent the emergences of morphine withdrawal syndrome. Selection of doses of mitragynine was based on previous studies (37–43). Mitragynine (0, 5, 10, 15, 30 mg/kg) was injected 30 min before withdrawal testing, i.e. 23.5 *h* after the last morphine dose (44, 45). Thereafter, mitragynine was repeatedly administered every 12 h (46) for testing the duration of withdrawal inhibiting effects. Treatment with mitragynine was then disrupted on day 5 in order to evaluate whether withdrawal signs would resurface after abrupt cessation. The withdrawal syndrome was evaluated 12 h after the last dose of mitragynine.

Experiment III: Methadone Substitution Treatment in Morphine Withdrawn Rats

The selection of methadone doses was based on pharmacological range and below LD_{50} value which might be effective and safe for the use in this experiment (47, 48). Methadone (0, 0.5, 1.0, 2.0 mg/kg was dissolved in vehicle (20% Tween 80; Sigma Aldrich, UK) and injected intraperitoneally 10 min before withdrawal testing, i.e. 23 h 50 min after the last morphine dose (47). Thereafter, methadone was repeatedly administered every 8 h (47) for testing the duration of withdrawal inhibiting effects. This design is a modified version of a substitution routine described by Ruiz et al., 1996 (49).

Experiment IV: Buprenorphine Substitution Treatment in Morphine Withdrawn Rats

The selection of buprenorphine doses was based on the previous studies (50–52). Buprenorphine (0, 0.4, 0.8, 1.6 mg/kg, i.p.) was dissolved in vehicle (20% Tween 80; Sigma Aldrich, UK) and injected intraperitoneally 30 min before withdrawal testing, i.e.

23.5 h after the last morphine dose (52). Thereafter, buprenorphine was repeatedly administered every 12 h (53) for testing the duration of withdrawal inhibiting effects. On day 5, buprenorphine treatment was interrupted in order to measure whether withdrawal signs would resurface after abrupt cessation. The withdrawal signs were evaluated 12 h after the last dose of buprenorphine.

Assessment of Withdrawal Behaviors

Trained observers (RH and ZH, inter-rater reliability, r = 0.99) blinded to treatment and time points scored all images using the video and counted the frequency of the signs of spontaneous morphine withdrawal (chewing, head shakes, exploring, digging, yawning, teeth chattering, wet dog shakes, writhing, squeaking on touch, hostility on handling, diarrhea). Recording was conducted 24 h after the last dose of morphine administration. Animals were placed in an open field test box for 30 min and withdrawal behavior was scored. This test was performed on either day 28 (experiment I) or day 5 (experiment II–IV). The assessment of spontaneous opiate abstinence was performed by behavioral scoring. Withdrawal behaviors were distinguished as "counted signs," including chewing, head shakes, exploring, digging, yawning, teeth chattering, wet dog shakes, writhing and as "checked signs," including squeaking on touch, hostility on handling, and diarrhea. Thereby, counted signs and checked signs were further processed by multiplying with the respective weighing factors for evaluation of the severity of withdrawal signs using the previously described scoring methods by Rahman et al. (54), Bläsig et al. (55), Neal and Sparber (56), and Sabetghadam et al. (57) (**Supplementary Table 2**).

Hematological Analysis

At the end of substituted studies, blood samples were collected *via* cardiac puncture and transferred into ethylenediamine tetraacetic acid (EDTA) tubes. Then, the tubes were analyzed for determination of hematological parameters such as red blood cell count (total RBC), hemoglobin, percentage of packed cell volume (PCV%), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), percentage of red cell distribution width (RDW%), total of white blood cell count (WBC), percentage of lymphocyte, monocytes, eosinophils, basophils, and platelet counts (PLT).

Biochemical Analysis

For the biochemical analysis, the collected blood was transferred into serum-separating tubes. The biochemical parameters analyzed from these tubes were total bilirubin, aspartate amino transferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, sodium, potassium, chloride, urea, creatinine, total cholesterol, triglycerides, calcium, phosphorus, total protein, albumin, globulin, and albumin/globulin ratio (A/G ratio).

Histopathological Analysis

On day 5, animal tissue samples of targeted organs (heart, lung, kidney, liver) were harvested after behavioral testing in experiments II-IV. The tissues were stained using hematoxylin and eosin. Then, the slides were viewed under light microscope equipped with a digital camera. The sections were analyzed for structural changes, degenerative alterations, necrosis, and signs of inflammation.

Statistical Analysis

All data were expressed as mean ± standard error of the mean (SEM). The individual behaviors scores, the global withdrawal scores, and the substitution treatments were analyzed by two-way ANOVA for repeated measures with test "day" as within factor and treatment combination as a "treatment" between factor. In order to analyze single group differences on each treatment day, pre-planned comparisons were calculated using Bonferroni test (58). Hematological and biochemical were also analyzed by two-way repeated measures ANOVA and Bonferroni test. A significance level of $p < 0.05$ was used to test for statistical significance. GraphPad Prism 6.0 software (GraphPad Software Inc., La Jolla, CA, USA) was used to perform the statistics.

RESULTS

Global Withdrawal Scores After Spontaneous Morphine Withdrawal

The withdrawal model was adopted and modified from the dependence model of Rahman et al. (54). Single behavior scores were then calculated and translated into global withdrawal score to reduce variability and improve the reliability of results of morphine dependence (**Supplementary Table 3**) (59). Following abstinence, morphine dependent rats showed significant withdrawal signs 24 h after the last drug dose, with 11.614 ± 0.912 of global withdrawal score for the morphine group and 2.023 ± 0.291 in the vehicle group. Two-way ANOVA result showed significant effect of treatment ($F_{1, 168} = 509.0$, $p < 0.0001$), days ($F_{27, 168} = 7.000$, $p < 0.0001$), and an effect of the interaction ($F_{27, 168} = 6.121$, $p < 0.0001$). Bonferroni's multiple comparisons test revealed a significant difference of withdrawal scores between MOR-treated and vehicle control animals, which were observed from day 1 to day 16 ($p < 0.05$), and no statistical differences between day 17 and 28 ($p > 0.05$; **Figure 1**). Results indicated that behavioral signs of morphine withdrawal emerged after 24 h and might alleviated without any replacement drug treatment after 16 days abstinent period.

Mitragynine Attenuates Morphine-Withdrawal Behavior

The established model was used to induce withdrawal effects that were clearly observed in the morphine group. Mitragynine attenuated morphine withdrawal effects significantly on day 1 to 4 (**Figure 2**). A two-way ANOVA showed a significant treatment ($F_{5,150} = 13.02$, $p < 0.0001$) and day effect ($F_{4,150} = 5.742$, $p = 0.0003$), but no significant interaction ($F_{20,150} = 0.8071$, $p = 0.7021$). Substitution treatment was not given on day 5, which resulted in the

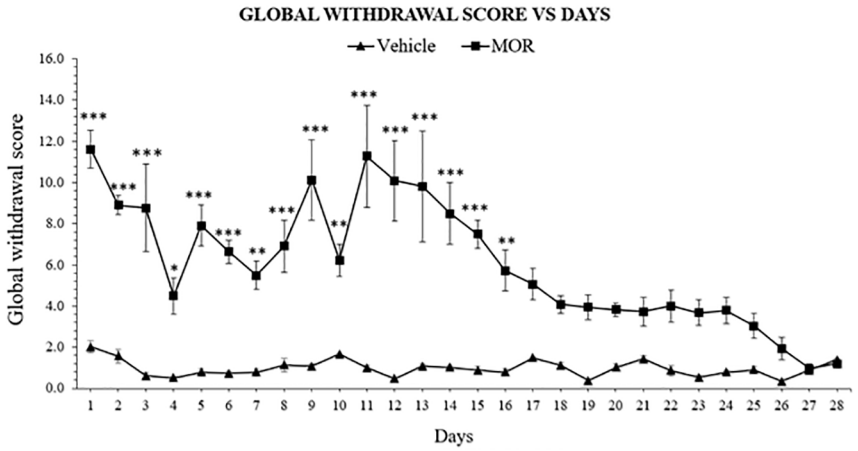

FIGURE 1 | Escalating morphine (MOR) treatment induces withdrawal signs in rats. Data represent means (± SEM) of global withdrawal signs (n = 6/group; *p < 0.05, **p < 0.01, ***p < 0.001 vs. Vehicle).

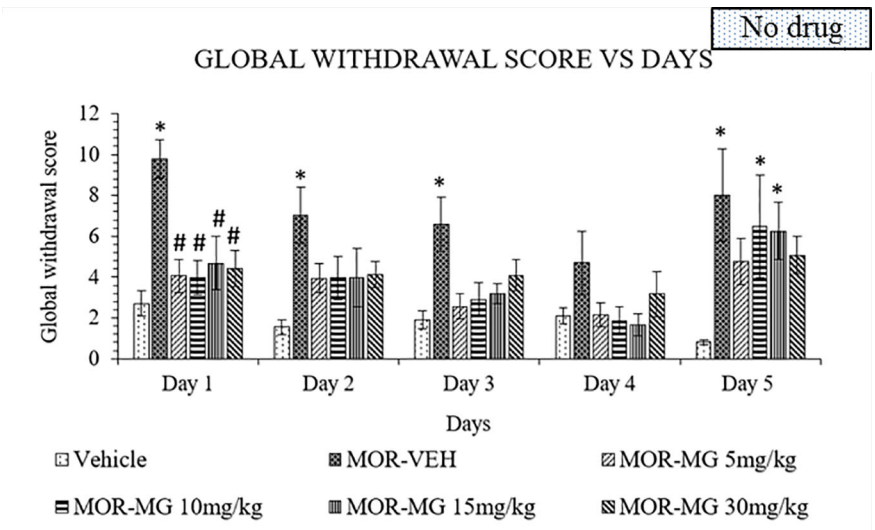

FIGURE 2 | Mitragynine (MIT) reduces behavioral signs of morphine withdrawal in rats. Data represent means (± SEM) of global withdrawal signs (n = 6/group; *p < 0.05, vs. Vehicle, #p < 0.05 vs. morphine-vehicle, MOR-VEH).

appearance of withdrawal signs in all previously mitragynine treated groups. On day 5, both 10 and 15 mg/kg doses of mitragynine treatment showed significant difference compared to vehicle group ($p < 0.05$ vs vehicle). This might suggest that both 10 and 15 mg/kg mitragynine have dose-dependent activity since the withdrawal sign effects increased slightly after treatment cessation on day 5. On the other hand, 5 and 30 mg/kg doses of mitragynine treatment showed no significance compared to both vehicle and morphine groups ($p > 0.05$). These findings suggest that mitragynine effectively reduced morphine withdrawal effects over 1 to 4 days of substitution. However, the number of substitution days for mitragynine should be prolonged since reduction in withdrawal scores could not be seen after cessation on day 5. Both 5 and 30 mg/kg doses were the best doses to be chosen in future, since they are able to reduce withdrawal and induce minimal withdrawal sign on day 5, during abrupt cessation.

Methadone Attenuates Morphine-Withdrawal Behavior

Methadone was also used as substitute treatment against morphine induced withdrawal rats for 4 days and abruptly

stopped on day 5. A two-way ANOVA showed a significant treatment ($F_{4, 115} = 8.756$, $p < 0.0001$), and day effects ($F_{4, 115} = 4.449$, $p = 0.0022$), but no significant interaction between treatment groups and days ($F_{16, 115} = 1.134$, $p = 0.3327$). From day 1 to 4, no significant differences could be seen between methadone and vehicle groups for all methadone doses (**Figure 3**). Cessation of methadone treatment on day 5 yielded an increased in global withdrawal score for 0.5 and 2 mg/kg doses of methadone compared to vehicle groups. On the other hand, 1 mg/kg methadone showed a minimal increase of withdrawal sign. Thus, 4 days of substitution were insufficient to persistently reduce withdrawal signs in morphine withdrawn rats.

Buprenorphine Attenuates Morphine-Withdrawal Behavior

Buprenorphine is another substitute treatment alternative for morphine withdrawal. Like in the previous experiments, treatment was continued for 4 days before abrupt cessation on day 5. A two-way ANOVA showed a significant treatment ($F_{4,110} = 11.49$, $p < 0.0001$), day effect ($F_{4,110} = 12.22$, $p <$

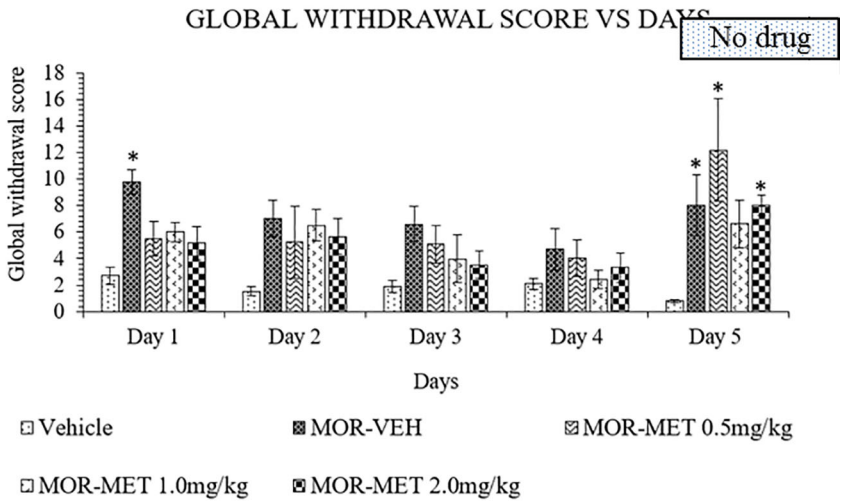

FIGURE 3 | Methadone (MET) reduces behavioral signs of morphine withdrawal in rats. Data represent means (± SEM) of global withdrawal signs (n = 6/group; *p < 0.05, vs. Vehicle).

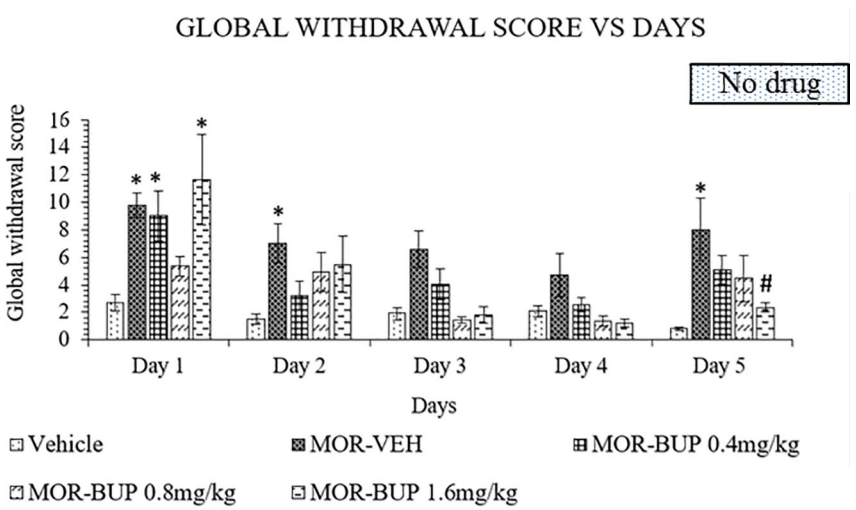

FIGURE 4 | Buprenorphine (BUP) reduces behavioral signs of morphine withdrawal in rats. Data represent means (± SEM) of global withdrawal signs (n = 6/group; *p < 0.05, vs. Vehicle, #p < 0.05 vs. morphine-vehicle, MOR-VEH).

0.0001), and interaction between treatment and days ($F_{16,110}$ = 1.803, p = 0.0393). Buprenorphine, however, failed to lower withdrawal score especially for doses 0.4 and 1.6 mg/kg on day 1 (**Figure 4**). The withdrawal scores were decrease on day 2 to 4 in both 0.4 and 1.6 mg/kg buprenorphine treatments compared to the vehicle group. While the 0.8 mg/kg dose of buprenorphine showed no significant effect on day 1 compared to the vehicle group, discontinuation of treatment on day 5 revealed no significant differences when compared to vehicle group. Although 1.6 mg/kg dose significantly reduce the withdrawal effect after cessation, buprenorphine still showed antagonistic effect on day 1.

Hematological and Biochemical Analysis

Hematological and biochemical analysis of the blood samples were taken on day 5 and results are presented in **Supplementary Tables 4** and **5**. All results were within the normal reference range (60–63), indicating no effects of the treatments on blood parameters.

Histopathology

All groups were further examined for the histopathological changes in the organs such as lung, heart, liver and kidney. Cross examination *via* the microscopic structures of the heart and lung showed no differences between the vehicle and treatment groups. However, histoarchitecture of the kidney revealed observable cellular damage in the MOR-VEH, MOR-MG 5 mg/kg, and MOR-MET 1 mg/kg treated groups as compared to VEH group. The kidney of control group (VEH) revealed normal glomerulus, Bowman's capsule and renal corpuscle. However, MOR-VEH, MOR-MG 5 mg/kg, and MOR-MET 1 mg/kg treated rats showed inflammation in the renal tubules, shrinkage of glomeruli with eroded Bowman's capsule with hemorrhage and increasing renal spaces were occasionally observed in the kidney, which was most clearly seen in the MOR-MG 5 mg/kg treated group. Cross examinations of MOR-MG 5 and 30 mg/kg, MOR-MET 1 mg/kg, MOR-BUP 0.8 mg/kg treated, and VEH groups preserved hepatic architecture with well-organized hepatic cell and central vein. Normal appearance of central vein and hepatic sinusoids lined by endothelial cells with normal radiating hepatocytes was observed in all groups. However, MOR-VEH treated rats showed slight degeneration in the liver with dark eosinophilic cytoplasm (**Supplementary Table 6**).

DISCUSSION

Opiate abuse is a major health problem in many countries. Managing opiate withdrawal appears as a key challenge in the treatment of opiate addicts. There are substitution drugs that can be used, but all come with major drawbacks and risks so that an improvement is much warranted. Here we report that the main psychoactive alkaloid of the kratom plant, mitragynine, mitigates morphine withdrawal symptoms. Although preclinical studies have shown that mitragynine may have an abuse potential and adverse cognitive effects by itself (23, 36, 43, 64), field studies have shown that these effects emerge usually at doses way higher than what humans voluntarily consume (65, 66). In addition, we did not find negative effects of mitragynine substitution on hematological, biochemical, and tissue level in this study, which confirms field studies that report mild impairments even after long term chronic use (67, 68). These findings may suggest considering further exploration of mitragynine as a potential substitution drug.

Various methods have been established to model morphine withdrawal in rats including implantation of morphine pellet (55, 56, 69–71), infusion method *via* implantation of intravenous catheters (72, 73), subcutaneous mini osmatic pumps (74, 75), drinking morphine solution containing water or sucrose (76–78), morphine-admixed food (79), or subcutaneous injection (80–83) and intraperitoneal route (54, 84, 85). However, all these methods have certain disadvantages. For instance, pellet and mini osmotic pump implantation require surgery. The implantation and removal of the pellets from animals' body may develop additional stress to the animals including the chances of getting infection at the implantation sites. Drinking morphine may develop a bitter taste and leads to considerable inter-individual differences in consumption between animals. Additionally, oral intake of morphine that achieves maximum plasma levels over a 4-h period with 83% bioavailability (86), can delay and lessen the effects compared to, e.g. parental administration. A substance's absorption, bioavailability and metabolism are affected by its chemical and physical properties as well as by its doses and route of administrations (87). In general, the extent of absorption reflects the total amount of drug entering the body which can be considered through this following order; intravenous > intraperitoneal > intramuscular> subcutaneous > oral (88). Therefore, the intraperitoneal route of administration is commonly used in small laboratory animals.

In the present study, the model used a slightly modified version of the Rahman et al. (54) model. The original model treated with morphine for 7 days. Further optimization, however, revealed that rats showed the full spectrum of withdrawal signs already after 6 days of morphine treatment. This would save time and cost. The maximum dose used in our model was 100 mg/kg morphine at day 6 compared to 180 mg/kg on day 6 (54). By reducing the number of days and dose, the mortality rate could be significantly reduced. The present model also evaluates the natural recovery from morphine withdrawal without any substitution treatment (**Figure 1**). Withdrawal signs include chewing, head shakes, exploring, teeth chattering, wet dog shakes, writhing, squeaking on touch, and hostility on handling. Each behavior develops its own pattern and duration of emergence. For example, in the present study, wet dog shakes behavior was more significant in the middle of the abstinence days. Other finding also reported that wet dog shakes act as a "recessive" behavior which declines when "dominant" signs, like teeth chattering, increase (55). Generally, the propensity of withdrawal signs was comparable to other studies (54, 55). Therefore, in order to better control the high variability of the

individual signs of spontaneous abstinence, a global withdrawal score was calculated. The scores were multiplied by a weighing factor (**Supplementary Table 2**). When the global withdrawal scores were calculated, the clarification of the withdrawal signs during abstinence was more reliable (59), and was used in the substitution treatment part of the present study.

The present withdrawal model revealed that the most severe withdrawal signs was exhibited 24 h after the last morphine intake. The severity and duration of opioid withdrawal symptoms varies as a function of half-life of the opioid, the duration of opioid use, and patient-specific characteristics including health status. Abrupt cessation of short-acting opioids (e.g. heroin, hydrocodone, and oxycodone) is associated with severe opioid withdrawal signs that typically begin within 12 h after the last dose, peak at 36–72 h, and gradually taper off over the following 4–7 days (89). In rats, regardless of their route of administration, the plasma half-life of morphine is approximately 115 min (90). The entire dose administered was almost cleared from the body by four to five cycle of half-life (91). Thus, morphine would be mostly cleared from the body in approximately 8 to 10 h in rats. The withdrawal signs emerged after 12 h of the last morphine dose and reached their peak after 24 h thereafter. The study was continued after cessation until the rats were fully recovered from withdrawal signs. The effect of withdrawal gradually lessens from day 17 until day 28, where withdrawal effect fully disappears. The present study is in line with Gold et al. (71), in which withdrawal became increasingly intense up to 24 h post-implant and lasted up to 13 days post-implant, with almost no abstinence signs were observed after 18 days post-implant. Similar findings were also reported in a study by Goeldner et al. (92) which revealed that physical dependence to morphine is no longer exist after 4 weeks of abstinent period. In humans, opioid withdrawal signs will generally resolve after 5–14 days, depending on the half-life of the respective opioid (89). Most patients would not be able to cope with opioid withdrawal without proper substitution treatment. With regard to the above information, this model can induce acute withdrawal signs after 24 h and recover naturally after 16 days of abstinent without any treatment with drugs.

Kratom efficacy in managing withdrawal signs has been repeatedly reported in the literatures. Earliest reports by Burkill in 1935 had been widely acknowledged in kratom's research for the treatment of opium withdrawal (93). In the present study, the main indole alkaloid of kratom, mitragynine was capable to lessen withdrawal signs in morphine dependent rats. This finding was in line with a previous study which reported that mitragynine had low abuse liability and could attenuate the acquisition and expression of morphine-induced conditioned place preference (94). In addition, based on *in vitro* study stated that mitragynine acts at mu- and delta- opioid receptors (95). It can be readily assumed that analgesic effects as well as the mitigation of opiate withdrawal signs are mediated through these receptors (96). Moreover, antinociceptive activity of mitragynine has been proposed to be mediated by activation of descending noradrenergic and serotonergic pathways in the spinal cord (97). In another study, Khor et al. (98) suggested that mitragynine may attenuate stress-related swimming behaviors in morphine-withdrawn zebrafish. The mitigation of corticotropin releasing factor receptors and prodynorphin mRNA expression in zebrafish brain during the morphine withdrawal phase, indicates mitragynine's capability of reducing anxiety *via* the stress-related corticotropin pathway during opiate withdrawal. Thus, these findings might be related to the mechanism in which mitragynine mitigates withdrawal signs in morphine withdrawn rats.

Methadone has been used as an alternative substitution and maintenance therapy for the treatment of opioid addicts. Methadone acts as mu agonist, which accounts for its analgesic and antitussive properties with side effects like respiratory depression, decreased bowel motility, miotic pupils, nausea, and hypotension. In the present study, the methadone maintenance therapy at doses of 0.5, 1, and 2 mg/kg reduced withdrawal signs in morphine withdrawn rats. Abrupt cessation of methadone on day 5 revealed that rats given a 1.0 mg/kg methadone dose showed a minimal increase in withdrawal signs. On the other hand, rats given 0.5 and 2 mg/kg showed again an increase in withdrawal signs. A previous study by Ruiz et al. (49) suggested that 2 mg/kg of methadone was able to block opiate dependence following naloxone administration after methadone substitutive treatment. This might be due to differences in the animal model used. The half-life of methadone in rats is 1.5 ± 0.4 h (47) and 24-36 h in human after oral intake (99). Elimination of methadone is much more rapid in rats compared to humans (100, 101). Eight hours after last methadone dose, withdrawal signs could be seen, similar to the morphine group without treatment. Hence, a longer period of methadone maintenance therapy may possibly suppress the withdrawal signs in morphine withdrawn rats.

Buprenorphine substitution treatment 24 h after the last morphine dose indicates the failure of both doses 0.4 and 1.6 mg/kg buprenorphine in suppressing withdrawal signs on day 1 compared to the vehicle group. However, 0.8 mg/kg buprenorphine treatment showed no significant difference when compared to vehicle group, suggesting that this dose was able to suppress the morphine withdrawal effects on day 1. A previous study reported that the antinociceptive effect of buprenorphine reaches its peak at an approximate dose of 0.5 mg/kg s.c. (102). The 1.6 mg/kg buprenorphine dose on day 1 surprisingly caused a small increase in withdrawal score in morphine withdrawn rats. This might be due to the antagonistic effect of buprenorphine. Buprenorphine is a partial opioid agonist that can act as an antagonist under certain condition due to its low intrinsic activity (103). A study from Dum and Herz (102) showed that buprenorphine was able to precipitate withdrawal in rats at doses above 1 mg/kg and 30 mg/kg was the greatest withdrawal-precipitating potency. Compared to full agonist drug such as methadone, buprenorphine has a lower ceiling effect to euphoria (104). It might also be used as a safer intervention, especially for its ceiling effect on respiratory depression (105). Cessation of buprenorphine maintenance therapy on day 5 increases

withdrawal signs except for the previously 1.6 mg/kg buprenorphine treated group. A study on buprenorphine pharmacokinetics in rats suggested that its plasma half-life is 5.3 h after bolus intravenous administration (106). Since the final scoring was performed 12 h after the last dose, the remaining buprenorphine in the plasma could still attenuate withdrawal signs, which might explain the minimal increase in withdrawal signs in comparison to methadone and mitragynine on day 5.

Morphine-induced damages on the vital organs (liver, kidney, heart, and lung) are frequently reported in rodent models, especially at high dose for a short period (for example, higher than 120 mg/kg/day) or at lower dose for chronic use (107). In this study, histopathological and biochemical changes due to the usage of morphine and/or the substitution drugs in selected vital organs were assessed. In all groups, particularly the morphine group, no histopathological changes were observed, indicating that the selected doses of drugs administration at determined duration, were too small to cause histopathological damage but sufficient to show signs of drug intoxication. This study also further investigated the effects of morphine and drug substitutes administration on hematological and biochemical indices in rats. Similarly, no apparent changes observed in all parameters. This data further confirmed the selected doses of morphine is effective in leading to significant phenotypic readout (upon morphine withdrawal) with low-to-no toxicity effect. Behavioral outcomes are associated with neural circuits, and, hence, morphine-induced neurochemical changes is warrant for further investigations.

Although all the results for hematological and biochemical analysis of the blood samples were within the normal reference range values, significant effects of treatment against the PLT and alkaline phosphatase were observed in this study (**Supplementary Tables 4** and **5**). The significant effects of treatment against the PLT could be considerably affected in healthy rats by biological variations such as variability between individual rats and temporal variation (108) after the treatment which warrants further investigations. In addition, MOR-MG 5, 15 and 30 mg/kg, MOR-BUP 0.8 mg/kg, and MOR-MET 0.5 mg/kg treatments were significantly affected the serum liver enzyme activity of alkaline phosphatase in this study. Serum liver enzyme activity was used to monitor the presence or absence of liver injury after the rats were subjected to various treatments in this study. Furthermore, the findings of this study also suggest that MOR-MG 5, 15, and 30 mg/kg, MOR-BUP 0.8 mg/kg and MOR-MET 0.5 mg/kg treatments might mildly affect the structural integrity of hepatocellular membrane of healthy rats, thus facilitate the alkaline phosphatase leakage into the blood circulation (109). Moreover, the increased in the activities of alkaline phosphatase observed in this study might correspond to mild ignorable liver damage induced in the treated rats since the increment still within the normal reference range values. However, further, prolong detailed studies are warranted to directly examine the effects of treatments against alkaline phosphatase leakage.

Based on the above findings, it is suggested that long period of maintenance therapy is required for the treatment of morphine dependent rats. Mitragynine might be a possible new alternative therapy for opioid addicts in replacement of methadone and buprenorphine. Since mitragynine is extracted from kratom leaves, it can be accessed easily and cheaper as compared to other drugs. Methadone replacement therapy is still subjected to overdose and fatalities due to a lack of ceiling effects at the level of respiratory depression and sedation, as seen in morphine overdose (110). The methadone dose varies between patients and it is very hard to identify the best dose to be given to patients. On the other hand, buprenorphine is potentially safer than methadone. As a partial agonist, it produces less physical dependence compared to methadone. Yet, buprenorphine develops poor retention and is less satisfying for patients since they develop a mild withdrawal syndrome when displacing heroin. An overdose of an opioid can cause respiratory depression and death. These side effects have been linked to the alteration of MOR regulation. Previous studies have shown that mice lacking the G-protein-coupled receptor regulatory protein, β-arrestin 2, display profoundly altered morphine responses. β-arrestin 2 knockout mice enhanced and prolonged morphine analgesia, attenuated the respiratory suppression and acute constipation (32). In *in vitro* study conducted by Kruegel et al. (29), mitragynine acts as a partial agonist at human MORs and did not result in recruitment of β-arrestin 2 providing a potential mechanism for low abuse and respiratory depression liability. The effect of mitragynine might be mediated through opioid receptor or interaction with other opioid agonist. Several studies proposed the possibility that mitragynine effects were mediated through opioid receptors (29, 41, 111, 112), Hiranita et al. (113) however suggested that mitragynine has different pharmacological mechanism as compared to morphine. Its antinociceptive effect is not mediated *via* opioid receptor since naltrexone which antagonize morphine's effects on schedule-controlled responding and thermal response latency did not alter mitragynine's effects significantly (113). Furthermore, a study by Hemby et al. (114) showed that mitragynine is a good candidate for pharmacotherapies, since it reduces morphine intake.

In conclusion, the morphine withdrawal model induced withdrawal signs for 16 days in rats. Four-day replacement treatment with mitragynine attenuated the withdrawal symptoms significantly, suggesting that mitragynine is able to reduce morphine withdrawal symptoms similar to methadone and burprenorphine. These findings suggest that mitragynine, the major indole alkaloid of kratom, may be used as a potential treatment of opioid addiction-related withdrawal. Further research is required including clinical trials to evaluate the application of mitragynine as a supplementary treatment of opioid addiction in humans.

IMPLICATIONS

The present study suggests that mitragynine may serve as an alternative treatment for opiate withdrawal effects as they occur in opiate addiction. Although mitragynine may possess some

addictive properties on its own, it may, in low-medium doses, in which humans voluntarily use it, help to manage opiate addiction. The current report details the efficacy in comparison to methadone and buprenorphine. While mitragynine is equally effective in reducing opiate withdrawal effects in rats, it may be the safer drug with less undesired side-effects.

LIMITATION AND FUTURE RESEARCH

A general limitation of this study is the experimenter administered substitution treatment, which does not allow to make predictions about acceptance of a mitragynine pharmacotherapy by human opioid addicts (115). While a morphine withdrawal state was induced in this study, it is still not the full picture of an opioid addiction, as manifested in the current opioid crisis. Whether mitragynine is equally effective in addicted individuals still has to be evaluated. The current study may also encourage research in the question of how mitragynine affects other addiction-related behaviors, such as drug seeking and self-administration.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ **Supplementary Material**.

ETHICS STATEMENT

The animal study was reviewed and approved by Animal Ethics Committee of Universiti Sains Malaysia.

AUTHOR CONTRIBUTIONS

ZH, SM, and CM planned the study. RH, CP, and SS performed the experiments and analyzed the data together with ZH. RH, CM, and ZH wrote the first draft of the manuscript. All the authors commented on the manuscript. All the authors contributed to and have approved the final manuscript.

ACKNOWLEDGMENTS

This work was supported by the Higher Education Centre of Excellence (HiCoE) PHASE II special funding (304/CDADAH/4401009) and Yang di-Pertuan Agong (BYDPA) scholarship.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00411/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

OPINION
published: 15 May 2020
doi: 10.3389/fpsyt.2020.00372

The Role of Dehumanization in Our Response to People With Substance Use Disorders

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Keywords: addiction, harm reduction, dehumanization, stigma, chem sex

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *26 February 2020*
Accepted: *15 April 2020*
Published: *15 May 2020*

Citation:
Brown TR (2020) The Role of Dehumanization in Our Response to People With Substance Use Disorders. Front. Psychiatry 11:372. doi: 10.3389/fpsyt.2020.00372

STIGMA AND DEHUMANIZATION SURROUNDING ADDICTION

The way we respond to substance use disorders (SUD) says more about our society than it does about those using illicit drugs. In the United States, in particular, the very distinction between illicit and legal use depends on politics and power more than a drug's specific risk profile. While inconsistently penalized, drug use has largely been framed as a criminal justice issue. This framing has fueled, and been fueled by, the intense stigma surrounding addiction. The process of stigmatization relies on sticky overgeneralizations, which in turn are used to justify social exclusion, prejudice, and discrimination. Addiction is one of the most stigmatized social disorders, with "addicts" being described as "filthy junkies" who do not deserve social support or empathy (1). A recent study found that nearly 73% of those surveyed would be unwilling to spend even *one* evening socializing with an "addict." (2) This social distancing contributes to the low self-esteem and depression people with SUD experience. It can also foster punitive policies such as insurance coverage disparities and housing discrimination (3).

Stigma also relates to dehumanization, which is when we deny out-groups human characteristics that we extend to ourselves—namely, the capacity to feel and the capacity to make decisions. Throughout history when groups are dehumanized, they are seen not as individuals but as members of a mindless cluster to whom we can direct our moral outrage and punishment (4). On scales of dehumanization, drug addicts often rate as "the lowest of the low," (5) triggering reactions of disgust due to their perceived unpredictability and lack of agency. This can even be evidenced at the neurological level, as viewing images of people with SUD does not activate regions of the brain normally recruited when viewing humans (6).

DIFFERING LEVELS OF MORAL OUTRAGE MEDIATE OUR RESPONSE

Given that stigma and dehumanization take root when we fail to take the perspective of the affected person, it is not surprising that this lack of empathy is exaggerated when the particular type of "addict" is dissimilar to us. This may be why the level of collective disgust and moral outrage shown

to people with SUD has been inconsistent over time. Our moral outrage, and not our public health priorities, determine our social response. We need look no further than the recent history regulating drug use in the United States for confirmation of this.

Crack Cocaine and the "War on Drugs"

In the 1970s, the racialized "war on drugs" began with poor black communities placed in the government's crosshairs. Congress passed harsh mandatory minimum sentences, that decimated communities of color. These laws were supported by dehumanizing media portrayals of black "crack whores" and black "crack babies." (7) Even when the drug was pharmacologically identical, our criminal and public health response focused not on the harms but on the population affected. While powder cocaine, "associated with a wealthier, whiter class of drug users," required possession of 500 grams to trigger a 5-year federal prison term, one only needed to possess 5 g of crack cocaine, "regarded as a drug of the black urban ghetto," to trigger the same sentence (8). Drugs rarely stay in the hands of a discrete subpopulation and tend to spread to many other communities. However, the initial framing of the using population can steer our legal and public health response.

The Modern Opioid Crisis

Today, the opioid crisis has exposed the truth that addiction does not discriminate between the powerful and the poor. Many suburban, white, teenagers began their opioid addiction in a doctor's office, filling pain prescriptions before turning to stronger drugs (9). Now, most opioid deaths in the United States are due to fentanyl overdoses (10). While still infused with criminalization, many agencies and legislators have responded to the crisis with a more therapeutic and prevention-based approach, that recognizes the humanity of those affected (11). Congress even passed a rare, bipartisan appropriation bill that provided funding for research into addiction stigma, and increased housing options for people in recovery (12). Politicians have thankfully also taken stock of the structural roots of the crisis: physician conflicts of interest, underregulation of greedy pharmaceutical companies, poverty, and a lack of access to quality mental health care. In part because of the devastating economic impacts, local governments are even attempting to hold all of the participants in the supply chain responsible through tort litigation, rather than focusing blame on the end user (13). These delayed but significant efforts laudably treat addiction as a disease with devastating public health impacts. However, it is not coincidental that this addiction crisis struck the white suburbs before the urban poor, which framed, and likely facilitated, the more empathic response (14).

The Use of Cognitive Enhancers

Cognitive enhancement is the nontherapeutic use of drugs to boost memory, attention, or alertness. While the fatality risk from stimulants like methylphenidate and amphetamine (sold as Ritalin and Adderall) is lower than for opioids or cocaine, there is still considerable, underexplored risk of their off-label use (15). People can become dependent or addicted to these substances, and in high doses they can cause toxicity and cardiac arrest. The perceived market for these study drugs is largely young, privileged, college students, who are looking for a competitive edge (16). And while many see this use as unfair and troubling (and indeed illegal if the result of diversion), it has not triggered the same level of moral outrage. There is a growing market for such drugs on the dark web. However, cognitive enhancement is still chiefly identified with college campuses. This framing has enabled a more libertarian approach. The regulatory response has been mainly left to university administrations, a minority of which have declared the use of cognitive enhancers a violation of their honor codes. This can be understood through the lens of dehumanization—privileged, white, college students are considered to have maximum levels of agency and emotionality. They are thus granted the status of full humans, similar to those who were tricked into being addicted to prescription pain medication, but unlike those lesser humans who willingly became addicted to crack cocaine. The consequence of this are startling. Being held to have violated a university honor code and being labeled a "cheater" is a far cry from a mandatory prison sentence of up to 5 years and a lifetime label as "convict."

"Chem Sex" and a Chance to Do Better

The use of drugs before, during, or after sex is not new. However, sexualized drug use, or "chem sex" has recently been increasing among men who have sex with men (MSM), and is linked with high-risk sexual behaviors such as condomless anal sex and the transmission of sexually transmitted infections (17). The drugs consumed vary according to geography and access, but common combinations include mephedrone, GHB, methamphetamine, and drugs for erectile dysfunction (18). These drugs may be taken to reduce sexual inhibitions, stimulate arousal, intensify orgasm, or keep individuals awake. The risks associated with this practice depend on the frequency and patterns of use, and drug-drug interactions (19). For example, the effects of GHB are exaggerated in people on certain HIV medications, and chem sex can reduce compliance with these protocols.

So far, our societal response to chem sex has been a bit muted. Insufficient epidemiological data has been gathered to describe its prevalence and features. There are vulnerable intersectionalities at play, as drug users and gay men are both dehumanized. Gay men are routinely dehumanized with metaphors of deviance and animalistic sexual practices which deny their status as fully thinking and feeling individuals. Indeed, this might contribute to their chem sex drug use—as they may be isolated, anxious, and unprepared to negotiate their sexual lives in a world that does not allow them to develop this openly. Chem sex, like other drug use, might be a form of self-medication. Referring to "chem sex" as a "second plague" which is "unnatural" and filled with "animalistic orgies" perpetuate this hypersexualized and monolithic narrative.

We have a chance to do better when it comes to our response to chem sex. While the public health concerns are already mounting, it is not too late to frame our response in a way that maximizes the humanity of those affected. We can start with using less sexualized terminology that focuses on the environment in which people use. Just as we are beginning to do with those with opioid use disorder, we must invest in harm reduction measures and evidence-based prevention and treatment strategies (20). Encouraging group use of drugs can

be a method of harm reduction rather than a means for stigmatization, as individuals can monitor each other for signs of cardiac arrest or shallow breathing. Legislators should consider enacting "Good Samaritan" statutes, which immunize fellow users from prosecution if they call emergency responders when someone overdoses. Many states have passed such laws in the wake of the opioid crisis, but they should be applied to the same extent when MSM engage in chem sex. It is unlikely that chem sex will be dismissed as an autonomous exercise of agency, as many unfortunately do with the enhancement uses of stimulants. Without denigrating those who engage in chem sex as subhuman, we should recognize that there are serious potential harms that flow from this choice. These harms must be shared in a nonjudgmental way with affected communities. We must better understand the causal relationships between risky sex and drug use, and explore the reasons why people use, and how they are using, to understand the best paths toward encouraging healthy behaviors (21). None of these strategies will be effectively pursued if we ignore the humanity of those affected, or allow the sexual nature of this practice to stifle good epidemiological research. Substances have different risk factors for abuse, which cannot be ignored. But each underlying population is completely human—with complete capacity to think and feel. It does violence to our prevention and treatment efforts when we allow our social response to be guided by sympathy for those "like us" and antipathy for those who are different.

AUTHOR CONTRIBUTIONS

TB is the sole author and contributed 100% to the research and writing of this Opinion.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 25 May 2020
doi: 10.3389/fpsyt.2020.00464

Post-Mortem Toxicology: A Systematic Review of Death Cases Involving Synthetic Cannabinoid Receptor Agonists

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OPEN ACCESS

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: 08 January 2020
Accepted: 06 May 2020
Published: 25 May 2020

Citation:
Giorgetti A, Busardò FP, Tittarelli R, Auwärter V and Giorgetti R (2020) Post-Mortem Toxicology: A Systematic Review of Death Cases Involving Synthetic Cannabinoid Receptor Agonists. Front. Psychiatry 11:464. doi: 10.3389/fpsyt.2020.00464

Background: Synthetic cannabinoid receptor agonists (SCRAs) have become the largest group of new psychoactive substances monitored by the European Union Early Warning System. Despite the wide diffusion on the market, data regarding effects, toxicities, and mechanisms as well as toxic/lethal doses are still scarce.

Methods: A comprehensive literature search for articles published up to January 2019 was performed in multiple electronic databases. Only cases of death in which toxicological analyses revealed the presence of SCRAs in blood or urine and at least an external examination was performed, including those occurred in emergency departments, were included.

Results: Of 380 studies identified, 354 were excluded, while 8 additional manuscripts were included through the screening of relevant references cited in the selected articles. A total number of 34 manuscripts (8 case series and 26 case reports) were included.

Conclusions: Typical toxic ranges for SCRAs have not been so far identified, and the results of toxicological analyses should be interpreted with caution. In death cases involving SCRAs, a thorough post-mortem examination is a prerequisite to assess the role of the substance use in the deceased and to identify a probable mechanism of death. Even after a comprehensive analysis of clinical, circumstantial, toxicological, and autoptic data, the cause and manner of death remain unclear in some cases.

Keywords: forensic toxicology, novel psychoactive substances, synthetic cannabinoids, post-mortem examination, toxicological significance score

INTRODUCTION

Synthetic cannabinoids or synthetic cannabinoid receptor agonists (SCRAs) are a heterogeneous group of compounds designed to mimic the effects of *delta*-9-tetrahydrocannabinol (Δ9-THC) by binding to the cannabinoid receptors CB_1 and CB_2. In contrast to Δ9-THC, a partial agonist at the CB_1 and CB_2 receptors, most of the SCRAs marketed so far are full agonists at these receptors and additionally show much higher potency (1, 2). Since their first detection in herbal blends in 2008 (3, 4), they have become the largest group of new psychoactive substances (NPS), with 190 compounds reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) until the end of 2018 and an extraordinary dynamic market (5), even though there has been a relative reduction of the rate of new compounds per year (5). It was initially claimed that SCRAs could be "safe" alternatives to marijuana, due to similarities of their pharmacological profile to Δ9-THC and other phytocannabinoids, and lots of compounds binding to the cannabinoid receptors have been synthesized and evaluated regarding their binding affinities and activity in animal or cell models since then (6). However, a huge number of in-vitro and in-vivo studies, reports, and alerts have highlighted severe adverse events and enhanced toxicity (2, 7, 8) prompting the United States Drug Enforcement Administration to classify some of these compounds as Schedule I substances. Signs and symptoms of SCRAs consumption include psychomotor agitation, euphoria, anxiety, confusion, and psychosis on the one side, sedation and loss of consciousness on the other (9, 10). Adverse cardiac effects are among the most frequently encountered adverse reactions after SCRA intake. Particularly, both tachycardia (more frequently) and bradycardia have been reported. Gastro-intestinal symptoms with nausea and vomiting are also common. Moreover, rhabdomyolysis, hyperthermia, and hypothermia, seizures, respiratory depression, nephro- and hepatotoxicity were described in combination with SCRA intake (11, 12). Some of these effects might be mediated also by interference with other neurotransmitter pathways, since certain SCRAs can also bind to glutamatergic, serotonin (5-HT), opioid, and both adrenergic and cholinergic receptors and to calcium, sodium, potassium channels (13).

Several cases of intoxication have been reported caused by, e.g., MDMB-CHMICA and AB-CHMINACA, which can cause severe symptoms requiring hospitalization and prolonged recovery time (14). Other compounds, such as Cumyl-PEGACLONE, have been suggested as "relatively safe" due to the low number of poisonings despite the abundant presence in herbal blends (25–30% of tested products) and their widespread use (prevalence of 29% in samples positive for SCRAs, including testing for driving under the influence, insult, and threat, criminal offenses). Moreover, the role of the SCRA was deemed minor or contributory in the majority of death cases (15).

Despite the wide diffusion in the market, data regarding effects, toxicities, and mechanisms as well as toxic/lethal doses are still scarce, making SCRAs one of the most "unpredictable" classes of substances (16). Moreover, only few studies regarding the time of detectability, the diffusion in tissues, and the post-mortem distribution of the drugs can be retrieved in the literature. The limited knowledge regarding the pharmacodynamics and pharmacokinetics of SCRAs contributes to the difficulties of the interpretation of toxicological results. Furthermore, several aspects, such as interactions among SCRAs or in the combination with other drugs, are difficult to assess in cases of SCRA-related deaths.

To our knowledge, there are no previous detailed review papers, which report fatalities caused by the misuse of synthetic cannabinoids providing circumstantial, analytical data, and complete results of post-mortem examination.

The aim of the present study is to offer an overview of thoroughly investigated fatalities involving SCRAs, considering not only analytical results, but also an in-depth analysis on investigative data, analytical methods, and macro and microscopic findings.

MATERIALS AND METHODS

Literature Search and Inclusion/Exclusion Criteria

In February 2019 a literature search for articles published until January 2019 was performed in electronic databases (Pubmed, Scopus), using the following research terms: "synthetic cannabinoids" AND (death OR fatal OR fatalities OR autopsy OR forensic OR post-mortem). Search was done in English language and duplicates were manually deleted. Titles and abstracts were screened and only cases of death, in which toxicological analyses revealed at least one SCRA in blood or urine, and at least an external examination was performed were included. Patients rushed to the emergency department and subsequently died were also included in the selected cases.

Exclusion criteria were: irretrievability of a full-text; off-topic articles (e.g., death cases in which other NPS, but no SCRAs, were detected); *in vitro*/animal model studies; herbal blends analyses; non-fatal cases of intoxication; books/reviews not including unpublished cases of death due to SCRAs; autopsy/external examination not performed.

Data Extraction

An electronic database with the selected papers was built in Excel ® (Microsoft Office, 2006). For each included manuscript, authors, title, journal, year, and type of publication (e.g., case report, case series), number of death cases and type of involved SCRA were extracted.

A separate database was built with the retrieved papers and, for each death case, the following information was extracted:

- type of victim, referring to age and sex;
- concentrations of SCRA retrieved during toxicological analyses in central and peripheral blood, urine, and tissues;
- other substances detected in blood;
- circumstantial data (and whatever relevant emerged during the death scene investigation), with particular reference to a history of drug abuse and to the availability of herbal blends/paraphernalia at the scene,

- post-mortem gross and microscopic findings;
- cause, manner, and suggested mechanism of death;
- post-mortem interval (PMI)
- role of the SCRA as described by the authors.

Data Analysis/Interpretation

Only a descriptive statistic was applied. For each death case, two independent observers assigned a Toxicological Significance Score (TSS) to the involved SC, in accordance to the methodology proposed by Elliott et al. (17). When no agreement was achieved, a third person was consulted. This rating was compared with the likely role in death assigned by the authors.

Information related to toxicological analytical methodology (linearity, calibration curve, accuracy, precision, limit of detection/quantification, matrix effect), in accordance with what suggested by Welter-Luedeke and Maurer (18) were also noted and taken into consideration when evaluating the single cases.

RESULTS

Literature Review

The literature search resulted in 380 sources after elimination of duplicates. Of these, 354 were excluded applying the criteria listed in "Materials and Methods," while 8 additional manuscripts were included through the screening of references cited in the selected articles. Details of the literature search are listed in **Figure 1**.

Finally, a total of 34 manuscripts were included (authors, title, journal, date of publication, and involved SCRAs are shown in **Table 1**), corresponding to 74 published cases. Of the 34 manuscripts, 8 consisted in case series and 26 in case reports, including articles only providing new analytical data on previously reported death cases (**Table 1**). **Tables 2** and **3** both refer to the single cases. Particularly, **Table 2** displays the epidemiology of the victim, the involved SCRA(s), other substances detected, anamnestic/circumstantial, and clinical data, macroscopic and microscopic features, cause, and suggested mechanism of death, toxicological significance score, and role of SCRA as suggested by the authors of the paper. In **Table 3**, concentrations in peripheral, central blood, urine, and tissues, together with the PMI are shown.

Analytical Issues

Sample preparation and extraction procedures varied widely: liquid-liquid extraction was the most frequently used, though solid-phase extraction (24, 44, 47, 53) and QuEChERS dispersive solid-phase extraction (29, 30, 35, 50) were also reported. Only in a minority of the cases, the standard addition method was employed for quantification (19, 23, 28, 30). In two cases, liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QToF-MS) was used to detected and quantitate parent compounds and/or metabolites in blood and ante-mortem serum (38, 48).

Overall, 31 SCRAs (EAM-2201, AB-PINACA, 5F-PB-22, 5F-AKB-48, 5F-ADB, AB-CHMINACA, UR-144, XLR-11, JWH-022, MAB-CHMINACA, MDMB-CHMICA, 5F-AMB, Mepirapim, JWH-018, AM-2201, JWH-210, JWH-122, JWH-250, JWH-175, ADB-FUBINACA, AB-FUBINACA, 5F-APINACA, MAM-2201, STS135, THJ 2201, AM-1220, AM-2232, PB-22, NNEI, AM-604, and JWH-073) were detected, some being more frequently identified in the revised cases, such as 5F-ADB, XLR-11, AM-2201, AB-CHMINACA, and JWH-018.

Even if reported with lower rates, 5F-PB-22, UR-144 were also common. XLR-11 was mostly reported in 2016, while 5F-ADB showed a peak in 2017 and 2018. However, a clear trend cannot be determined on the sole basis of this data.

While some laboratories applied national or international validation guidelines, such as those of the German Society of Toxicological and Forensic Chemistry (GTFCh), "in house" methods have also been adopted, stating overall good results

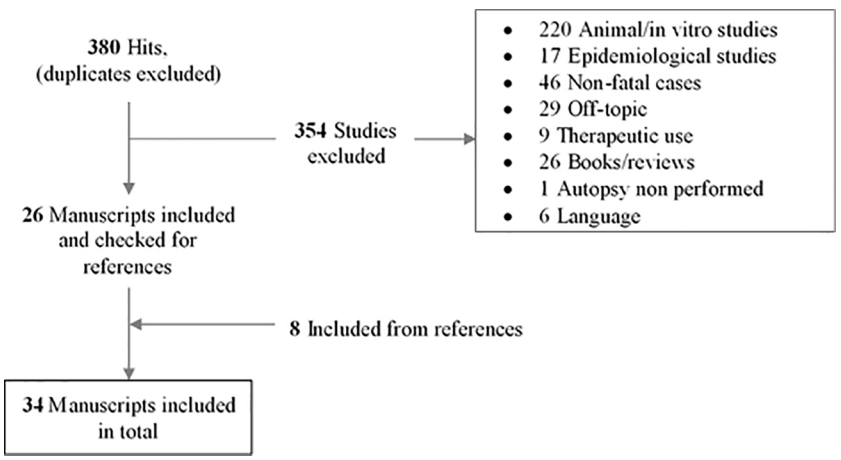

FIGURE 1 | Flow diagram of study identification, screening, and selection.

TABLE 1 | Characteristics of the included studies: authors, titles, journal, and year of publication, number of cases reported and type of SCRAs involved (semisystematic names).

Title	Journal	Year	No. of cases	SCRA	Author
A case of intoxication with a mixture of synthetic cannabinoids EAM-2201, AB-PINACA and AB-FUBINACA, and a synthetic cathinone α-PVP.	Leg Med (Tokyo)	2018	–	EAM-2201, AB-PINACA, AB-FUBINACA	Yamagishi et al. (19)
Synthetic cannabinoids: variety is definitely not the spice of life.	J Forensic Leg Med	2018	1	5F-PB-22, 5F-AKB-48	Langford and Bolton (20)
Teens and Spice: A review of adolescent fatalities associated with synthetic cannabinoid use	J Forensic Sci	2018	2	UR-144, XLR-11, JWH-022	Paul et al. (21)
Identification and quantification of predominant metabolites of synthetic cannabinoid MAB-CHMINACA in an authentic human urine specimen.	Drug Test Anal	2018	–	MAB-CHMINACA	Hasegawa et al. (22)
Fatal intoxication by 5F-ADB and diphenidine: Detection, quantification, and investigation of their main metabolic pathways in humans by LC/MS/MS and LC/Q-TOFMS.	Drug Test Anal	2018	1	5F-ADB	Kusano et al. (23)
Post-mortem distribution of the synthetic cannabinoid MDMB-CHMICA and its metabolites in a case of combined drug intoxication.	Int J Legal Med	2018	1	MDMB-CHMICA, EG-018	Gaunitz et al. (24)
Sensitive identification and quantitation of parent forms of six synthetic cannabinoids in urine samples of human cadavers by liquid chromatography–tandem mass spectrometry	Forensic Toxicol	2017	1	5F-ADB, MAB-CHMINACA	Minakata et al. (25)
New challenges in toxicology of new psychoactive substances exemplified by fatal cases after UR-144 and UR-144 with pentedrone administration determined by LC-ESI-MS-MS in blood samples.	Arch Med Sadowej Kryminol	2017	3	UR-144	Rojek et al. (26)
Three fatalities associated with the synthetic cannabinoids 5F-ADB, 5F-PB-22, and AB-CHMINACA	Forensic Sci Int	2017	3	5F-ADB	Angerer et al. (27)
Identification and quantitation of 5-fluoro-ADB, one of the most dangerous synthetic cannabinoids, in the stomach contents and solid tissues of a human cadaver and in some herbal products	Forensic Toxicol	2015	–	5F-ADB, 5F-ADB-PINACA, MAB-CHMINACA	Hasegawa et al. (28)
Postmortem distribution of MAB-CHMINACA in body fluids and solid tissues of a human cadaver	Forensic Toxicol	2015	1	5F-ADB, 5F-ADB-PINACA, MAB-CHMINACA	Hasegawa et al. (29)
Postmortem distribution of AB-CHMINACA, 5-fluoro-AMB and diphenidine in body fluids and solid tissues in a fatal poisoning case: usefulness of the adipose tissue for detection of the drugs in the unchanged forms	Forensic Toxicol	2015	1	AB-CHIMINACA, 5F-AMB	Hasegawa et al. (30)
Fatal poisoning with the synthetic cannabinoid AB-CHMINACA and ethyl alcohol – a case study and literature review	Problems of Forensic Sciences	2016	1	AB-CHMINACA	Gieron et al. (31)
Death after use of the synthetic cannabinoid 5F-AMB	Forensic Sci Int	2016	1	5F-AMB	Shanks and Behonick (32)
Synthetic cannabinoid drug use as a cause or contributory cause of death	Forensic Sci Int	2016	25	JWH-018, AM-2201	Labay et al. (33)
Death associated with the use of the synthetic cannabinoid ADB-FUBINACA.	J Anal Toxicol	2016	1	ADB-FUBINACA	Shanks et al. (34)
Clinical and toxicological findings of acute intoxication with synthetic cannabinoids and cathinones	Acute Med Surg	2016	1	Mepirapim	Fujita et al. (35)
Case report: fatal intoxication with synthetic cannabinoid MDMB-CHMICA	Forensic Sci Int	2016	1	MDMB-CHMICA	Adamowicz (36)
Death due to diabetic ketoacidosis: Induction by the consumption of synthetic cannabinoids?	Forensic Sci Int	2015	1	AB-CHMINACA, AB-FUBINACA, AM-2201, 5F-AMB, 5F-APINACA, EAM-2201, JWH-018, JWH-122, MAM-2201, STS135, THJ2201, UR-144, XLR-11	Hess et al. (37)
High-resolution mass spectrometric determination of the synthetic cannabinoids MAM-2201, AM-2201, AM-2232, and their metabolites in postmortem plasma and urine by LC/Q-TOFMS.	Int J Legal Med	2015	1	MAM-2201, AM-1220, AM-2232	Zaitsu et al. (38)
Case reports of synthetic cannabinoid XLR-11 associated fatalities.	Forensic Sci Int	2015	2	XLR-11	Shanks et al. (34)
Deaths linked to synthetic cannabinoids.	Forensic Sci Med Pathol	2015	3	PB-22	Gerostamoulos et al. (39)

(Continued)

TABLE 1 | Continued

Title	Journal	Year	No. of cases	SCRA	Author
Four postmortem case reports with quantitative detection of the synthetic cannabinoid, 5F-PB-22	J Anal Toxicol	2013	4	5F-PB-22	Behonick et al. (40)
Toxicological findings of synthetic cannabinoids in recreational users.	J Anal Toxicol	2013	1	JWH-210	Kronstrand et al. (16)
K2 toxicity: fatal case of psychiatric complications following AM2201 exposure	J Forensic Sci	2013	1	AM-2201, JWH-018	Patton et al. (41)
An accidental fatal intoxication with methoxetamine	J Anal Toxicol	2013	1	AM-694, AM-2201, JWH-018	Wikström et al. (42)
Detection of JWH-018 and JWH-073 by UPLC-MS-MS in postmortem whole blood casework	J Anal Toxicol	2012	3	JWH-018, JWH-073	Shanks et al. (43)
A fatal case of MAM-2201 poisoning	Forensic Toxicol	2013	1	MAM-2201	Saito et al. (44)
A case of death caused by abuse of a synthetic cannabinoid N-1-naphthalenyl-1-pentyl-1H-indole-3-carboxamide	Forensic Toxicol	2014	1	NNEI	Sasaki et al. (45)
A fatal case involving several synthetic cannabinoids	Toxichem Krimtech	2013	1	JWH-122, JWH-018, JWH-210, MAM-2201, AM-2201, UR-144	Schaefer et al. (46)
A report of novel psychoactive substances in forensic autopsy cases and a review of fatal cases in the literature	Legal Medicine	2017	4	5F-AB-PINACA, 5F-AMB	Kubo S et al. (47)
Sudden cardiac death following use of synthetic cannabinoid MDMB-CHMICA	J Anal Toxicol	2016	1	MDMB-CHMICA	Westin et al. (48)
Analysis and clinical findings of cases positive for the novel synthetic cannabinoid receptor agonist MDMB-CHMICA	Clin Toxicol (Phila)	2016	2	MDMB-CHMICA	Seywright et al. (49)
Identification of 5-Fluoro ADB in human whole blood in four death cases.	J Anal Toxicol	2018	4	5F-ADB	Usui et al. (50)

"-": further analyses were performed on a previously published case.

(31, 32, 43). Analytical details were not always given and not all of the above-mentioned parameters, especially matrix-effects, were systematically assessed (19, 27, 31, 37, 38, 41, 44, 52).

According to previously published cases (33, 43), concentrations of SCRAs in post-mortem cases covered a wide range, from 0.01 (19) to 199 ng/mL (43), although lower concentrations, in the range 0.5 to 2.5 ng/ml, were most frequently encountered.

Peripheral blood was analyzed in 53 cases out of 74 (72%). In 8 cases (11%) only heart blood concentrations were stated, while both peripheral and central concentrations were published in 10 cases (14%). Other biological matrices, apart from urine, were quantitatively analyzed in only 8 cases (11%) (**Table 3**). Other substances were found in 44 out of 74 cases (59%).

As regard other xenobiotics detected, ethanol was detected in 13 cases (17%), though levels ≥ 1.5 g/L were found only in 6. A co-consumption of NPS, as synthetic cathinones (pentedrone, α-PVP, DL-4662), hallucinogens (6-APB, 6-MAPB, methoxetamine), anesthetics (diphenidine), and synthetic opioids (AH-7921) was seen in 11 cases (15%). Common drugs of abuse detected included antidepressive/neuroleptics/antipsychotics (quetiapine, trimipramine, olanzapine, sodium valproate, mirtazapine, amitriptyline, phenytoin, paroxetine, aripiprazole, citalopram, fluoxetine, haloperidol, trazodone, venlafaxine, pregabalin, topiramate) (12/74, 16.2%), cannabinoids (10/74, 13%), amphetamines, benzodiazepines (both 6/74, 8%) and opioids (5/74, 7%).

Case Reports

The age of the deceased ranged from 14 to 61 (19). Mean age was 32, median 29. The 38.5% belonged to the 20 to 29 decades. Teenagers were also represented (15.4%) (**Figure 2**). With reference to the gender of the victims, 88.1% were male and 11.9% were female. A past use of drugs and/or alcohol was reported in 18 out of 74 cases (24%), while poor mental health was only reported in 5 cases (7%).

Herbal blends, smoking devices (e.g., pipes) and other paraphernalia were found during the death scene investigation (DSI) in 30 of 74 cases (41%) and were variably labeled as "Aladdin platinum/limited," "Herbal incense, the super lemon," "F1," "Hammer Head," "Magic Gold," "Desert Premium Potpourri," "AL 37," "AP 31," "Strongman," "GM sapphire," "Heart Shot Black," "Apollo," "Mocarz," "Smoke XXX. A potent potpourri," "Mad Hatter Incense," "Fairy evolution," "Mary Joy Annihilation," "Passion Flower Herb – Zonk," "Stoner Pot-Pourri K11," "Supanova Pot-Pourri," "K2 Cherry," "Space Cade Flight Risk," "Game over," "Orange Flame," "Legal Phunk," "Mojo." Clinical data was available in 15 cases (20%) and mostly included the detection of cardiac arrest/asystolia/fibrillation at the arrival to an Emergency Department.

Results of post-mortem examination, as for macroscopical or gross findings, were available in 55 cases (74%), including those cases in which only a short referral to "unremarkable findings" was reported. In most cases in which a SC was later discovered during toxicological analysis, the post-mortem examination had revealed only non-specific signs of intoxication, such as pulmonary edema and congestion, brain edema, hemolysis, and signs of aspiration (34, 40). In some cases, stomach and gastroduodenal erosions (20, 35), abundant hypostasis coupled to petechiae (27, 29, 37) and intracutaneous skin bleedings (vibices) (30) were reported. Lastly, cardiac abnormalities, such as cardiomegaly (33, 43), dilatative or hypertrophic cardiomyopathy (21), stenosis due to atherosclerosis (33, 46) or acute thrombosis of the coronary arteries were seen (32).

TABLE 2 | Results of the literature revision for each case.

Age, sex	SCRA(s) in peripheral blood (ng/ml)	Other substances in blood (ng/ml, ethanol g/L)	Anamnestic and Circumstantial data	Clinical data	Gross findings	Histopathology	Cause of death	Suggested mechanism	TSS	Role of SCRA(s) (authors)	Study
-, M	EAM-2201: 0.0566 ± 0.0042; AB-PINACA: 0.0126 ± 0.0001	α-PVP: pos	Dead in a bathtub, with water level lower than the shoulder	No medical history	Lung congestion and edema	NP	Possible intoxication due to synergic effect	NP	TSS U	Possible intoxication due to synergistic effect	Yamagishi et al. (19) .Minakata et al. (25)
35, M	5F-PB-22: pos 5F-AKB-48: pos	Ethanol 3.11	History of schizophrenia, alcohol and alcohol withdrawal, seizures; he was found dead in an alleyway within 30 min of having been given a smoking pipe	Shock advisory defibrillator	Lungs congestion, scattered erosions within the mucosa of the stomach	Confirmation of macroscopic findings	Combination of alcohol and SCRAs	Sudden onset of cardiac arrhythmias or cardiac death	TSS U	Possible contributory role in emotional and mental imbalance	Langford and Bolton (20)
20s, M	5F-ADB: 0.12 (iliac)	–	Found dead in a sitting position in his room. The police found an opened sachet labeled "Heart Shot BLACK" on a table.	No medication history	Unremarkable	NP	Acute circulatory failure after drug inhalation	NP	TSS 2	The SCRA involvement on death is unknown	Usui et al. (50)
50s, M	5F-ADB: 0.23 (iliac)	–	The decedent was lying on the floor in a supine posture. An opened sachet labeled "Heart Shot BLACK" was found on a table.	NP	Ischemic heart disease	NP	Acute circulatory failure after drug inhalation	NP	TSS 2	The SCRA involvement on death is unknown	
20s, M	5F-ADB: 0.16 (iliac)	–	Found dead in a prone position in a hallway, after vomiting and bleeding from nose	No medication or medical history	Unremarkable	NP	Acute circulatory failure after drug inhalation	NP	TSS 2	The SCRA involvement on death is unknown	
50s, M	5F-ADB: 1.38 (iliac)	–	History of schizophrenia under medication, he was found dead in his car in a parking lot while he was holding a plastic pipe and with an unsealed "Heart Shot BLACK" package in his hands	For the treatment of schizophrenia he was taking risperidone, biperiden, and olanzapine.	Unremarkable	NP	Acute circulatory failure after drug inhalation	NP	TSS 2	The SCRA involvement on death is unknown	
14, M	AB-CHMINACA: 8.2 (subclavian)	–	Daily SC intake for 6 months, last use an hour before experiencing sudden cardiac death following an unwitnessed collapse in his bathroom	No history of any other substance use, or any relevant medical, surgical or family history	Dilated cardiomyopathy, cardiomegaly (520 g), bilateral pulmonary edema, bilateral pleural effusion and ascites	Cardiomyocyte hypertrophy, contraction band necrosis, pulmonary edema and pulmonary vascular congestion	SCRA intoxication	Sudden cardiac death and dilated cardiomyopathy	TSS 3	SCRA intoxication	Paul et al. (21)
17, M	UR-144: 12.3 (subclavian), XLR-11: 1.3 (subclavian), JWH-022: 3 (subclavian)	–	Occasional user of SC ("Black Mamba"), last use 4-5 h before death. He was found in his bedroom	NP	Unremarkable	Unremarkable	SCRAs intoxication	Sudden death	TSS 3	NP	
34, M	MAB-CHMINACA: 6.05	Ethanol: 0.3 Quetiapine: pos Nicotine: pos	Severe drugs dependence with multiple admission to mental health hospital; found dead in his room	NP	Massive aspiration of gastric content occluding the airways	NP	Asphyxia due to aspiration of stomach contents into the trachea	Vomiting under reduced consciousness	TSS 3	NP	Hasegawa et al. (22, 28, 29)
53, M	5F-ADB: 0.19 ± 0.04 (*)	Diphenidine: 12 ± 2.6	Found dead at his apartment. Near the deceased were found an open package of a branded herbal blend ("Heart Shot BLACK").	NP	Unremarkable	NP	Probably SC and diphenidine intoxication	NP	TSS U	Acute mixed intoxication	Kusano et al. (23)

(Continued)

TABLE 2 | Continued

Age, sex	SCRA(s) in peripheral blood (ng/ml)	Other substances in blood (ng/ml, ethanol g/L)	Anamnestic and Circumstantial data	Clinical data	Gross findings	Histopathology	Cause of death	Suggested mechanism	TSS	Role of SCRA(s) (authors)	Study
27, M	MDMB-CHMICA: 1.7	Amphetamine: 1050 MDMA: 275 MDA: 22 THC: 9.3 THCCOOH: 65	Eyewitnesses reported that the man fell from the 24th floor of a building.	NP	Multiple injuries to head (including partial debraining), left lung and internal bleeding due to rib fractures.	NP	Fall from height	Psychosis-induced or loss of attention	TSS 1	Under the influence	Gaunitz et al. (24)
30, M	AB-CHMINACA: pos 5F-AMB: pos	Diphenidine 715	Found dead in a parked car	NP	Livor mortis associated with vibices for wide areas of the body surface with a few subcutaneous hemorrhages	NP	NP	NP	TSS U	NP	Minakata et al. (25) .Hasegawa et al. (30)
30s, M	5F-ADB: pos MAB-CHMINACA: pos	–	Found dead at home	NP	Unremarkable	NP	NP	NP	TSS U	NP	Minakata et al. (25)
16, M	UR-144: 2.1	–	He smoked “dope” and a cigarette with UR-144, experienced hallucinations and psychosis, lost control of himself and jumped out of the window from the second floor of the building	NP	Multiple fractures to skull, thoracic and lumbar spine, pubic and ischial bones and multi-organ injuries	NP	Fall from height	Psychosis-induced	TSS 3i	NP	Rojek et al. (26)
22, M	UR-144: 1.4	Pentedrone: 2300	History of alcohol and drugs abuse, previous suicidal ideations; showed mental disorders and aggressive behavior, injured a witness with an axe	NP	NP	NP	Asphyxia due to hanging	Behavioral abnormalities	TSS 1i	NP	
40, M	UR-144: 4	Pentedrone: 290	History of mental instability; psychomotor agitation, aggressive behavior, after smoking a legal high called Orange Flame	Acute toxic liver damage, kidney failure, rhabdomyolysis, disseminated intravascular coagulation, bleeding in the gastrointestinal tract and traumatic hematomas; cardiac arrest	NP	NP	Massive multi-organ failure due to the effect of toxic substances	Behavioral abnormalities with desire of enhancing stimulating effects	TSS 1i	NP	
25, M	5F-PB-22: 0.37	Ethanol: 2.6	History of alcohol and illicit drug use, found dead in his apartment; witnesses reported that the decedent had drunk a lot of alcohol on the evening before his death. Packages of products named “F1,” “Hammer Head,” and “Magic Gold” were found at the scene	NP	Cerebral edema, pulmonary edema, acute blood congestion of internal organs, petechial hemorrhage in eyelids, facial skin and on the lungs	NP	Partial or complete obstruction of the upper airways	Suffocation in presence of SC and ethanol in a state of unconsciousness	TSS 2	Direct contribution	Angerer et al. (27)
28, M	AB-CHMINACA: 4.1	Ethanol: 1.45	Extensive consumer of alcohol and illicit drugs, found dead in his flat. Three packages of the herbal blend “Desert Premium Potpourri 2 g” were located besides the decedent	NP	Cerebral edema and pulmonary edema	NP	Mixed ethanol and SC intoxication with fatal outcome	NP	TSS 2	Direct contribution	
41, M	5F-ADB: 0.38	Ethanol: 0.09 Trimipramine: 170 Olanzapine: 41	Methamphetamine user, found at home	NP	Cerebral edema, pulmonary edema, acute blood congestion of	Myocardial cells death, amorphous material in alveoli as a sign of aspiration of stomach content	Coma and subsequent aspiration of vomit	NP	TSS 3	Direct contribution	

(Continued)

TABLE 2 | Continued

Age, sex	SCRA(s) in peripheral blood (ng/ml)	Other substances in blood (ng/ml, ethanol g/L)	Anamnestic and Circumstantial data	Clinical data	Gross findings	Histopathology	Cause of death	Suggested mechanism	TSS	Role of SCRA(s) (authors)	Study
					internal organs, petechial hemorrhages in eyelids, facial skin and on the lungs						
-, -	AB-PINACA: 26	α-PVP: 9900 MDPV: 55	NP	NP	NP	NP	Fall from height	NP	TSS U	NP	Kubo et al. (47)
-, -	5F-AMB: 8	α-PVP: 90 AH-7921: 1100	NP	NP	NP	NP	Intoxication	NP	TSS U	NP	
-, -	Mepirapim: 157	6-APB: 2.7 6-MAPB: <1 α-PHP: 338 DL-4662: 138, Sodium valproate: pos	NP	NP	NP	NP	Intoxication	NP	TSS U	NP	
-, -	5F-AMB: <1	DL-4662 <1, α-PHP 15, metamphetamine 30, amphetamine 10	NP	NP	NP	NP	Intoxication	NP	TSS U	NP	
30s, M	AB-CHMINACA: 1.5 (**)	Ethanol: 1.8	Alcohol addiction. After smoking a pipe with a herbal mixture ("Strongman"), he collapsed and had a slurred speech. An hour later, was found with vomit, weak pulse, shallow breathing. About half an hour later, was declared dead by the emergency doctor	NP	Congestion of internal organs and pulmonary edema	NP	Acute cardiorespiratory failure	SNC depression	TSS 3	Intoxication due to alcohol and SCRA consumption	Gieron and Adamowicz (31)
22, M	MDMB-CHMICA: 1.4 (ante-mortem serum)	Mirtazapine: 5.3 THC: 1.5 Cetirizine: pos	Found lifeless 15 minutes after smoking a brown organic powder	Asystole, declared dead due to brain hypoxia	Anoxic brain damage and pneumonia	NP	Sudden cardiac death	NP	TSS 3	Overdose	Westin et al. (48)
44, M	MDMB-CHMICA: 1 (**)	Amitriptyline: 130	History of poor mental health	NP	NP	NP	Suicidal by hanging	NP	TSS 1	Not attributable to SCRA	Seywright et al. (49)
38, M	MDMB-CHMICA: <1 (**)	Ethanol: 2.37 Acetone: < 100 BHB: 249	History of alcoholism: found dead at home	NP	NP	NP	Complications of chronic alcohol abuse and acute alcohol toxicity	NP	TSS 1	Not attributable to SCRA	
34, M	5F-AMB: 0.3 (subclavian)	–	History of ethanol abuse, found supine on the floor. An opened bag of "Apollo" brand herbal incense was found in his pocket	NP	Unremarkable medical history	NP	SC toxicity	NP	TSS 2	Related (SCRA toxicity)	Shanks and Behonick (51)
41, M	JWH-018: 0.11, AM-2201: 2.5	Phenytoin: 8800	Erratic and aggressive behavior, restrained by the police	NP	Cardiomegaly with four chamber dilation	NP	Complications of excited delirium associated with synthetic marijuana use following police arrest and restraint procedures	Delirium-induced	TSSi 2	NP	Labay et al. (33)
23, M	JWH-210: pos	Fentanyl: pos	Single motor vehicle crash, no significant injuries, restrained by the police	NP	NP	NP	Agitated delirium associated with SCRA use following police arrest and	Delirium-induced	TSS 1	NP	

(Continued)

TABLE 2 | Continued

Age, sex	SCRA(s) in peripheral blood (ng/ml)	Other substances in blood (ng/ml, ethanol g/L)	Anamnestic and Circumstantial data	Clinical data	Gross findings	Histopathology	Cause of death	Suggested mechanism	TSS	Role of SCRA(s) (authors)	Study
							restraint procedures				
25, M	AM-2201: 0.21 JWH-018: 0.65 JWH-122: pos JWH-210: pos	Ethanol: 0.15 delta-9-THC: 1.1 THC-COOH: 6.0	Unresponsive after a party, recent binge drinking and jumping from a patio. He was found "frozen" after the jump.	NP	No evidence of head, chest or abdomen injury.	NP	Complications of acute ethanol toxicity, acute SCRA toxicity, possible hypothermia	NP	TSS 2	NP	
42, M	XLR-11: pos	Methamphetamine: 730 Amphetamine: 90	Seizure-like activity after methamphetamine and K2 intake	Asystole at emergency arrival	Hemorrhagic pulmonary edema, obesity, cardiomegaly, moderate coronary artery atherosclerosis, hepatomegaly, splenomegaly, cholesterolosis, abrasions on hip and face	Macrosteatosis, chronic active hepatitis	Mixed drug intoxication	NP	TSS 1	NP	
55, M	AM-2201: 17 JWH-018: 0.47	Chlorpheniramine: < 100, Paroxetine: pos, Benzodiazepines: pos, Alprazolam: <50, Aripiprazole pos	Recent chest pain and heart palpitations in history of cardiac problems	Diagnosed type 2 diabetes	Coronary artery disease, obesity, cholelithiasis, rectal polyps, diabetes	NP	Ischemic heart disease, obesity diabetes SCRA toxicity	NP	TSS 1	NP	
34, M	XLR-11: pos UR-144: pos	Ethanol 0.03 Lidocaine pos	Collapse on public street, after intake of alcohol and drugs	NP	Presence of a needle puncture in the left antecubital fossa	NP	SCRAs and alcohol	NP	TSS U	NP	
21, M	JWH-018: pos	Ethanol: 0.013 Delta-9-THC: 7 THC-COOH: 17 Caffeine: pos Theobromine: pos Atropine: 110	Decedent found unresponsive in bedroom	NP	Pulmonary congestion, vomitus in upper airway, aspiration pneumonia, patchy alveolar hemorrhage	Pneumonitis	Mixed drug intoxication, aspiration pneumonia	NP	TSS 1	NP	
24, M	JWH-122: pos JWH-210: pos AM-2201: 0.16	Delta-9-THC: 2.7 THC-COOH: 6.4 Caffeine: pos Nicotine: pos Cotinine: pos	Learning disability, found lying prone on floor of his bedroom	NP	Bloody froth in airway, cardiomegaly	NP	SCRAs adverse effects	NP	TSS 2	NP	
38, M	UR-144: pos	Amphetamine: pos Alprazolam: pos Citalopram/ escitalopram: 130 Hydrocodone: 26 Morphine (free): pos	Found deceased lying on bed, after "partying" with others	NP	NP	NP	Mixed drug intoxication	NP	TSS U	NP	
24, M	JWH-210: pos AM-2201: 1.1	Fluoxetine: 620 Norfluoxetine: 520 Phenobarbital: pos Benzodiazepines: pos Diphenydramine: pos Methadone: pos	Found unresponsive in bed, in therapy with methadone	NP	NP	NP	Mixed drug intoxication	NP	TSS U	NP	
NP, M	XLR-11: pos	Delta-9-THC: 4.3 THC-COOH: 38 Oxycodone 420 Haloperidol 4.7 Fluoxetine 1300 Norfluoxetine 370 Trazodone 250	Death in private residence	NP	Congested lungs, froth in airway, bilateral pleural effusions, remote lesions in brain, variable discoloration of liver	NP	Mixed drug intoxication	NP	TSS 1	NP	
56, F	XLR-11: pos	–	Previously afflicted with cancer, noncompliant diabetic, shortness of	Cardiac arrest at emergency arrival	NP	NP	SCRA abuse, carcinoma of breast, diabetes	NP	TSS U	NP	

(Continued)

TABLE 2 | Continued

Age, sex	SCRA(s) in peripheral blood (ng/ml)	Other substances in blood (ng/ml, ethanol g/L)	Anamnestic and Circumstantial data	Clinical data	Gross findings	Histopathology	Cause of death	Suggested mechanism	TSS	Role of SCRA(s) (authors)	Study
			breath after smoking "Diablo Spice"								
15, M	XLR-11: pos	–	Found next to bathtub with the face submerged and vomit from nose	Anoxic brain injury	NP	NP	SC	NP	TSS U	NP	
42, F	AM-2201: 2.8 JWH-018: 0.11	Carbon monoxide: 4300 Caffeine: pos Cotinine: pos	History of alcohol and SC use. Heart disease. Vomit and diarrhea after binge-drinking and smoking "Spice," then found supine on bedroom floor	NP	Congestion in lungs, fatty liver, cardiomegaly, chronic obstructive pulmonary disease, mild coronary arteriosclerosis	NP	SCRA toxicity	NP	TSS 2	NP	
25, M	JWH-122: pos, JWH-250: 0.23 AM-2201: 7.3	Caffeine: pos Theobromine: pos Nicotine: pos Cotinine: pos	Found prone on bed	NP	Obesity, foam in external nares and pulmonary edema	NP	Adverse effects of drugs	NP	TSS 2	NP	
17, M	JWH-122: pos	THC-COOH: 5.2	Cardio-pulmonary arrest after use of "Legal Phunk"	NP	NP	NP	Sudden death associated with SCRA use	NP	TSS U	NP	
25, M	JWH-122: pos JWH-210: pos AM-2201: 0.22	–	Found unresponsive in the bathroom after vomiting	Anoxic brain injury	NP	NP	Anoxic brain injury due to SCRA toxicity	NP	TSS U	NP	
55, M	AM-2201: 0.13	Hydrocodone < 20	Found unresponsive and cold on garage floor with a large "goose egg" on the back of his head and a small amount of blood	NP	Hypertensive heart disease, blunt force injuries of the head, pulmonary emphysema, obesity, hemangioma in liver	NP	Hypertensive heart disease, blunt force injuries to the head, SCRA presence	NP	TSS 1	NP	
29, M	JWH-122: pos	–	Sweating and vomiting for several days, found dead at home	NP	Coronary artery disease, multiple sharp force injuries to foot	NP	Acute myocardial ischemia, coronary artery disease	NP	TSS 1	NP	
61, F	XLR-11: pos	Ethanol: 0,03 Metoprolol: pos Metoclopramide: trace	Found unresponsive in bed	NP	No autopsy	NP	Atherosclerotic cardiovascular disease	NP	TSS 1	NP	
52, M	JWH-018: 0.28	Chlordiazepoxide: 2000 Nordiazepam: 750 Norchlordiazepoxide: detected Demoxepam: detected Oxazepam: trace detected	Struck by two vehicles while he was crossing a road	NP	No autopsy	NP	Multiple blunt force injuries	NP		NP	
15, F	XLR-11: pos	–	Passenger in auto collision	NP	NP	NP	Multiple injuries	NP	TSS 1	NP	
30, F	XLR-11: pos	Lorazepam: 28 Cotinine: pos Lidocaine: pos	Chest pain	Pulseless ventricular fibrillation, successful resuscitation, acute ST-elevation, myocardial infarction, ventricular fibrillation	Complete occlusion of left anterior descending coronary artery with a thrombus	NP	Acute myocardial infarction due to coronary artery thrombosis	NP	TSS 1	NP	
31, F	JWH-175: 105	MDEA: 217 MDA: 111	Immunosuppression due to kidney transplant, diabetes, consumed a pot brownie, experiencing vomiting and drowsiness, bewilderment. Fell from a fire escape	NP	Subdural hematoma, pelvic fracture, liver laceration, facial and elbow fractures	NP	Multiple blunt traumatic injuries, acute mixed drug intoxication	NP	TSS 1i	NP	

(Continued)

TABLE 2 | Continued

Age, sex	SCRA(s) in peripheral blood (ng/ml)	Other substances in blood (ng/ml, ethanol g/L)	Anamnestic and Circumstantial data	Clinical data	Gross findings	Histopathology	Cause of death	Suggested mechanism	TSS	Role of SCRA(s) (authors)	Study
58, M	JWH-210: pos	–	Collapse in a parking after a wavering gait, after smoking K2	Seizure	Atherosclerotic cardiovascular disease and cardiac hypertrophy	NP	Acute myocardial infarction due to coronary artery thrombosis	NP	TSS 1	NP	
41, F	ADB-FUBINACA: 7.3 (*)	THC: 1.1 THC-COOH: 4.7	Aggressive after smoking SC known as "Mojo," physically restrained by her children, then became unresponsive.	NP	Pulmonary edema, vascular congestion, thrombotic occlusion of the lumen of the left anterior descending coronary artery by hemorrhagic disruption of coronary arterial plaque, ischemia of the anterior left ventricular myocardium	NP	Coronary arterial thrombosis in combination with SCRA use	Block of the artery's blood flow leading to dysrhythmia	TSS 1	Contribution proved by temporal relationship	Shanks et al. (51)
23, M	Mepirapim: 950 (serum)	A-EAPP 3100	Fell asleep after ingestion of the drugs in the restroom; he was found without respiratory signs and was transferred to a hospital	Cardio-pulmonary arrest and confirmed dead approximately 3.5 h after drug use	Congestion of the organs (particularly the lungs) and gastrointestinal bleeding from the stomach into the duodenum	NP	Acute circulatory failure due to SCRA intoxication	Acute circulatory failure	TSS 2	NP	Fujita et al. (35)
25, M	MDMB-CHMICA: 5.6 (ante-mortem blood), MDMB-CHMICA: < 0.2 (0.09 estimated) (post-mortem blood)	Ethanol: 1.48 (ante-mortem blood) Ethanol: 0.81 (post-mortem blood)	History of alcohol and NPSs abuse. After smoking two different SCRAs in a day and drinking a beer, he was wheezing, vomited and then lost consciousness. He was found lying on the floor, without a circulation and a pulse	On hospital admission, he was deeply unconsciousness, limp, circulatory and respiratory inefficient, without deep tendon, pharyngeal and tracheal reflexes. During hospitalization, severe redness of the skin, pathological muscle contraction of chest were observed. Purulent and watery content was expelled and diarrhea and bleeding diathesis	Respiratory, circulatory, heart, kidney and liver failures as well as hypoxic-ischemic damage of the CNS	NP	SCRA intoxication in combination with ethanol	Asystole, loss of consciousness, multiple organ failure and then cardiac arrest	TSS 2	SCRA main cause of poisoning	Adamowicz, (36)
25, M	AB-CHIMINACA: 2.8 AB-FUBINACA: 0.97 AM-2201: <0.1 5F-AMB: 0.19 5F-APINACA: 0.51 EAM-2201: <0.1 MAM-2201: <0.1 STS 135: 0.16 THJ 2201: 0.16	XLR-11 m and UR-144 m in urine	History of SCRA use with previous intoxications, insulin dependent diabetes. Found dead in his apartment	NP	Brain edema, pulmonary edema, subepicardial petechial hemorrhages, hepatic steatosis, aorta angusta, small myocardial scars	Pulmonary congestion and edema, microvesicular steatosis of the liver, Armanni-Ebstein cells in kidneys	Diabetic ketoacidosis, probably following SCRA consumption	Skipping of insulin doses due to intoxicated state or SCRAs induced hyperglicemia	TSS 1	Contributory	Hess et al. (37)
20, M	MAM-2201: 16.3, AM-1220: 140, AM-2232: 0.86	–	10 min after smoking an herbal product, violent behavior. Found dead after 1.5 h	NP	Lungs, heart and liver congestion	NP	NP	NP	Indirect	Unrated contribution	Zaitsu et al. (38)
29, F	XLR-11: 1.4	Diphenhydramine: 81	Known user of SC, found dead on the floor of the bedroom	NP	Unremarkable		SCRA intoxication	NP	TSS 2	Causative	Shanks et al. (34)
32, F	XLR-11: 0.6	–	History of drug abuse (methamphetamine, heroin and SCRAs). The day before, presented to the emergency room with chest pain, nausea, and agitation, diagnosed	NP	Pulmonary edema and congestion, acute visceral congestion and mild pulmonary anthracosis	NP	NP	NP	TSS 2	Probable contributory	

(Continued)

TABLE 2 | Continued

Age, sex	SCRA(s) in peripheral blood (ng/ml)	Other substances in blood (ng/ml, ethanol g/L)	Anamnestic and Circumstantial data	Clinical data	Gross findings	Histopathology	Cause of death	Suggested mechanism	TSS	Role of SCRA(s) (authors)	Study
			with anxiety. Later found unresponsive at a friend's house.								
15–35	PB-22: pos	–	Found at home	NP	Unremarkable	Unremarkable	Unascertained	NP	TSS U	Unknown, no competitive cause	Gerostamoulos et al. (39)
15–35	PB-22: pos	–	Found at home	NP	Unremarkable	Unremarkable	Unascertained	NP	TSS U	Unknown, no competitive cause	
15–35	PB-22: pos	–	Found at home	NP	Unremarkable	Unremarkable	Unascertained	NP	TSS U	Unknown, no competitive cause	
20s M	NNEI: 0.99, 0.64 (*)	–	Found dead on the floor of his room, a package containing dried herbal blend labeled "Fairy evolution" was found in the room, previous history of weight loss	No medical history	Marked lungs congestion	Organs and lungs congestion. Lungs: marked congestion and edema, alveolar macrophage infiltrations. Liver: slight lymphocytic infiltrations in the Glisson's sheat. Spleen: arteriolar hyalinizations and severe congestion. Brain: Corpora amylacea. Heart: arteriolar wall hypertrophy, slight interstitial fibrosis and contraction bands	Acute circulatory disturbance induced by NNEI	Hypertension and hyperactivity of cardiac function	TSS 2	SCRA poisoning	Sasaki et al. (45)
17, M	5F-PB-22: 1.1	Ethanol: 0.033, Amiodarone Caffeine (not quantified)	His friends reported that he began gasping for air and then fell to the ground, after SCRA consumption and ethanol intake	NP	Unremarkable		SCRA intoxication	Possible anaphylactic etiology characterized by sudden onset cardiac dysrhythmias or seizure	TSS 2	NP	Behonick et al. (40)
27, M	5F-PB-22: 1.3 (ante-mortem serum)	THC-COOH	History of marijuana use of several times per week.	Acute liver injury, severe coagulopathy, acute kidney injury, acute respiratory failure, hypoxemia, severe anion gap metabolic and lactic acidosis. Brief episode of cardiac arrest, and pulseless electrical activity and poor oxygenation secondary to acute respiratory distress syndrome likely the result of aspiration and pulmonary contusions following chest compressions.	NP	NP	Fulminant liver failure in the setting of THC and SC exposure	Acute hepatic failure caused by the accumulation of a toxic metabolic intermediate still unidentified.	TSS 2	NP	
18, M	5F-PB-22: 1.5 (iliac)	–	Found dead at home after a night of partying, with alcohol intake and SCRAs smoking (K2/Spice)	NP	Bilateral pulmonary vasocongestion and congestion in the abdominal organs (liver, spleen and kidneys)	NP	Sudden death, in association with synthetic cannabinoid use	NP	TSS 2	NP	
19, M	5F-PB-22: 1.5 (*)	–		NP	Bilateral pulmonary edema and congestion of viscera	Necrotizing granulomatous inflammation with histoplasma microorganisms	Acute drug intoxication using the synthetic cannabinoid 5F-PB-22	NP	TSS 2	NP	
36, M	JWH-018: 0.1 JWH-122: 0.39 AM-2201: 1.4 MAM-2201: 1.5 UR-144: 6 (estimated)	Amphetamine: 250	Sudden collapse after smoking herbal blend named "Mary Joy Annihilation"	Seizures, multiple attempts of resuscitation	Stenosing coronary sclerosis, pulmonary and cerebral edema and congestion of inner organs	NP	Acute influence of several SCRAs and amphetamine	NP	TSS 1	Contributory	Schaefer et al. (46)

(Continued)

TABLE 2 | Continued

Age, sex	SCRA(s) in peripheral blood (ng/ml)	Other substances in blood (ng/ml, ethanol g/L)	Anamnestic and Circumstantial data	Clinical data	Gross findings	Histopathology	Cause of death	Suggested mechanism	TSS	Role of SCRA(s) (authors)	Study
17, M	JWH-210: 12	–	Found dead outdoors (temperature during the night was 6–8°C), after having smoked a mixture of herbs labeled "Smoke XXX. A potent potpourri"	NP	Low BMI (16.4), lung edema	NP	Hypothermia in combination with SCRA intoxication	Hypothermia	TSS 2	Significant role	Kronstrand et al. (52)
23, M	AM-2201: 12, AM-2201 m: 2.47 JWH-018 m: 123, 50.8 (*)	–	A sibling heard 30 minutes of "stomping noises." Significant damage to a wall and glass window at the scene, a large volume of blood covered the floor, windows and walls	No known history of mental illness, seizures disorder, previous psychiatric care or past or current use of illicit drugs or over-the-counter medication (OTC)	Multiple blunt-force injuries to both hands and sharp force wounds on the head and upper extremities, including a fatal stab wound at the neck	NP	Self-inflicted fatal wound due to SC use. No evidence indicating the intent of self-harm	Psychiatric complications caused by AM-2201 use	TSS 2i	Psychiatric complications caused by SCRA	Patton et al. (41)
26, M	AM-694: 0.09 (0.00009 µg/g) AM-2201: 0.3 (0.0003 µg/g) JWH-018: 0.05 (0.00005 µg/g)	Methoxetamine: 8600 Venlafaxine 300 O-desmethylvenlafaxine: 400, THC: pos	Found on the floor in his apartment	History of drug abuse and depression (treated with venlafaxine)	Pulmonary edema	NP	Acute fatal intoxication with methoxetamine		TSS 1	Possible contributory	Wikström et al. (42)
59, M	MAM-2201: 12.4 (*)	–	Found dead on a sofa at home	NP	Unremarkable	Unremarkable	Acute intoxication	NP	TSS 3	Fatal intoxication	Saito et al. (44)
57, M	JWH-018: 199 (*)	Clonazepam: 5.5 7-aminoclonazepam: 56.6 Methadone: 887 EDDP: 115 Morphine: 122 Pregabalin: 1800 Topiramate: 4100 Naloxone: pos (prescribed)	The man had smoked herbal incense (Spice) and a white powder presumably containing JWH-018	Unresponsive to Narcan, asystole	Enlarged heart	NP	NP	NP	TSS U	NP	Shanks et al. (43)
52, M	JWH-018: 19.6 JWH-073: 68.3 (*)	–	Avid herbal incense user, found nude and unresponsive at home	NP	NP	NP	NP	NP	TSS U	NP	
29, M	JWH-018: 83.3 (*)	–	Avid SCRAs user, history of suicidal tendencies	NP	NP	NP	Suicide by exsanguination	NP	TSS 3i	NP	

Ref, reference; age, -s: decade (e.g., 30s: from 30 to 39 years old); PBC, peripheral blood concentration; m, metabolites; pos, positive; NP, not provided; TSS, Toxicological Significance score.

**Quantified in central blood.*

***Unclear if central or peripheral concentration.*

-: no other compounds detected.

TSS indexed with "i" marks an indirect mechanism.

TABLE 3 | Post-mortem concentrations in peripheral blood (PBC), central blood (CBC) and other tissues.

Cannabinoid(s)	PBC (ng/mL)	CBC (ng/ml)	PMI	Urine	Other organs concentration (ng/g)	Author, Year
EAM-2201, AB-PINACA, AB-FUBINACA	EAM-2201: 0.0566 ± 0.0042; AB-PINACA: 0.0126 ± 0.0001	EAM-2201: right heart 0.0287 ± 0.0045; EAM-2201: left heart 0.031 ± 0.0056; AB-PINACA: right heart 0.0196 ± 0.0038; AB-PINACA: left heart 0.0206 ± 0.001	2 days		EAM-2201: lung 0.35, liver 0.13; kidney 0.12; AB-PINACA: lung 0.36; liver 0.17; kidney 0.14; AB-FUBINACA: lung 0.12, liver 0.05, kidney 0.02	Yamagishi et al. (19) Minakata et al. (25)
5F-PB-22, 5F-AKB-48	.unquantified	unquantified	8 h			Langford and Bolton (20)
AB-CHMINACA	(subclavian) 8.2					Paul et al. (21)
UR-144, XLR-11, JWH-022	.UR-144: (subclavian) 12.3; XLR-11: (subclavian) 1.3; JWH-022: (subclavian) 3					Paul et al. (21)
5F-ADB, 5F-ADB-PINACA, MAB-CHMINACA	MAB-CHMINACA 6.05	MAB-CHMINACA: right heart 10.6; left heart 9.30	35-40 h	m		Hasegawa et al. (22, 29)
5F-ADB		0.19	2 days	m		Kusano et al. (23)
MDMB-CHMICA	1.7	2.1	12 h	0.01 + m	brain: 5.5; lung: 2.6; liver: 2.6; stomach content: 2.4; kidney: 3.8; psoas muscle: 1.2	Gaunitz et al. (24)
5F-ADB	(iliac) 0.12	right heart 0.24, left heart 0.45				Usui et al. (50)
5F-ADB	(iliac) 0.23	right heart 1.35				
5F-ADB	(iliac) 0.16	right heart 0.14, left heart 0.11				
5F-ADB	(iliac) 1.38	right heart 1.92				
AB-CHMINACA, 5F-AMB			2 days	AB-CHMINACA, 5F-AMB	AB-CHMINACA: brain 15.6, heart 20, lung 8.02, liver 21.2, spleen 7.55, kidneys 24.7, pancreas 38.9, adipose tissue 24.8; 5F-ADB: adipose tissue 18.7	Minakata et al. (25), Hasegawa et al. (28)
5F-ADB, MAB-CHMINACA			1 day	5F-ADB, MAB-CHMINACA		Minakata et al. (25)
UR-144	2.1					Rojek et al. (26)
UR-144	1.4					
UR-144	4					
5F-PB-22	0.37			m		Angerer et al. (27)
AB-CHMINACA	4.1			m		
5F-ADB	0.38					
AB-PINACA	26					Kubo et al. (47)
5F-AB-PINACA, 5F-AMB	5F-AMB: 8			5F-AMB: 176; 5F-AB-PINACA: 152		
Mepirapim	157			5200		
5F-AB-PINACA, 5F-AMB	5F-AMB: <1			5F-AMB: 28; 5F-AB-PINACA: 21		
AB-CHMINACA	1.5**		3 days	0.1	brain blood 2.2, lung blood 2.7, liver blood 0.3, kidney blood 1.3, intestines blood 1.0	Gieron et al. (31)
5F-AMB	(subclavian) 0.3					Shanks and Behonick (32)
JWH-018, AM-2201 JWH-210	JWH-018: 0.11; AM-2201: 2.5					Labay et al. (33)
JWH-018, AM-2201, JWH-122, JWH-210	JWH-018: 0.65; AM-2201: 0.21; JWH-122: pos; JWH-210: pos					
XLR-11	pos					
JWH-018, AM-2201	JWH-018: 0.47; AM-2201: 17					

(Continued)

TABLE 3 | Continued

Cannabinoid(s)	PBC (ng/mL)	CBC (ng/ml)	PMI	Urine	Other organs concentration (ng/g)	Author, Year
XLR-11, UR-144	pos					
JWH-018	pos					
JIWH-122, JWH-210, AM-2201	JWH-122: pos; JWH-210: pos; AM-2201: 0.16					
UR-144	pos					
JWH-210, AM-2201	JWH-210: pos; AM-220: 1.1					
XLR-11	pos					
XLR-11	pos					
XLR-11	pos					
AM-2201, JWH-018	AM-2201: 2.8; JWH-018: 0.11					
JWH-122, JWH-250, AM-2201	JWH-122: pos; JWH-250: 0.23; AM-2201: 7.3					
JWH-122	pos					
JWH-122, JWH-210, AM-2201	JWH-122: pos; JWH-210: pos; AM-2201: 0.22					
AM-2201	0.13					
JWH-122	pos					
XLR-11	pos					
XLR-11	pos					
JWH-175	105					
JWH-210	pos					
ADB-FUBINACA		inferior vena cava 7.3				Shanks et al. (51)
MDMB-CHMICA	1**					Seywright et al. (49)
MDMB-CHMICA	<1**					
Mepirapim	950 (serum, 3.5 h after use)					Fujita et al. (35)
MDMB-CHMICA	5.6 (ante-mortem), <0.2 post-mortem				brain 2.6, stomach content 0.2, bile < 0.2, kidney 0.2	Adamowicz (36)
MDMB-CHMICA	(ante-mortem serum) 1.4				spleen 0.1	Westin et al. (48)
AB-CHMINACA, AB-FUBINACA, AM-2201, 5F-AMB, 5F-APINACA, EAM-2201, JWH-018, JWH-122, MAM-2201, STS135, THJ2201, UR-144, XLR-11	AB-CHIMINACA: 2.8; AB-FUBINACA: 0.97; 5F-AMB: 0.19; 5F-APINACA: 0.51; STS 135: 0.16; THJ 2201: 0.16	AB-CHIMINACA: 1.1		m		Hess et al. (37)
MAM-2201, AM-1220, AM-2232	MAM-2201: 16.3; AM-1220: 140; AM-2232: 0.86 + m	MAM-2201: right ventricle 30.7, left ventricle 85.8; AM-1220: right ventricle 222, left ventricle 438; AM-2232: right ventricle, 1.76 left ventricle 1.95	20 h	AM-1120: traces		Zaitsu et al. (38)
XLR-11	1.4					Shanks et al. (34)
XLR-11	0.6					
PB-22						Gerostamoulos et al. (39)
PB-22						
PB-22						
5F-PB-22	1.1					Behonick et al. (40)
5F-PB-22	(ante-mortem) 1.3					
5F-PB-22	(iliac) 1.5					

(Continued)

TABLE 3 | Continued

Cannabinoid(s)	PBC (ng/mL)	CBC (ng/ml)	PMI	Urine	Other organs concentration (ng/g)	Author, Year
5F-PB-22 NNEI	0.84-0.99	superior vena cava 1.5 right atrium 0.75, left atrium 0.64	3 days		brain 0.76, heart 0.82, lung 1.06, liver 1.31, kidney 0.92, adipose tissue 42.9	Sasaki et al. (45)
JWH-210	12					Kronstrand et al. (52)
AM-2201, JWH-018		AM-2201: 12; AM-2201 m: 2.47; JWH-018 m: 123 and 50.8				Patton et al. (41)
MAM-2201		12.4	4 days		brain 4.3, liver 18.1, kidneys 11.2, adipose tissue 1535	Saito et al. (44)
JWH-122, JWH-018, JWH-210, MAM-2201, AM-2201, UR-144	JWH-018: 0.1; JWH-122: 0.39; AM-2201: 1.4; MAM-2201: 1.5; UR-144: 6 (estimated)					Schaefer et al. (46)
AM-694, AM-2201, JWH-018	AM-694: 0.09 (0.00009 µg/g), AM-2201: 0.3 (0.0003 µg/g), JWH-018: 0.05 (0.00005 µg/g)					Wikström et al. (42)
JWH-018, JWH-073		JWH-018: 199				Shanks et al. (43)
JWH-018, JWH-073		JWH-018: 19.6; JWH-073: 68.3				
JWH-018, JWH-073		JWH-018: 83.3				

PBC, peripheral blood concentration; CBC, central blood concentration; PMI, post-mortem interval; h, hours; m, metabolites; pos, positive, not quantified.

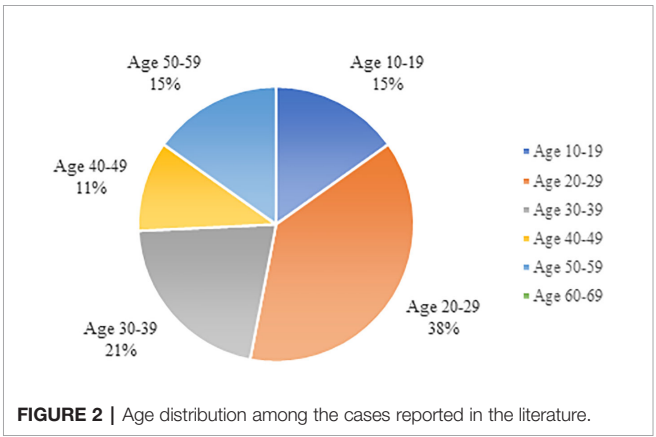

FIGURE 2 | Age distribution among the cases reported in the literature.

Histological data, as a specific result of a microscopical analysis, was clearly described only in 13 cases (18%).

Cause of death was stated in all but 4 cases (5%). Cardiac arrhythmias and cardio-circulatory acute effects were listed in 17 cases (23%) as cause of death or as underlying mechanisms in a group of mono and poly-drug intoxications, involving both teenagers and adults (20, 21, 35, 40, 48). A number of death cases were associated with excited delirium and police restraints (33), as well as fall from height, either due to drug-induced psychosis or reduced awareness with accidental falling (24, 26). Behavioral effects could also lead to suicide (26), self-inflicted self-injuries (41) and further consumption of other drugs (26, 55). Respiratory depression (27), especially in the setting of mixed intake of xenobiotics (33, 51), and asphyxia due to aspiration of gastric content in a state of coma (22, 27, 28) were also declared.

Manner of death was mostly accidental or not given and 4 cases of suicide (5%) were recognized.

Post-mortem interval (PMI) was stated in 11 cases (15%) and ranged from 8 hours to 4 days (**Table 3**).

DISCUSSION

The systematic review of the literature has resulted in an unexpectedly high number of cases of death involving SCRAs. Though, given the widespread use of the compounds, similar fatalities might be under-reported (publication bias) or under-recognized as a result of the challenges of post-mortem analyses. Indeed, the delay in developing and updating analytical methodologies affects the capability of many laboratories to detect and report cases of SCRA-related death, particularly when novel compounds which just entered the market are involved (55). Accordingly, the results here presented cannot be taken to estimate the prevalence.

Circumstantial Data

In almost the totality of cases, a possible involvement of SCRAs was suggested by either a past history of drug/alcohol abuse, by

witnesses' statements of partying or smoking shortly before collapse, or by the DSI, which revealed paraphernalia and herbal residues. Depending on the market availability, it emerged that the content of such packages varied over time (31, 36, 55). Thus, it must be kept in mind that the product names do not validly predict the ingested substances.

Although e-cigarettes and e-liquids represent an innovative and attractive way to consume SCRAs (56, 57), no vaping liquids were reported in the circumstantial data of the reviewed death cases. The link between e-cigarettes and SCRA consumption might be less familiar and known to the investigators, possibly resulting in such liquids not being systematically seized and/or analyzed. When such paraphernalia are found, an analysis of vaping liquids collected at the DSI should be strongly encouraged.

SCRAs are not detected by common immunoassays and require a target analysis, which is usually only requested by authorities and conducted when a suspicion is raised, due to analytical limitations and economic reasons (21). This factor could lead to a failure to recognize such cases and consequently to a massive underestimation of the number of death cases involving SCRAs. This underlines the importance of an appropriate awareness and of an in-depth experience in forensic toxicology during DSI and when interviewing witnesses.

Analytical Issues

The data extracted from the revision of the literature regarding toxicological analyses once again highlights the role of liquid chromatography-mass spectrometry (LC-MS/MS) for the quantification of SCRAs in biological specimens, although a singular preferred method for sample extraction is not known, given the variety of chemical differences among analytes (52). The use of standard addition methods, as recently suggested in a series of intoxications (58) is limited, possibly due to the low amount of post-mortem blood collected at the autopsy.

Only a small number of SCRAs emerged from the literature review, compared to the quantity of compounds included in the NPS category. We do not believe that this is a bias due to an attention to recent molecules, since the follow-up period ended in 2019 and more recent molecules, such as SCRAS bearing a γ-carbolinone core, were not found. This observation could be on the contrary related to difficulties in detecting SCRAs in the absence of a dedicated and updated method. The main challenge in forensic toxicology from an analytical point of view resides indeed in keeping methods updated, in order to detect novelties as soon as they are involved in death cases. Although there was a decrease in the last years, the frequent emergence of novel compounds might lead to missing relevant analytes. This was clearly demonstrated by cases where re-analysis of samples with novel and more sensitive methods allowed for identification of substances previously undetected (19, 22, 25). Very sensitive methods are needed in blood, given the low concentrations reported in the literature (52) and urine analysis can reveal a previous intake even when nothing is detected in blood (22, 23).

Once a new methodology for the analysis of biological specimens has been established, even in case reports, a so-called short validation, including selectivity, linearity, accuracy, precision, and matrix effect, is strongly recommended even if not always performed or published (59). In the case described by Langford et al., for example, the analyses were granted by a private licensed forensic laboratory, and no information was disclosed due to alleged "competition and market issues" (20). The absence of a clearly stated methodology and validation process questions the reliability of the analytical results and limits the comparability of the data. The validation could be further hampered by the lack of material for re-analysis and/or by the lack of isotopically labeled standards (27, 33). Lack of material represents a serious limitation particularly in the case of measured concentrations being far above the linear range of the calibration, even though results might be estimated by extrapolation (27, 38, 43). It has to be underlined that the vast majority of the methods for SCRAs quantification were validated in serum and not in post-mortem blood.

When evaluating the concentrations, several aspects need to be considered, including site of sampling, post-mortem interval, possible tolerance of the user, co-consumption of other drugs, potency of the compounds, chemical characteristics, and time delay between intake and death.

Some compounds, such as 5F-ADB, are known to be particularly unstable (29) and this could explain the extremely low concentrations of the highly potent SCRAs in our review (27). Rapid degradation due to pyrolysis, ante-mortem drug metabolism, as well as post-mortem redistribution and degradation (due to remaining esterase activity) were considered as further main factors for reduced concentrations and should be considered for all SCRAs, though with different weighting (19, 23, 44).

When compared to others SCRAs, mean concentrations were relatively higher for AB-CHMINACA, despite its high potency (21, 27). This could be due to the narrow time interval between drug smoking and death, approximately an hour in the case described by Paul et al. (21), or to a high tolerance of the subject implying high doses (21).

Concerning post-mortem redistribution (PMR), disparities among central and peripheral blood levels were mostly slight (19, 45) (PMI: 2 days). A 1.2 quotient of central/peripheral blood (C/P ratio) was found in a case of MDMB-CHMICA 12 h after death, and this result was interpreted as not indicative of PMR (24). Similarly, concentrations were in the same range in all tissues in a case described by Yamagishi et al. (19). On the contrary, cardiac blood levels strongly exceeded the peripheral ones in the case of Zaitsu et al. (38) for MAM-2201, AM-1220, and AM-2232 (PMI: 20 h), where left and right ventricle blood levels were 2 to 5 and 1.5 to 2 times higher than femoral blood concentrations. Quantification employed LC-QTOF, a full validation was not performed and concentrations of some analytes were far above the highest calibration point. Nevertheless, C/P ratios appear to tend to values above 1 especially in the case of short time intervals between smoking and death (in this case 1.5 h). A death shortly after smoking, with high concentrations of SCRAs in lungs being released to the surrounding vessels and tissues could explain the higher levels in the blood of the left ventricle (60), although the authors

suggested a myocardial accumulation instead (38). C/P ratios of 1.75 to 1.54 were also seen by Hasegawa et al. (29) (PMI: 2 days).

Divergences among compounds suggest that the chemical characteristics (e.g., greater or lower lipophilicity) as well as the pattern of use should be considered when hypothesizing PMR (45). Ingestion and smoking probably result in higher concentrations in stomach content and lungs, respectively. This could lead to a release into nearby vessels of the central compartment. Since femoral blood levels increase mostly due to release/redistribution from fat and muscle tissues, an inversed central/peripheral ratio would suggest a greater lipophilicity of the compound and/or chronic accumulation of SCRAs in deep compartments. However, the scarce information regarding time between last consumption and death as well as the PMI complicates the situation. Stability and matrix effects additionally limit the capability of drawing valid conclusions based on blood concentrations.

The distribution of SCRAs in tissues varied widely. Concentrations in tissues have been assessed only in a minority of cases and results may strongly depend on the employed methods of analysis, the description of which is beyond the scope of this article. Given the rarity of this type of measurement, which afford a time-demanding standard addition method (19), the available data regarding tissue distribution does not allow for general conclusions. However, they can be used to evaluate the specific case and might allow identifying potential sites of accumulation. For example, extremely high levels in the adipose tissue were seen for MAM-2201 (124 fold higher than blood concentration), leading to the suggestion of fatty tissue as a suitable target specimen for analysis (PMI: 4 days) (44). High adipose levels were also found for NNEI (45) (PMI 3 days) and might be interpreted as a result of continued substance use. According to Kusano et al. (23) adipose tissues are a suitable matrix for the detection of the parent compound, while other tissues (with higher esterase activity) could contain higher levels of metabolites.

High levels in liver and kidney tissue could be found in the case of more hydrophilic compounds (e.g., MAB-CHMINACA; PMI: 2–3 days) (29), especially when the interval between intake and death was short. In these cases, an accumulation in fatty tissue might not have occurred yet, requiring longer time (24, 29). Brain concentrations were high for MDMB-CHMICA in a case described by Gaunitz et al. (PMI: 12 h) and this allowed to confirm that the victim was under the effect of cannabinoids at the moment of death (24). High concentrations in lungs were also reported, pointing towards an intake through smoking.

In summary, blood and tissue concentrations should always be interpreted with caution, due to the multiple factors which have to be taken into account (e.g., PMR, PMI, active metabolites, stability, chemical characteristics, plasma/blood ratio, tolerance etc.) (61).

Pathology and Histopathology

The un-specificity of gross pathological findings heightens the risk of missing deaths involving SCRAs. Vomiting and aspiration of gastric content are highly suggestive for drug-induced coma or loss of consciousness in otherwise healthy and young subjects (22, 29). This was also seen in a case in which, originally, only urine was found positive for SCRAs, and further analyses demonstrated high blood concentrations of MAB-CHMINACA (22, 29). It should always be kept in mind that acute gastrointestinal bleedings could be due to several diseases and factors, such as Mallory-Weiss disease or hypothermia, and an accurate differential diagnosis remains fundamental before attributing such findings directly to SCRA consumption. For example, erosions seen in the case described by Langford and Bolton (20), could have been the result of ethanol intake, which was in his fatal ranges (3.11 g/L).

Bleedings and abundant hypostasis could raise the suspicion for a recent intake of SCRAs. In 2018, fatal and life-threatening bleedings were connected to superwarfarin-type drugs such as brodifacoum added to products allegedly containing SCRAs as reported by the Centers for Disease Control and Prevention (CDC), which released a health advisory. Long-acting anticoagulant rodenticides (LAARs) were occasionally found as adulterants in herbal blends (62). A case of death connected to anticoagulants is described in the literature (63), even though the case was not included in the review, since the past use of SCRAs emerged only from circumstantial data (thus, the paper did not fit into the inclusion criteria). It is not clear if hemolysis, abundant hypostasis, and intracutaneous or soft tissue bleedings can be caused by such adulterants or represent a hematological effect, maybe liver-mediated, of SCRAs themselves (40). As LAARs are usually not detected by urine screening analyses, highly sensitive LC-MS/MS methods are required for their detection (62).

The interpretation of cardio-vascular findings is discussed in the following subsection.

Cause and Mechanism of Death, TSS

Several preclinical studies and case reports addressed the increased cardiovascular risk related to SCRAs use, though scientific evidence is still limited (14, 64–68). This was reflected by our literature review, since abnormal findings in heart were seen and death related to acute cardiovascular arrest or collapse certified. However, it could be unclear if these deaths are actually related to SCRAs or not (69). Marijuana exerts some cardiovascular effects, acutely resulting in increased catecholamine release and, consequently, increased heart rate and vasodilation, with orthostatic hypotension (68). Cannabis is told either to exert negligible effects on blood pressure or an increase in blood pressure, and might increase the risk of myocardial infarction, particularly in predisposed subjects (68, 70–72). SCRAs, being more potent cannabinoid receptor agonists, have been linked to the occurring of myocardial infarction (64) even in the absence of coronary artery disease, and of arrhythmia-related sudden cardiac death (65–67). Sasaki et al. (45) found signs of hypertension and aging in a 20-year-old victim, coupled to myocardial suffering, and thus hypothesized a cardio-circulatory hyperactivity due to prolonged SCRA use. The diversity of potential injury mechanisms (between myocardial infarction and arrhythmia) may explain why in some cases band necrosis proved a myocardial damage (21, 45), while in others neither macroscopic nor microscopic signs were noted (20, 21, 35).

In the cases where post-mortem examination failed to identify signs of heart diseases, the attribution of cardiac death to the

SCRA was mostly based on circumstantial data, e.g., the victim reported having smoked shortly before dying and/or a sudden collapse after smoking occurred (20, 35, 40). In a similar case, the possible role of SCRAs was confirmed by a serum sample collected only 2 h after a sudden collapse with asystolia, revealing 1.4 ng/mL of MDMB-CHMICA (48).

Moreover, asystole was initially noted in a case of death where, after resuscitation, a multi-organ failure finally led to cardiac arrest (36).

Atherosclerotic disease and other cardiac abnormalities, such as cardiomegaly and dilatative cardiomyopathy, pose an additional challenge to the assessment of the role of SCRAs in death cases (50, 61). In fact, drugs can either exacerbate a pre-existing condition, or be considered an irrelevant finding (33). In a case described by Tse et al. (64) a triple-vessel coronary thrombosis was found and death was attributed to myocardial infarction with a possible contributory role of SCRAs, despite the absence of analytical confirmation. In a case involving ADB-FUBINACA, Shanks et al. (51) concluded that, due to occurrence of behavioral effects followed by a sudden death, a SCRA-induced dysrhythmia contributed to the death, notwithstanding the presence of a potentially fatal thrombolytic occlusion. Similarly, a contributory role was stated by Tse et al. (64) despite morphological findings which could have explained the death by themselves. These cases demonstrate that it can be difficult to assess the cardiac effects of SCRAs, particularly in the presence of findings potentially constituting a cause of death on their own. In such cases, a TSS of "1," which does not exclude a partial contribution, seems to be appropriate (17).

In cases of polydrug abuse, the evaluation of role cannot leave aside concentrations of xenobiotics, leading to attribution of different TSS on a case-by-case basis, e.g., TSS U with 3 g/L of ethanol, positive unquantified SCRAs and suspected arrhythmias (20) vs TSS 3 with 1.8 g/L ethanol, 1.5 ng/mL AB-CHMINACA and acute cardiorespiratory depression (50).

Coma/somnolence can lead to death directly, through vomiting/aspiration or indirectly due to environmental exposure and hypothermia (54). In a case presented by Kronstrand et al. (52), death occurred due to "hypothermia and SCRA use," despite the absence of typical hypothermia-related signs such as freeze-erythema and Wischnewsky spots (52). Hypothermia after the use of SCRAs was seen in experimental studies on animals (e.g., male rats and monkeys) (73, 74) and has been partially related to the effects of cannabinoids on dopamine receptors (75), but has not been confirmed in humans yet. However, in a case described by Adamowicz (36) a cadaveric temperature of 35.1°C was measured, despite the victim was at home and the measurement took place only 30 minutes after the sudden collapse. This finding would be in line with the animal experimental data regarding the effect of SCRAs on body temperature and highlights the need to evaluate body and ambient temperatures in cases of death possibly related to such compounds. An "intoxicated-state" was also considered as the underlying mechanism of a death due to ketoacidosis, even though an AB-CHMINACA-induced hyperglycemia was also possible (37).

A behavioral contribution of SCRAs to the death appears to be an additional source of concern. Anxiety and psychosis might be also explained by the affinity of SCRAs to dopaminergic (D2), serotoninergic (5-HT2A) or glutamatergic (NMDA) receptors (76, 77). In a case described by Labay et al. (33), the victim fell from a high building after feeling sick and vomiting several times and was found intoxicated with MDEA, MDA, and JWH-175. While psychiatric consequences of SCRAs intake are clear in the absence of other drugs (41), the evaluation of role in polydrug consumption is puzzling, as in the case of low levels of both SCRAs and phenytoin, which can induce psychosis (78). Data on toxic/fatal levels might lack for NPS (e.g., for co-consumption of pentedrone resulting in behavioral abnormalities) (26) and even therapeutic or negligible levels of common drugs of abuse could assume relevance in combination with SCRAs. The influence of SCRAs on non-cannabinoid receptors and on serotonin, dopamine, catecholamine levels further complicate potential interpretations. In such cases of polydrug abuse, it is possible that the death would not have occurred without SCRA consumption, although no direct causality can be established. A TSS of "1" ("i" indicating the indirect role) is suggested due to the presence of multiple drugs with unknown contributory role, despite behavioral toxicity being an important risk factor for fatal outcome (33).

On the other hand, in the first case reported by Rojek et al. (26), the victim jumped from a building after a reported "loss of control" and no other drug was detected. Thus, notwithstanding the behavioral toxicity and the indirect mechanism, a contribution to death is likely (TSS of "3" was assigned).

Finally, cases of acute liver and/or kidney failure have been described (40, 55).

In general, if only toxicological results are listed in the absence of macroscopical and microscopical data, uncertainties regarding the role of the substance increase, as in the case reported by Kusano et al. (23). However, the mechanism of death could remain unclear, despite having a more complete data set (40) and the agreement between independent reviewers judging the very same pieces of information could be weak (e.g., unanimous agreement in 2 cases out of 25 submitted to multiple evaluations) (33, 40). Thus, a multidisciplinary evaluation should be recommended for each case, in order to possibly limit such uncertainties.

Most of the publications identified a possible contributory role of SCRAs, even in the absence of findings clearly pointing towards a drug-related death (32, 34, 39, 45, 48). In the present review, a TSS of 3 was assigned when no competitive cause was seen, and the hypothesized mechanism of death was in line with the most frequently reported SCRA toxicities. Affinity and activity of new compounds are often unknown, and unexpectedly severe or idiosyncratic effects may occur (19). Given the uncertainty regarding toxic levels and toxic effects, even when the mechanism of death remains unclear and/or other substances might have played role, the possibility of a

contribution of SCRAs should not be ignored, and a TSS of "2" justified.

The likelihood of a high significance score is greater when multiple compounds with potentially synergic effects are detected, despite low concentrations of each single compound (19).

On the contrary, even though SCRAs could exacerbate an intoxication due to alcohol or other drugs, in cases with relatively very low SCRA concentrations or with concentrations of the competitive drug above the toxic threshold, a TSS of "1" is suggested. This does not necessarily mean that the SCRA has not exerted any negative effect, and the stability of the analyte of interest should further be considered as a cause of low concentrations.

TSS was rated "U" in cases with lack of sufficient data, as for example in the case described by Langford and Bolton (20), where high alcohol concentrations were retrieved, and no quantification of SCRAs was possible, or in the case of Minakata et al. (25) and Kusano et al. (23), where the effects of the other substance detected was difficult to assess.

LIMITATIONS

There are several limitations in this study. First of all, despite the extensive research involving multiple databases, the process of inferring scientific evidence is strongly limited by the possibility of under-reporting of similar cases and by the necessity of establishing a temporal limit for the review. Thus, the information presented have to be regarded as incomplete. Secondly, no weighting of selected articles regarding their quality was undertaken. A third significant limitation resides in establishing the TSS (16) of the selected cases, since the TSS is so far a non-validated scale. However, given the lack of criteria for establishing the role of substance(s) in death cases, the TSS appeared to be a flexible and easy-to-use tool to assign a contributory weight to SCRAs, and thus to evaluate and compare different cases. In order to avoid misinterpretations and to appreciate the point of view of the authors of the manuscripts, in each death case the role of the substance was also supplied in their own words. Finally, only death cases in which at least one SCRA was analytically confirmed, and in which an autopsy was presumably performed, were included. The authors are aware that this could have resulted in a partial loss of information, but on the other hand our aim was to possibly achieve a higher level of evidence.

CONCLUSIONS

Several mechanisms could lead to death after SCRAs consumption, and behavioral risks as well as cardiovascular effects or central nervous system depression appear to play important roles. Given the limited pharmacodynamic and pharmacokinetic data and the overlap between fatal and non-fatal concentrations, typical toxic ranges for SCRAs have not been identified so far. The results of toxicological analyses should be interpreted with caution, considering the many confounding and influencing factors, particularly regarding the reliability of LC-MS/MS methods validated insufficiently or validated only in serum. Furthermore, pattern of consumption (e.g., occasional v. chronic) and tolerance of the subject should be estimated or evaluated on a case by case basis.

A complete and accurate post-mortem examination is a fundamental part in the evaluation of death cases involving SCRAs, since a comprehensive and multi-disciplinary evaluation of clinical, circumstantial, toxicological, and autoptic data is the only possibility to assess the toxicological significance of a substance and to tentatively identify a plausible mechanism of death, which could remain unclear despite an in-depth analysis of all data available.

AUTHOR CONTRIBUTIONS

All authors materially participated in the article preparation and have approved the final article.

FUNDING

Role of funding source: The study was supported by Presidency of the Ministers Council, Department of Antidrug Policy.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 26 May 2020
doi: 10.3389/fpsyt.2020.00460

Novel Psychoactive Substances in Custodial Settings: A Mixed Method Investigation on the Experiences of People in Prison and Professionals Working With Them

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OPEN ACCESS

Edited by:
Simona Pichini,
Istituto Superiore di Sanità (ISS), Italy

Reviewed by:
Andres Roman-Urrestarazu,
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Specialty section:
This article was submitted to
Addictive Disorders,
a section of the journal
Frontiers in Psychiatry

Received: 18 March 2020
Accepted: 06 May 2020
Published: 26 May 2020

Citation:
Corazza O, Coloccini S, Marrinan S, Vigar M, Watkins C, Zene C, Negri A, Aresti A, Darke S, Rinaldi R, Metastasio A and Bersani G (2020) Novel Psychoactive Substances in Custodial Settings: A Mixed Method Investigation on the Experiences of People in Prison and Professionals Working With Them. Front. Psychiatry 11:460. doi: 10.3389/fpsyt.2020.00460

Introduction: Novel Psychoactive Substances (NPS), especially Synthetic Cannabinoid Receptor Agonists (SCRAs), pose a substantial challenge to health and the security of the prison environment. This study analyses the phenomenon from the perspective of people in prison and that of professionals working with them.

Methods: A phenomenological qualitative approach was used to analyze self-reported experiences with 'Spice' (NPS) among users in prison. A semi-structured questionnaire was also disseminated among professionals working in these settings to better understand (a) the impact of NPS on their work; (b) perceived issues on safety in their working environment; (c) approaches used to tackle the phenomenon and best practices.

Results: Psychotic events resulting from the collected Spice accounts (5) were marked by hallucinations, depression, self-harm, and suicidal ideations. Other emerging elements included fear, paranoia, inability to be with others, mistrust, breakdown and other risky behaviors. Overall, 186 responses from prison staff were collected across the country. 67% claimed NPS to have had a deep impact on their work as they commonly witnessed espisodes involving outbursts of anger, slurred speech, hallucinations, psychosis, and significant mental deterioration among those in prison. Some 91% have witnessed aggression at least once, with 53% experiencing direct harm. Suggested interventions included enhanced training and education (84%), improved detection (92%) and treatment and support services (93%).

Conclusions: Findings highlight the urgent need for joint multi-disciplinary efforts to tackle the exponential escalation of NPS in prisons as well as to facilitate the recovery and

societal reintegration of those affected. Phenomenology can be recommended as a valuable methods to study drug induced experiences.

Keywords: novel psychoactive substances, spice drugs, prison system, violence, Synthetic Cannabinoid Receptor Agonists (SCRAs)

INTRODUCTION

Novel Psychoactive Substances (NPS) pose 'the most serious threat to the safety and security of the prison system' (1). Emerging data from British prisons are of great concern with an estimate range between 33 and 90% of people in prison regularly using these substances, especially Synthetic Cannabinoid Receptor Agonists (SCRAs) (1, 2). NPS are typically analogs of other psychoactive substances, created in makeshift laboratories without any safety protocols or testing in humans, thus posing a severe health challenge for this vulnerable population and professionals working with them. Although prisons have comprehensive security systems in place to detect contraband items, NPS more easily evade standard detection methods, as they are often colorless, odorless and active in very small quantities. In addition to the usual methods of import such as hiding in bodily orifices, SCRAs have also been sprayed onto clothing, food items, letters and even children's drawings sent into prisons. As the use of these drugs in prisons has reached alarming levels, so has the number of cases of self-harm, suicide attempts, aggressions and assaults, and ambulance call-outs (2–4). According to the most recent review of the Ministry of Justice, there were 308 deaths in custody in the year to September 2019. Incidents of self-harm have risen by 22% from the previous year and the number of assaults increased by 5% up to June 2019, with a rate of 451 episodes of violence per 1,000 prisoners (5). The use of NPS in prisons has also been associated with organized crime, bullying, debt and suicides (1, 6). Associated violence can often extend to the wider community; the family and friends of those who are experiencing addiction or accumulating debts in prison may also be pressured to provide funds or carry NPS into prison.

Overall, there are currently 118 prisons in England, each with a dedicated healthcare team for prisoners. In 2018–19, 53,193 adults received treatment in such secure settings (99% of which was in the adult prison estate) (7). Of these, 11% presented to treatment services for NPS related issues, either on their own or alongside other substances, up from 6% in 2015–16. Health risks associated with NPS use include convulsions, paralysis, tachycardia, psychosis, anxiety, depression, self-harm and suicide. This is due to their higher potency and affinity for the cannabinoid receptors CB1 and CB2 compared to THC. In particular, the regular use of SCRAs has been associated with aggressive behaviors and other psychotic symptoms, especially among those already affected by addiction or mental illness (8). More in detail, NPS use, and particularly SCRAs have been linked with the diagnoses of bipolar disorder, personality disorders and the onset of schizophrenia and related disorders (9). Acute and long term consequences of NPS consumption may have a number of important clinical implications, especially for young users (10, 11). Incidents involving NPS also carry a higher risk of hospitalization (88.9% of admission by drug with an emergency medical treating was using SCRAs) compared with traditional drugs (12). Furthermore, NPS use has been associated with a high prevalence of fatalities (13). These figures may also be under-estimated as NPS related fatal intoxications may be under-investigated due to difficult and expensive methods of post-mortem detection. Treatment is also challenging because of the potential interaction between NPS and prescription medications common in prison settings, such as benzodiazepines and other psychotropic medications (9). Because of the novelty of the phenomenon, training for health and other professionals working in such settings has not kept pace with evolving trends in drug use, resulting in a lack of confidence in some staff responding to NPS related emergencies (14, 15). This study aims evaluate the experiences of both people in prisons and professionals working with them in order to inform the development of new targeted responses. The study was approved by the University of Hertfordshire Ethics Committee (LMS/SF/UH/03868). Additional ethics approval was gained by the National Research Committee (NRC) for the secondary analysis of the accounts collected from Her Majesty's Prison Service (HMP) & Young Offenders' Institution *Parc*.

MATERIALS AND METHODS

Accounts from people in prison affected by NPS use were collected at Her Majesty's Prison Service (HMP) & Young Offenders' Institution *Parc*, which is Category B Training Prison in South Wales, operated by G4S Custodial and Detention Services. A selected number of individuals, known to the substance misuse team as users of SCRA, also known as 'Spice', were approached by the Drug Strategy Manager and informed about the study. Those who agreed to participate prepared a written account about their experiences of using 'Spice'. This was written either on their own, or with the support of staff. The collected accounts have sometimes been edited for clarity, but strongly reflect the submissions of each of the individuals. These were analyzed according to a qualitative phenomenological approach focusing on the assessment of subjective experiences, through personal narratives, to trans-personal constructs (16). Phenomenology is an increasingly valued research methods in the context of clinical research for bringing forth the typical feature(s) of personal experiences. In our study, particular attention was given to the approach proposed by Paul Ricoeur, which emphasizes the conceptualization of the participant as an 'agent', a self among other selves, in an effort to experience freedom (17). Written

informed consent was obtained for the publication of any potentially identifiable data included in this article.

In addition, a semi-structured questionnaire was designed and disseminated among professionals working in prisons and acute mental health settings *via* a previously established network of collaborators. The tool consisted of 19 questions on four different themes: (a) basic demographic information; (b) knowledge of NPS and impact on their work; (c) issues of perceived safety in the working environment; (d) approaches used to tackle the phenomenon and best practices. The questionnaire was created on Qualtrics, a cloud-based software developing online surveys that provides data analysis, sample selection, bias elimination, and data representation tools. Responses to the questionnaire were collected both in person and online and anonymized. Face-to-face interviews with a selected number of staff also took place. Research material was securely stored and shared only between members of the research team. A group of ex-offenders, currently undertaking a degree at the University of Westminster, was consulted at different stages in order to facilitate the development of the study material. All participants gave individual informed consent to participate in the study and further authorization was obtained from the heads of prisons where the questionnaire was disseminated.

DATA ANALYSIS AND RESULTS ASSESSMENT

Analysis of 'Lived Experiences' With NPS Among People in Prison

Five case studies were collected and analyzed according to a phenomological approach.

Case 1:

> *"I first used Spice in 2013 in prison, my mate gave it to me. I didn't know what it was but it blew my mind. The vents at the back of the cell were moving, it looked like a mouth so I thought they were talking to me. I moved to another prison and was just using it all the time. I got into debt, I was stressed out all the time and it didn't help that I was in a cell with my Uncle who was pressuring me to get more and more. I ended up having a breakdown because of it all, and tried to throw myself off the 3s. Just before my breakdown I had a really bad trip. I saw a hole in the floor of my cell, and when I looked down into it I was pulled down and I am convinced I went to hell. There was a wrinkly dog that had a big studded collar on. I was shitting myself, really scared, and then my Uncle who has passed away since, pulled me back out and told me it wasn't my time. Spice is great when you're on it, when I'm off it's the worst I've ever been. After I heard about my friend dying from it, it really shook me up. I realised I was 33 and had nothing to show for my life. I moved out of the cell with my Uncle and have been determined to stay away from it. I want more for myself."* JP. 32 years old, White British, Level 1 Literacy, Entry 3 Numeracy

Analysis: JP shows a very high awareness of his experience with Spice, recalling vivid memories of the first time and most of all the 'bad trip', which seems to mark a turning point. He presents with a complex multimodality anomalies of perceptions where illusions and hallucinations (visual, audiotry and tactile) were mixing. The abnormalities of perception are mood congruent with his despair. The subject is dragged to a 'dark hole' that he identified with hell. Of particular relevance is also the second part of the experience, where the others in the story—the mate and the uncle intervened and saved him. This element is very important because although the contest of the perceptual abnormalities was the same, his experience changed with the introduction of the salvific role of the recently deceased uncle, who saved him from hell and therefore from the 'bad trip'. When experiencing hell only others around us can offer a glimpse of hope in order to recover our true self. Despite all good intentions and determination, JP knows he needs a hand to overcome the cycle of stress, debt and breakdown which will inevitably take him back to hell. But his cry for help—wanting more for himself—cannot be silenced.

Case 2:

> *"I've never felt so afraid ever in my life of dying. I think of loads of reasons why I shouldn't take spice but it's that massive cloud of rush that comes all over my whole body that keeps me saying 'yes I want it'. It started 7 years ago. I'd been released from prison homeless and went into town to see who was about, and saw a group of boys making a spliff. I just thought it was skunk so didn't ask any questions and just took 6 long drags and held it in. It was Christmas time so there were people everywhere and the paranoia kicked in. I was walking through crowds of people and everything was zooming in and out, the people and the buildings, and it was just like being in a weird bubble with everything echoing around me. That should have been the end. Spice is the only drug where I hear a voice saying 'you're going to die, you're going to die'. That alone should be enough for me to stop smoking it but it's not. But at the same time I don't want to die. I certainly shouldn't enjoy spice if that voice keeps telling me I'm going to die, and I honestly don't want to leave prison in a body bag. But I can't stop. Spice scares the shit out of me but when I get the urge to score some more, it's not that I forget about the scary signs, I just make the effort to forget them. That scares me even more."* GC. 35 years old, White British, Entry 1 literacy, entry 2 numeracy.

Analysis: The fear of death, in itself traumatic, is accentuated when experienced, as in GC's case, under the influence of Spice. The awareness of finitude and fallibility is pushed by GC to its limit when recognising that he is able to push away the 'scary signs'—the voice inside him—so as to satisfy 'the urge'. This ability to forget, and in a way to trick himself, is indeed even

more scary, as GC honestly admits: he is still struggling with this contradiction, despite the many reasons he can list to stop taking Spice. The phenomenological analysis also shows a significant change in the quality of the experience expressed by the evolution of the psychopathology. The individual's symptoms starts, when using spice, with complex multimodal illusions (mainly visual) and evolve to audiotry hallucinations with a voice making terrifying remarks. Under the influence of the drugs, therefore, the patient has an experience similar to the one that individuals with schizophrenia have.

Case 3:

> *"I started smoking Spice in 2016 in prison. Subby (Subutex, i.e. Buprenorphine) was my thing at the time, when I couldn't get that I was told I was told smoking Spice would help with my withdrawals, so I started smoking small amounts of it but it wasn't doing what my friend told me it would, so I started smoking much more. Bigger the pipe the better as it's called in here. When Code Blueing (needing emergency health attention in prison), the only way I can describe it's like going into an epileptic fit where you blank out and come around feeling really stoned, so being high like you would when you smoke weed, but if you're not used to Spice you go into instant paranoia, you feel like all the walls are caving in on you, and when you lie on the bed it feels like you're sinking into it. Smoking Spice took me to a really dark place, got to a point where I was so paranoid and thought everyone was out for me. I didn't even feel safe walking to get my dinner and I lost 3 and a half stone in weight as I thought that people were putting poison in my food. The more I smoked the more in debt I got, and didn't really care what would happen to me. It's so addictive that getting more was all I cared about. I was even letting people give me happy slaps or punches to the face so I could get my fix. It was mentally draining, I was getting no sleep whatsoever, getting really bad cramps in my stomach. Seeing people smoke Spice goes through me as I know what it did to me. I fell out with my family as I was constantly asking for money, making up lies like saying my trainers had been robbed from the cell but really I'd sold them to get a bit of Spice. I got to the point where I'd sold everything in my cell, even my last shower gel and last toothpaste, I even sold my TV to someone on basic (basic regime on the prison IEP scheme), so that I could get high for the next hour and spent the rest of the day just looking at the walls. I've even drunk washing liquid from the washing machine to get Spice from someone. It ruined my life, I stopped speaking with my family for years because I chose to smoke Spice, it takes you to a really dark place where you have no respect for anyone and you don't give a shit about yourself. At one point, I didn't shower for three and a half months. When I last got out of jail I carried on smoking Spice and smoked a strong strand of Mamba with two friends, we all ended up in hospital, one of my mates died and the other ones got to wear a colostomy bag for the rest of his life. Luckily enough nothing bad happened to me but it made me take a long look in the mirror and I thought I need to change now or end up in a body bag and so since that happened I can't even stand the smell of Spice. If anyone was thinking about starting to smoke Spice, I'd tell them to stay away from it, it ruined my life. I'm doing much better now, all my family are speaking to me, I've got my health back. So that's my story of the Devil's drug, Spice."* RB. White British, 29 Years old, Entry Level 3 education literacy and numeracy.

Analysis: RB is the youngest of this group, but also the one who has gone all the way 'to a really dark place' (and 'mentally draining'), and back: no respect for anyone or himself, falling out with his family and loved ones, on a clear path towards self-loathing and self-destruction and carrying on smoking Spice when out of jail. Only when a mate died and another one remained permanently injured he managed to 'take a long look in the mirror'. Redemption is seen here as a process of self-reflexivity that awakens the inner-self to return to the original conditions of selfhood. The first sign of this is re-establishing ties with his family, being recognized and accepted again by them and, in the end, also being 'forgiven', as full part of the course of redemption.

Case 4:

> *"I started smoking Spice in 2015 when I was in Cardiff Prison. I was introduced to it by my mate, I had no idea what it was before I took it. It numbed me and made me feel nice, but i know you can die from it which isn't good. I was stressed and bored and I used to numb that, but I was getting stomach cramps because of it. I didn't really have anybody around me looking out for me, my Dad died when I was young and I lost my girlfriend to an overdose, so there's been a lot of trauma in my life and Spice blocks all that out. When I moved into a cell with somebody who was using all the time it dragged me down, but since moving in with my new padmate, I feel more encouraged to stay away from it, I'm back in the gym, I've got myself a job on the wing and I'm doing much better. My advice to anyone thinking of using Spice is don't start it, because you can't stop."* LD. White British, 35 Years old, Entry Level 3 literacy and numeracy in education.

Analysis: LD's story helps us to place his narrative in a wider scenario, beyond prison and prior to the encounter with drugs or Spice in particular. This is the case also in other accounts, but here the 'trauma' takes the shape of specific faces of loved ones—his father and his girlfriend—who are dearly missed. But blocking trauma with Spice is an illusion, and while some might influence negatively, others (even prison mates) encourage him to take a different path.

Case 5:

"I used around 2012 or 2013, I was out in the car and gave a mate a lift. I was only taking him about half a mile. When my mate got in the car he was rolling up a spliff, he told me it was Spice and I'd heard a bit about it but never had it. I had a couple of puffs whilst we were driving and i got carried in the conversation and kept smoking without realising. Once he'd got out of the car I realised I couldn't drive anymore, it was a really rapid onset, not as fast as when you're pinnin' but really quick. I dunno how much he'd put in there, but it affected me really badly. I started off feeling really relaxed, which is why I guess they link it to cannabis, but it intensifies really quickly. I had no control of my limbs, hands, arms, legs, couldn't move them if i wanted to. luckily I was on my own so I didn't feel too paranoid. I definitely would have panicked with people around me. After a while, I thought I was OK, so tried to drive, but quickly realised I was doing it really badly. I got stopped by the police a short while down the road, managed to convince them I was just really tired and after breathalysing me they let me go. Never used it since, and I'd never use it again. I'm a regular drug user, including heroin, but Spice really is the bottom of the barrel." MD. 56 years old. Level 2 literacy and numeracy. Mixed origin, British.

Analysis: One single experience by MD was enough to convince him to stay away from Spice. As an older and 'regular drug user' he was fully aware that Spice was 'the bottom of the barrel', given the paralysing effect of this drug. This account makes reference to the lesser detectability of SCRAs, which has contributed to their popularity.

Survey Results Among Professionals Working in Prison

Study Sample

Overall 186 individuals (92 females; 93 males), aged 25–65, took part in the study. Participants belonged to different occupational sectors, including prison and probation services (70%), clinical and health care (15%), education (3%), social work/care (2%) and to a lesser extent to business administration, Government facilities, Public Health, Human Rights, and Police (**Table 1**). The majority of participants (76%) were working in a prison setting, 7% reported working in such environments predominantly, 8% sometimes, 8%'rarely or never worked in prisons; two participants had previously worked in prisons but no longer did so. 45% of the sample had worked in prisons for more than 10 years; 15% for 5–10 years, 15% for 2–5 years, 10% for 1–2 years; 7% of participants had 6–12 months experience. 8% had been working there for less than 6 months.

TABLE 1 | Q. What is your occupational sector?

	Occupational sector	%
1	Clinical and Health care	15
2	Education	3.2
3	Social work and care	1.6
4	Prison and probation services	70.4%
5	Academia	0.5%
6	Other	9.1%

Impact of NPS on Staff Working Environment

The majority of respondents considered their work "largely affected" by NPS (81%). All participants agreed that NPS have a negative impact on their working environment. Operational instability, bullying, potential staff corruption, and time constraints were also mentioned as contributing factors during the interviews. Limited access to training opportunities was another influencing factor. A participant stated: "The amount of emergency health care codes makes the planned work too much difficult" (**Table 2**).

Violence and Aggression

For the majority of the sample, outburst of anger, aggression and violence were of great concern. While 9% stated to have never seen any aggression, others witnessed it at least once or twice (9%), less than 10 times (18%), more than 10 times (28%) and more than 50 times (36%) (**Table 3**).

Overwhelmingly, respondents thought that NPS were the main cause for such episodes. While 47% have never experienced direct harm, such as an assault, 13% declare to have been a victim of it (or to know a colleague with such a history behind) on one occasion, 21% between two and five times, 19% more than five times (**Table 4**).

Substances

Survey participants reported witnessing, or being otherwise aware of, use of a number of other substances in the prisons in which they work (**Figure 1**). These included cannabis (14%), heroin (7%), alcohol (14%) and also drug replacement medication or other prescription drugs, such as methadone, gabapentin, pregabalin, «Oids» (steroids), buprenorphine, and painkillers (14%).

During the interviews, staff also mentioned the deliberate consumption of products with the intention of inducing an intoxicated state. These included rat poison, alloy wheel cleaner, and bug killer repellant among others. It is not clear whether these are examples of 'urban myths' or hear-say, or first-hand observations. The likelihood of a person in prison being able to access some of these items is remote. "I work on a substance misuse induction wing and a recovery wing as an SMS worker so see and deal with a lot of hardened substance users. There is a regular supply of drugs with "Throw overs" and new receptions although there is now a body scanner in place so the new reception supply has reduced. The prisoners will use any form of NPS largely without questioning. Valium is very popular at the moment and buprenorphine snorting and concealment is popular although the prison is very restrictive with its issue. There is a lot of pressure on prisoners who are in receipt of ADHD meds to conceal them and pass them on. Tablets like Pregablin are regularly chased by prisoners seeking additional drugs or to conceal and sell on".

TABLE 2 | Impact of NPS on staff working environment.

Issue	Description
Aggression/ Violence	*« It is difficult to get people to listen, to respond. They may be agitated, unreasonable, aggressive. Their priorities are not around progress and growth »* *« Affects vary from adverse health effects, to violence related to debt (this includes being assaulted through not being able to pay off debt, being violent to others to pay off debt, or violent as a side effect to use). Self-harm also linked with inability to manage use of NPS. Use of NPS has impacted on men attending work or education, as well as gym sessions and programs. »* *« We have noticed Increases risk of self-harm and suicide attempts, increases risk of violence towards others. »* *« …Increased levels of violence, bullying others to use to test drug levels, medical issues, falling over, sliding down walls, no recollection of their behaviors. »*
Time constraints	***« The impact it has on users renders them unable to keep appointments and/or progress. It can also kill them. The spice use within the wings and the prison regime frequently leads to lock downs due to incidents, so again it's impossible to keep appointments scheduled and many, many meetings have been cancelled. »*** *«It has impacted my ability to interview offenders for report and assessments. I have had to terminate these appointments and reschedule. NPS also affects the work that we are trying to do to rehabilitate offenders. It negates all the effects and support that is provided. »* *« We all noticed a failure to attend for interview for sentence planning. They are unable to work and get into debt, under threat … and many of them are coerced to do things. As a result, this is disruptive for the prison regime. »* *« It breaks up the normal day and the Prisoners who would have a full educational session only receive limited time with the Teacher/ Instructor. »*
Safety	***« NPS lead individuals in a zombie like state requiring further staff intervention with regards to their safety. This in turn destabilizes the regime and causes problems for non-NPS inmates. NPS can also lead to aggressions towards staff and others and it is largely responsible for most of debts and bullying in prison. »*** *« It has made the pressure on support services increase. It has increased the level of debt. It has led to more severe and sometimes fatal health issues. It demotivates prisoners. It has made the prison environment less safe. »*
Health	*« There is a lack of concentration, a lack of motivation to do anything other than use NPS. »* ***«NPS have an impact on many things.*** ***On their engagement,*** ***on their physical health,*** ***on their mental health.*** ***A cycle of events that lead them to continue their use.*** ***They can't function*** ***They can't work »*** *« Prisoners heavily using NPS can 'fall apart'. They have no interest in personal hygiene, they often sell their food and of course lose weight rapidly»* *« Working with individuals with extreme NPS addictions is difficult even when they are not under the influence at the time, they are often forgetful and experience extreme mental health issues. NPS makes drug users experience a variety of health problems that also interfere with their engagement, to attend health care appointments or because they are generally unwell.* *I have encountered individuals who have had strokes due to NPS use and this has damaged their ability to engage with rehabilitation in prison due to a lack of specialized care for these types of long term conditions. »* *« Some prisoners have had to be transferred to psychiatric inpatient units. Instances whereby some have completed stopped eating due to paranoia that the food is poisoned, others have completely refused all medication, either to help manage their mental state as a result of NPS use or medication to manage their pre-existing health conditions, such as diabetics or epileptics. »*

TABLE 3 | Q. In the past year, have you seen any episodes of violence or aggression within the prison setting?

#	Answer	%
1	More than 50 times	36%
2	More than 10 times	28%
3	Less than 10 times	18%
4	Once or twice	9%
5	No never	9%

TABLE 4 | Q. Have you or a colleague (in your presence) ever experienced direct harm, such as an assault, which you believe to be related to the use of NPS?

#	Answer	%
1	Yes on multiple occasions (more than five times)	19%
2	Yes, between two and five times	21%
3	Yes on one occasion	13%
4	No, never	47%

Consumption of these drugs was related by the participants to a considerable increase in the number of ambulance callouts and hospitalizations that they witnessed (more than 10 times for 52% of the sample; see **Figure 2**).

Safety

Although the large majority of the sample felt 'reasonably' (51%) or 'completely safe' (13%), 25% felt 'unsafe at times' and 5% 'often unsafe'. Some participants (6%) were not aware of the level of risks they were facing (**Table 5**).

All the participants agreed that NPS has a negative impact on their safety with 37% of them considering the risk 'extremely high', 38% 'high' and 19% 'substantial'. Only 6% found a marginal impact on their safety (**Table 6**).

Health-Related Harms

As shown in **Figure 2**, the most observed health-related harms were 'short-term mental health issues', such as hallucinations, psychosis, slurred speech, and a significant mental deterioration. 45% of the sample dealt with such issues more than 10 times in their life, 21% between five and 10 times, 21% less than 10 times and 4% only once; while 9% none. Half of the interviewees reported to have witnessed more than 10 hospitalizations or ambulance call-outs due to NPS. A clinician observed: "NPS use contributes to the worsening of existing psychosis and to the presentation of new psychotic episodes".

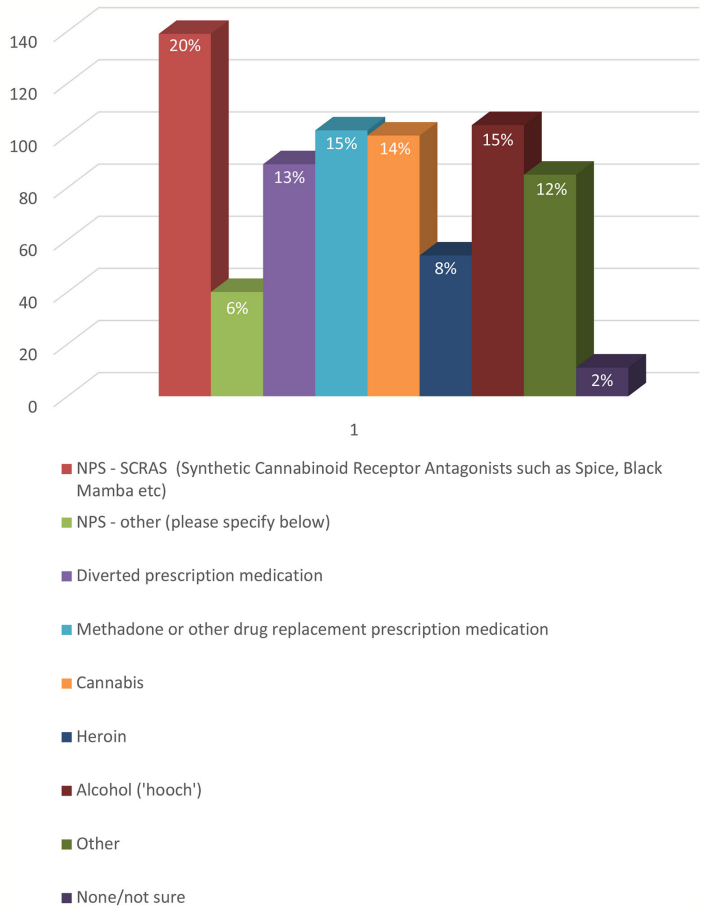

FIGURE 1 | Q. Are you aware of one or more prisoners using one of the following substances?

Less common were 'short-term effects on physical health', such as seizures or tachycardia, and long-term mental health issues. It is interesting to notice that 29% of interviewees have 'never observed long-term physical health problems' among inmates using NPS.

The main acute clinical consequences which were related to the consumption of NPS were represented by both 'severe mental disturbances', such as consciousness alterations or psychotic symptoms onset or exacerbations, and 'disrupting behavioral abnormalities', such as mostly dyscontrol, aggression and violence. These symptoms are not unique to any diagnosis, and often residents displaying these behaviors do not neatly satisfy the diagnostic criteria for any condition (such symptoms may be common in several mental disorders, or acute states). Such evidence confirms that a wide range of potential aspecific and mixed psychotic, affective and behavioral responses are reported as a result of NPS consumption. A general lack of self-care and personal hygiene was also perceived, as a healthcare professional stated: "*Prisoners heavily using NPS can 'fall apart'. They have no interest in personal hygiene, they often sell their food and of course lose weight rapidly*".

As a participant stated: "Patients are referred into mental health clinical settings following the use of NPS in prison. Diagnosis and management of presentation is increasingly difficult along with associated risks of violence and aggression for prolonged periods. Current clinical solutions are ineffective for longer periods until the substances begin to clear from the patient which can take several weeks. Until this time, medications have little clinical effect and there are no adequate means of containing disturbed behavior, even within Psychiatric Intensive Care Unit".

Concerns for their own health also emerged, including risks related to the secondary exposure to potentially highly toxic substances, as NPS are introduced to prisons *via* drones, letters and other hidden channels, such as food deliveries and children's drawings.

Approaches Used to Tackle the Phenomenon and Best Practices

A number of suggested approaches for managing NPS in prisons were rated by participants using a 5-point Likert scale.

Knowledge and Education Needs

Some 59% of the respondents rated their knowledge on NPS 'sufficient' (**Table 7**), but they strongly highlighted the need for training and more information on NPS, mainly to be delivered

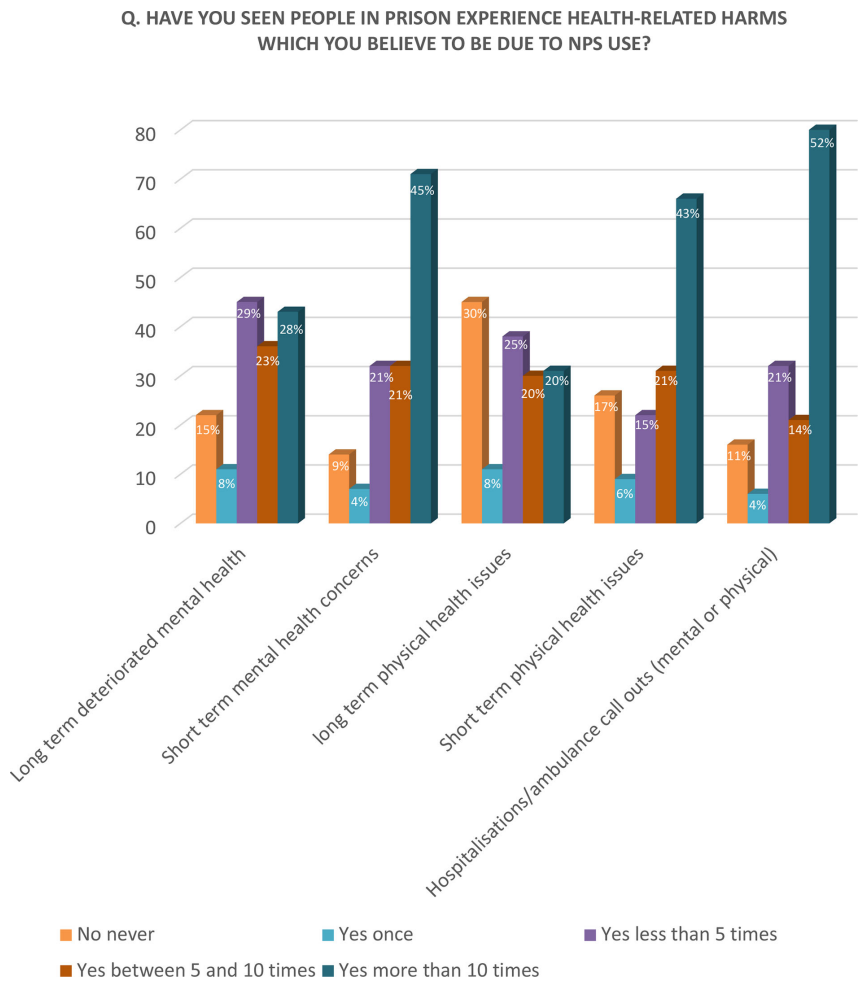

FIGURE 2 | Q. Have you seen people in prison experience health-related harms which you believe to be due to NPS use?

TABLE 5 | Q. Do you feel personally safe in your work in prisons?

#	Answer	%
1	Yes, completely safe	13%
2	Yes, reasonably safe	51%
3	I don't know	6%
4	Unsafe at times	25%
5	Unsafe often	5%

TABLE 6 | Q. To what extent do you feel the use of NPS affects the safety of those working in prisons?

#	Answer	%
1	No affect	0%
2	A small effect	6%
3	A substantial effect	19%
4	A large effect	38%
5	An extremely large effect	37%

via face-to-face workshops (29%), conferences (19%), newsletters (17%), scientific articles (10%), online programs (9%), among others (**Table 8**). Only 3% indicated the use of mobile phone app as a preference, possibly due to the limited use of the tool in such high-security settings.

Improving Current Detection Tools

The majority of interviewees (92%) reported a need for 'improving current detection tools' (see **Figure 3**).

Expanding Treatment and Support Services for Those With Drug Addiction or Mental Health Problems

Some 93% expressed the need for 'expanding treatment and support services for those with drug addiction or mental health problems'. They found that a better understanding of the underlying psychopathological issues will help the development of better assessment tools and both pharmacological and non-pharmacological treatment of those affected.

TABLE 7 | Q. How would you rate your knowledge and awareness of NPS?

#	Answer	%
1	Excellent	23%
2	Sufficient	59%
3	Not sure	7%
4	Somewhat insufficient	9%
5	Minimal	2%

TABLE 8 | Q. If you were to learn more about NPS and the implications for your work, how would you prefer to receive this information?

#	Answer	%
1	Conference attendance	19%
2	Webinar	3%
3	Face-to-face workshops	29%
4	Online CPD program	9%
5	Email bulletin/Newsletter	17%
6	Reference Website	7%
7	Mobile App	3%
8	SMS with updates/trends	3%
9	Scientific Literature/Academic articles	10%

Another major barrier to treatment was the fact that inmates using NPS often refused to participate in rehabilitation activities, making their attempts even harder. It was claimed that negative and disruptive behaviors often sabotaged the therapeutical bond between prisoners and staff. A respondent said: "I work in a medium secure unit. Many of the patients use NPS. This makes it difficult for them to sustain relationships with staff, or engage full in psychological therapy. It affects patients' mental states negatively, and slows up discharge".

Offering Alternative Activities Including Expanded Educational and Prison Employment Opportunities

Making available 'better education programs for people in prisons about NPS' was found essential by the large majority (84%) of the participants. Some found that the prison environment often restricted offenders' access to learning opportunities. According to them, training sessions were often cancelled due to 'Spice' incidents and staff being assaulted.

The development of Continuing Professional Development (CPD) courses for prison staff around NPS was also strongly supported (84%). As a participant stated: "The answer lies within

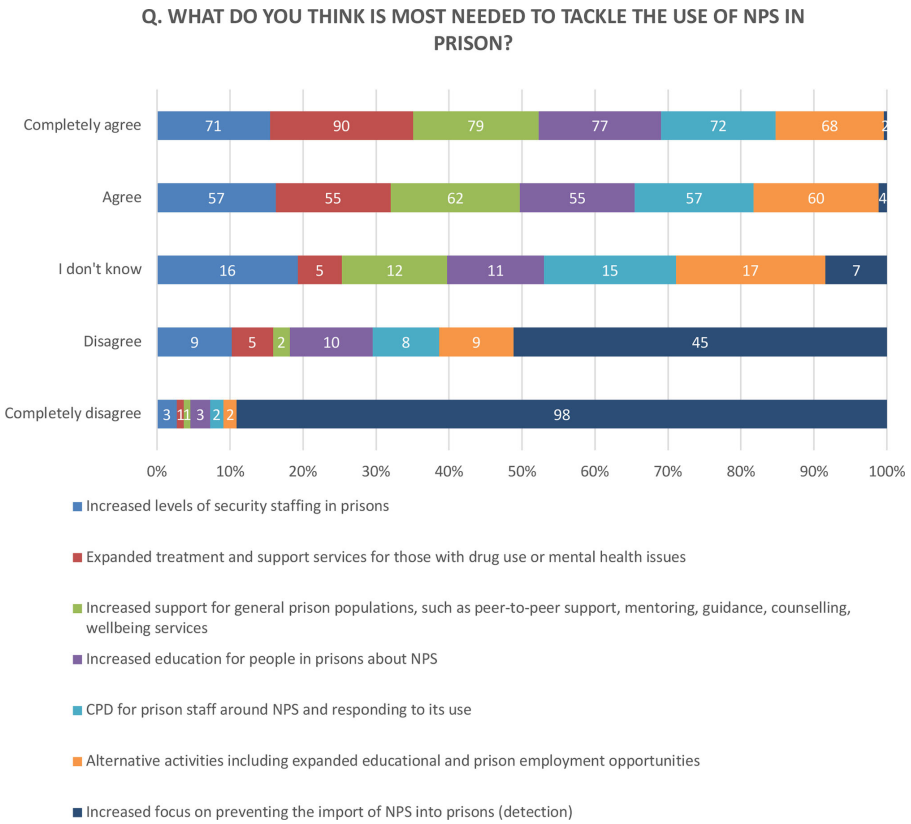

FIGURE 3 | Q. What do you think is most needed to tackle the use of NPS in prison?

prevention—we need to do all we can to prevent these items coming in. If we can achieve that or significantly reduce that—we have a better chance of getting these men clean and substance free and then we can work on interventions—i.e. substance misuse awareness, better education".

Increasing Support for General Prison Populations, Such as Peer-To-Peer Support, Mentoring, Guidance, Counselling, Wellbeing Services

About 82% also encouraged the provision of additional learning and employment opportunities for people in prisons.

DISCUSSION AND CONCLUSION

In a situation of emergency, our work provides a 'first-hand' perspective on 'Spice' (NPS) as experienced by people in prison in combination with the views, the concerns and the recommendations for best practices from professionals working with them. The phenomenological analysis of the five accounts shared by Spice users in prison allowed us to gain original insights on the underlying 'feeling of paranoia', such as the inability to be with others and the mistrust towards them. In one case the paranoia was so deep to generate prolonged periods of discomfort resulting in a complete breakdown. Psychological (and possibly physical) dependence was another common feature that emerged from our analysis. This was associated with unpleasant withdrawal symptoms. Psychotic outbreaks were marked by hallucinations, depression, suicidal ideations. Other negative experiences included self-harm, fear of death or seeing others dying or losing a friend. Even the language used to describe the experience was charged with negative connotations, such as: 'going to hell' (a hole in the floor), a 'dark place', hearing voices predicting one's death, 'the Devil's drug', and 'bottom of the barrel'. Taking Spice with others was perceived also as a way to overcome boredom due to lack of engaging and stimulating activities. Interestingly, some therapeutical elements could also be found in the narrative of these experiences. For instance, in the first case (JP), the hallucinatory experience changed from 'despair of hell' to 'redemption' mediated by a savior represented by the recently deceased uncle. This allows us to confirm the validity of the phenomenological approach to uncover the more hidden aspects of a person's inner world that would not be accessible otherwise and that could be used in future applications to address trauma and other causalities that perpetuate the misuse allowing new cues to emerge. Further, all the collected 'lived experiences' were part of a wider narrative, or "life-story". The residents' willingness to share their stories with Spice reflects a positive attitude aimed to regain the (self-)esteem and the recognition granted to them by the external community, which should be encouraged during the rehabilitation process. These findings well integrate with the results that emerged from the survey and the interviews with a wide range of professionals working in custodial settings. These helped us to shed new insights on the impact of NPS on their working environments, compared to that previously posed by other non-NPS substances. Although the majority of the sample had not been personally, or directly, affected by episodes of violence, a number of concerns were reported. Participants referred to their struggle to deal with the violent behavior of residents, resulting in aggressions between them, or towards staff members. Despite various mechanisms being in place, they highlighted the need for specialist training for those expected to respond to medical or welfare emergencies arising from use of NPS. Their unwanted exposure to potentially lethal or highly toxic substances was also emphasized. During the interviews, it was noticed that NPS were often misleadingly labeled by them as 'Spice', when in fact the term refers to only one category of NPS, SCRA and does not include a wide range of other substances. This discordance in understanding of what we mean by NPS constitutes a further challenge for clinicians and paramedics, since, as they stated, "they might be unaware of what they have taken and how". As a result, a "treat what you see" approach has been adopted, and while still being the most indicated approach in acute medicine, the full implications of this, along with all potential drug interactions with other medications, are not fully understood. The challenge of responding to drug-related psychotic episodes, and the variability and the unpredictability of acute symptoms were other issues of concern that emerged from our study. These did not differ substantially from those commonly observed outside of custodial settings, such as emergency departments, where reported cases are characterized by clinical signs of acute mental intoxication with a mixed symptom profile, not meeting the psychopathological criteria of any specific mental disorder. However, this plays an even more serious role in the prison environment, increasing the perception of risk and difficulty to manage situations by the staff. As previous argued (8), the accurate collection of data on the use of NPS, investigations, treatment, violence pre-admission, violence during admission, length of stay, and readmission should strongly be reinforced at this challenging time. Finally, most of the interviewees strongly emphasized the need for more educational programs to raise risk awareness on NPS and facilitate their responsiveness to emergency situations. This may play a major role to reduce threats to the health of consumers, particularly with the appearance on the illicit market of new highly potent compounds which may escape traditional screening tests, such as Novel Synthetic Opioids (NSOs) (18). In conclusion, the unprecedented outbreak of NPS in British prisons exerted a negative influence on the overall psychological atmosphere in such environments, enhancing the general level of alarm and unsafety. Joint multi-disciplinary efforts are required to tackle the phenomenon and facilitate recovery and reintegration into society.

The study presents various limitations. As far as we know, this is the first time that a phenomenological approach has been used to analyze drug related experiences. A small sample (5) was selected for the investigation, which considering the positive results could be further expanded in the future. Strict inclusion or exclusion criteria were not provided for the selection of both our samples. Furthermore, we did not investigate the type of prisons nor the sociodemographic of the cohort. This may have led to potential bias in the selection of the respondents. In terms of future research, a larger study cohort would allow for the consideration of differences

between the occupational sectors involved in terms of level of awareness, personal experiences, feelings and needs perceived, and of what has changed in professional practice. It is hoped that this study could help to build a clearer picture of where already-stretched resources may need to be focused and further extended to capture data from a greater number of prisons, from a more diverse professional cohort, and from wider territories, in particular beyond the United Kingdom, where the phenomenon is probably under-reported. The involvement of people in prison is also strongly encouraged in future studies as well as the consultation with a group of ex-prison residents to facilitate their implementation. Only a major joint effort among different key stakeholders can tackle the emergency caused by the spread of NPS in prisons and lead to the development of effective treatment and rehabilitation measures.

> *"I am a real person with a real experience. Studies can be done until we are blue in the face. Let's act now"*. A prisoner from HM Prison Guys Marsh (Dorset, England), August 2018.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Hertfordshire. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

OC designed and coordinated the study and the preparation of this manuscript. SC contributed to the data collection and analysis. SM and AN contributed to the literature review and the data collection. MV and CW collected the five case studies from prisons. CZ and AM carried out the phenomenological analysis. AA and SD coordinated the advisory group of ex-offenders. RR contributed to the literature review and provided clinical input. AA contributed to the phenomenological analysis and provided clinical input. GB contributed to the coordination of the overall project.

ACKNOWLEDGMENTS

We would like to thank the people in prison and all those working with them for sharing their valuable insights.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer GM declared a past co-authorship with one of the authors, OC, to the handling editor.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 30 June 2020
doi: 10.3389/fpsyt.2020.00618

Social and Non-Social Cognitive Enhancement in Cocaine Users—A Closer Look on Enhancement Motives for Cocaine Consumption

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: 25 March 2020
Accepted: 15 June 2020
Published: 30 June 2020

Citation:
Kexel A-K, Vonmoos M, Preller KH, Hulka LM, Seifritz E and Quednow BB (2020) Social and Non-Social Cognitive Enhancement in Cocaine Users—A Closer Look on Enhancement Motives for Cocaine Consumption. Front. Psychiatry 11:618. doi: 10.3389/fpsyt.2020.00618

Background: Cognitive disturbances of chronic cocaine users (CU) have been repeatedly investigated. However, it is yet unknown how CU using cocaine for cognitive or social enhancement differ from stimulant-naïve controls and CU that do not have these motives. More precisely, we assumed that CU with an enhancement motive self-medicate deficits in specific cognitive abilities, i.e., they use cocaine to enhance their performance in either social (social motive) or non-social cognitive situations (cognitive motive).

Methods: Forty-two CU were categorized according to their motives for cocaine consumption into social and non-social motive groups as well as cognitive and non-cognitive motive groups, respectively. Subsequently, CU motive groups were compared to 48 stimulant-naïve controls in their social and non-social cognitive functioning applying a comprehensive neuropsychological test battery.

Results: The social motive group showed deficits in cognitive empathy compared to controls (Cohen's $d = 0.65$) and the non-social motive group ($d = 0.60$). No mentionable effects were found for emotional empathy and Theory-of-Mind. Cognitive and non-cognitive motive groups both showed general cognitive deficits but with different patterns of impairments compared to controls: the cognitive motive group had deficits mainly in working memory ($d = 0.84$) and declarative memory ($d = 0.60$), whereas the non-cognitive motive group also had deficits in working memory ($d = 0.61$) but additionally in executive functions ($d = 0.67$). For the domains declarative memory and executive functions, the respective other CU group displayed intermediate performance.

Conclusions: This study demonstrates that cocaine is partially instrumentalized by CU with specific enhancement motives to counteract related cognitive impairments.

Keywords: cocaine, stimulants, neuroenhancement, cognitive enhancement, social enhancement, emotion recognition, perspective-taking, cognition

INTRODUCTION

It has been consistently demonstrated, that cocaine users (CU) show broad cognitive impairments spanning from basic functions such as attention and working memory to more complex abilities such as executive functions, social cognition, and social decision-making (1–8). A recent study suggested that 30% of dependent and 12% of recreational users displayed clinically relevant global cognitive impairment (2). While dependent users showed the strongest deficits in working memory and executive functions, recreational users displayed the strongest effect sizes in attention and memory functions (2). Regarding social cognition, CU generally show impaired basic emotion recognition from faces, specifically regarding fear and anger (9–12). Additionally, dependent and even recreational CU revealed moderate deficiencies in emotional empathy (4) as well as in emotion recognition from voices (13). However, only dependent CU showed impaired mental and emotional perspective-taking (Theory-of-Mind, ToM) (4). Finally, CU demonstrated reduced prosocial behavior in social interaction tasks (3) and were less rewarded by social feedback (14). Notably, longitudinal data recently suggested that both cognitive and social cognitive impairments are partially drug-induced and can be improved to a certain extent with decreasing cocaine consumption (15, 16).

Given these relatively broad cognitive deficits and the potential of cocaine to boost cognitive functions acutely (17), one might assume that at least some CU instrumentalize cocaine to self-medicate cognitive impairments that can be either preexisting or induced by chronic cocaine consumption (15, 16, 18). However, the association between cognitive impairment and pharmacological cognitive enhancement (PCE) with cocaine in CU has not been investigated yet. PCE has been defined as the use of psychoactive drugs aiming at "*improving cognition and everyday performance in individuals who suffer from impaired cognition due to brain injury or neuropsychiatric disorders*" [(19), p. 229]. Another definition—mostly employed by bioethicists—is that "*cognitive enhancement refers to the improvement of cognitive ability in normal healthy individuals*" also by pharmacological means [(20), p. 95]. The authors prefer the first definition, as it is broader and therefore includes self-medication of cognitive deficits in illegal substance use populations.

Non-medical use of stimulants for PCE purposes is sometimes practiced by healthy individuals (21, 22). In healthy individuals, the most commonly used stimulant drug for PCE is the medical stimulant methylphenidate (23). However, it has been recently shown in a representative Swiss sample that also illegal stimulants such as street amphetamine and cocaine are used for non-medical PCE, i.e., to increase attention, concentration and memory, even though less frequently compared to recreational purposes (24). Nonetheless, in this study 11.6% of participants who reported cocaine use indicated its use for PCE (24). Importantly, street amphetamine and cocaine as well as medical stimulants such as methylphenidate all share vigilance- and motivation-increasing effects, which are mediated by elevating postsynaptic catecholamine levels (23, 25). To shed further light on the relationship between PCE and illegal substance use, this study focuses on the illicit stimulant cocaine and its use as a cognitive enhancer. As we have shown previously, students reporting non-medical use of methylphenidate for PCE purposes showed superior cognitive performances (off drug) when compared to students not employing such strategies (26). It could therefore also be possible that CU, who apply cocaine for PCE, perform as well as stimulant-naïve controls or that they are less cognitively impaired than CU without PCE motives.

There is currently little knowledge on the reasons for cocaine use, specifically if CU employ PCE strategies in order to compensate for their non-social and social cognitive deficits. If this is the case, this knowledge has important implications for the treatment of cocaine addiction as the PCE motive needs to be addressed and alternatives to cocaine use for PCE have to be identified and implemented. Furthermore, it is unknown if a PCE cocaine use motive is associated with specific cognitive deficits in comparison to stimulant-naïve controls and CU who do not employ PCE strategies. We therefore aimed at characterizing the cognitive profile of CU that reported using cocaine for PCE. Specifically, we asked CU for their motives for cocaine consumption and identified two CU subgroups. CU with a social motive took cocaine to enhance their functioning in social situations and CU with a cognitive motive aimed at better performing in demanding non-social cognitive situations. We hypothesized that CU with a social motive for cocaine consumption have deficits in social cognition and, thus, use cocaine for social PCE. We further expected CU with a cognitive motive for cocaine consumption to have cognitive impairments and thus to use cocaine for non-social PCE.

METHOD

Participants

The sample of 48 stimulant-naïve healthy controls and 42 chronic CU derives from the follow-up assessment of the longitudinal *Zurich Cocaine Cognition Study* ($ZuCo^2St$) in which 132 individuals participated (for details please see **Supplementary Methods**). Data of this sample has already been reported in other publications from our group but with different outcome measures or research questions (13, 15, 16, 27). General inclusion criteria at the first assessment were: age between 18 and 60 years, German language proficiency, no current or previous severe medical diseases, neurological disorders or head injuries, no family history of Axis I disorders, no current intake of medication affecting the central nervous system and no regular cannabis consumption. Specific inclusion criteria for CU were cocaine abuse or dependence according to DSM-IV, cocaine as the primary used illegal drug and a current abstinence duration of <6 months. Further exclusion criteria for CU were history of opioid use, polytoxic substance use and previous or current DSM-IV Axis I psychiatric disorders with exception of cocaine, nicotine, cannabis, and alcohol abuse/dependence, attention-deficit/hyperactivity disorder and a previous depressive episode. Specific exclusion criteria for controls were previous or current DSM-IV Axis I psychiatric disorders with exception of nicotine dependence,

regular illegal drug use (lifetime use more than 15 occasions for each drug with exception of recreational cannabis use). The study was approved by the Ethics Committee of the Canton Zurich (No. E-14/2009). All participants provided written informed consent in accordance with the Declaration of Helsinki and received monetary compensation for their participation.

Group Assignment

Social motive group assignment: At follow-up CU filled out a questionnaire with ten predefined motives for cocaine consumption and indicated how often they used cocaine to ulfill this motive on a 5-point Likert scale ranging from "never" (1) to "always" (5). In order to identify participants with a social motive, the mean over the three items characterizing a social motive ("I use cocaine to go out", "to establish contacts more easily", "to flirt better") was calculated. CU were then categorized according to a median split on the mean of the three social motives into a social motive (SoM; $Mdn > 1.83$, $n = 21$) and a non-social motive group (NoSoM; $Mdn \leq 1.83$, $n = 21$).

Cognitive motive group assignment: In order to examine CU with a cognitive motive, participants were divided according to their rating of the item "I use cocaine to increase my performance (e.g., at work)" into a cognitive motive group (CoM; rating ≥ 2, $n = 19$) and a non-cognitive motive group (NoCoM; rating = 1, $n = 23$).

Clinical and Substance Use Assessment

Trained psychologists conducted the Structured Clinical Interview for DSM-IV Axis I disorders [SCID-I; (28)]. Additionally, participants carried out the DSM-IV self-rating questionnaire for Axis II personality disorders [SCID-II; (29)]. Because cocaine use was linked to higher ratings on antisocial and narcissistic personality disorder (PD) in this sample at the baseline measurement (4), scores for antisocial and narcissistic PD are reported here. Furthermore, participants filled out the Beck Depression Inventory [BDI; (30)] and the Attention-Deficit/Hyperactivity Disorder (ADHD) Self-Rating Scale [ADHD-SR; (31)] to control for symptoms of depression and ADHD. The *Mehrfachwahl-Wortschatz-Intelligenztest* (32), a standardized German vocabulary test, was used to estimate premorbid verbal intelligence (verbal IQ).

Subjective drug use was quantified with the standardized Interview for Psychotropic Drug Consumption [IPDC; (33)]. Furthermore, in order to objectively assess substance use in the time prior to the test session, hair samples were collected from all participants and analyzed with liquid chromatography-tandem mass spectrometry [LC-MS/MS; for details see (2)]. All participants were asked to abstain from illegal drug use for at least 72 h and from alcohol use 24 h prior to the assessment. Urine toxicology screenings by means of semi-quantitative enzyme multiplied immunoassays [for details see (2)] allowed controlling for compliance with these instructions. Current cocaine craving was measured with the brief version of the Cocaine Craving Questionnaire [CCQ; (34)] and severity of nicotine dependence was assessed with the Fagerström Test of Nicotine Dependence (35).

Social Cognition

Multifaceted Empathy Test (MET)

The MET is a computerized test assessing cognitive (CE) and emotional empathy by evaluating 40 photographs showing people in different positive and negative emotional situations (36). CE was estimated by inferring the mental state of the depicted person by choosing the correct emotion out of four response-alternatives. Emotional empathy was separately evaluated by explicit emotional empathy (EEE), a rating of participants' empathic concern, and implicit emotional empathy (IEE), a rating of participants' arousal, on a 9-point Likert scale. We calculated a global emotional empathy domain score (EES) by averaging participants' scores for EEE and IEE.

Movie for the Assessment of Social Cognition (MASC)

The MASC is a 15-min video-based task assessing ToM by asking participants about the video characters' mental states, hence their feelings, thoughts, and intentions (37). Participants' are presented with four response-alternatives, one representing the correct answer and three distractors representing each three different types of mistakes: (1) non-mental state inferences, the situation is explained by physical causation (no-ToM), (2) insufficient mental state inferences (undermentalizing, reduced ToM), and (3) excessive mental state inferences (overmentalizing, too much ToM). Based on Wunderli et al. (38), we created a global cognitive empathy domain score (CES) by averaging the MET CE score and the number of correct answers in the MASC after z-transforming them on the means and standard deviations of the control group.

Cognition

In order to assess cognitive performance participants completed the *Rapid Visual Information Processing*, *Spatial Working Memory*, and *Paired Associates Learning* tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB[1]) as well as the German version of the Rey Auditory Verbal Learning Test (39) and the Letter Number Sequencing Test (40). Following previous publications from our group investigating cognition in substance users (2, 15, 41, 42), 13 predefined cognitive test parameters were incorporated into the four cognitive domains: attention, working memory, declarative memory, and executive functions [for details see (15, 41)] after z-transforming them on the means and standard deviations of the control group. These four domains were further compiled into a global cognitive index (GCI). In order to avoid alpha-error accumulation, analyses were focused on the four domains and the GCI.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics 25.0 for Windows. To assess the hypothesized deficits in social cognition for CU of the SoM group and the hypothesized cognitive impairments for CU of the CoM group, we conducted analyses of covariance (ANCOVA) and included age and verbal IQ as covariates (43). Sidak-corrected post-hoc comparisons were carried out where appropriate. The

[1] http://www.cantab.com.

significance level was set at $p < 0.05$ (two-tailed). Cohen's *d* effect sizes were calculated using the means and pooled standard deviations and can be interpreted with Cohen's convention of small (0.2), medium (0.5), and large (0.8) effects (44). For more information on additional statistical analyses, please see the **Supplementary Methods**.

RESULTS

Social Cognitive Enhancement

Demographic Characteristics and Substance Use

Controls, NoSoM and SoM group did not significantly differ in age and sex distribution (**Table 1**). However, the groups were significantly different in years of education and verbal IQ, indicating fewer years of education and a marginally lower verbal IQ for the NoSoM group compared to controls and marginally fewer years of education for the NoSoM compared to the SoM group. Both CU groups scored significantly higher on the BDI and ADHD-SR than controls but did not differ from each other concerning their craving for cocaine.

CU of the SoM group have been using cocaine for a shorter period of time (years of use) and reported less cumulated lifetime dose of cocaine than CU of the NoSoM group (**Table 1**). Further drug reports and hair analyses of both CU groups for other drugs including alcohol revealed a clear preference for cocaine over other substances. For more drug use details see **Table S1** in the **Supplementary Material**.

Social Cognition

ANCOVAs controlled for age and verbal IQ showed that controls and CU groups did not significantly differ in EES ($F(2, 85) = 1.06$, $p = .351$). However, there was a significant main effect for group in the global CES ($F(2, 85) = 4.43$, $p = .015$, **Figure 1**). Sidak-corrected post-hoc comparisons revealed that the SoM group performed significantly worse than the control group ($p < .05$, $d = 0.65$) and on a trend-level also worse than the NoSoM group ($p = .091$, $d = 0.60$) with moderate effect sizes, respectively.

Further analyses on the individual scores of the MET and MASC revealed that the effect in the CES was mainly driven by an inferior performance of individuals of the SoM group in CE in the MET (group: $F(2, 85) = 6.25$, $p = .003$, **Figure 2**). Sidak-corrected post-hoc tests indicated significantly fewer correct responses for the SoM group compared to controls ($p = .020$, $d = 0.65$) and to the NoSoM group ($p = .004$, $d = 0.92$) with moderate and strong effect sizes, respectively. There were no group differences for EEE and IEE (for details see **Table S2** in the **Supplementary Material**). An ANCOVA controlling for age and verbal IQ did not reveal significant group differences in the number of wrong answers in the MASC ($F(2, 84) = 2.23$, $p = .114$) but small effect sizes ($d = 0.40–0.44$) indicate that both CU groups made slightly more errors in ToM than controls. Descriptive statistics for social cognitive domain scores, MET, and MASC can be found in **Table S2** in the **Supplementary Material**.

As ADHD is an important covariate when analyzing cognition and social cognition in CU (2, 4, 41), we excluded participants with a suspected diagnosis of ADHD according to the ADHD-SR ($n = 8$ CU) and repeated the analyses. Exclusion

TABLE 1 | Demographic data and cocaine use information for controls and cocaine users in the analysis of social cognitive enhancement.

	Controls ($n = 48$)	NoSoM ($n = 21$)	SoM ($n = 21$)	Value	df/df_{err}	*p*
Sex (m/f) (*n*)	32/16	16/5	17/4	$\chi^2 = 1.70$[a]	2	0.427
Age	31.35 (8.73)	35.48 (9.41)	30.10 (6.52)	$F = 2.46$[b]	2/87	0.092
Verbal IQ	107.58 (10.04)	101.62 (6.89)†	103.38 (11.17)	$F = 3.25$[b]	2/87	**0.044**
Years of education	10.76 (1.83)	9.57 (1.54)*	10.71 (1.65)‡	$F = 4.31$[c]	2/44.64	**0.019**
ADHD-SR sum score	7.69 (5.19)	12.81 (5.99)**	14.86 (10.02)*	$F = 8.96$[c]	2/35.99	**0.001**
BDI sum score	2.33 (3.27)	7.67 (7.54)*	8.81 (10.52)*	$F = 8.04$[c]	2/29.79	**0.002**
Narcissistic PD	2.07 (1.68)	3.05 (2.11)	5.15 (3.22)**‡	$F = 8.83$[c]	2/33.43	**0.001**
Antisocial PD	2.76 (2.06)	4.15 (3.00)	4.90 (3.96)	$F = 3.81$[c]	2/32.28	**0.033**
Cocaine						
Dependence (y/n) (*n*)	–	9/12	5/16	$\chi^2 = 1.71$[a]	1	0.190
Times/week[g,h]	–	0.46 (0.00–2.50)	0.46 (0.11–2.83)	$U = 263.50$[e]		0.278
Grams/week[g,h]	–	0.46 (0.00–11.25)	0.52 (0.13–2.67)	$U = 238.50$[e]		0.650
Years of use	–	11.78 (5.11)	7.56 (5.94)	$t = 2.47$[d]	40	**0.018**
Age of onset	–	24.10 (7.62)	22.60 (4.25)	$t = 0.79$[f]	31.35	0.437
Last consumption (days)[h]	–	8.00 (2.00–182.40)	5.00 (2.00–91.20)	$U = 171.50$[e]		0.216
Cumulative lifetime dose (grams)[h]	–	1,076.09 (90.87–28,103.25)	244.16 (30.42–3,361.96)	$U = 111.00$[e]		**0.006**
Cocaine craving	–	17.24 (10.05)	19.00 (9.61)	$t = -0.58$[d]	40	0.565
Urine toxicology (neg/pos)	48/0	13/8	14/7	$\chi^2 = 20.74$[a]	2	**<0.001**
Hair analysis (pg/mg)						
$Cocaine_{total}$[h,i]	–	10,155.00 (1,253–290,250)	5,010.00 (908–64,750)	$U = 146.00$[e]		0.061
Cocaine[h]	–	8,050.00 (1,110–200,000)	4,200.00 (790–59,500)	$U = 148.00$[e]		0.068
Benzoylecgonine[h]	–	1,950.00 (125–84,000)	670.00 (100–9,750)	$U = 133.00$[e]		**0.028**
Norcocaine[h]	–	210.00 (18–6,250)	90.00 (13–725)	$U = 133.00$[e]		**0.028**
Cocaethylene[h]	–	340.00 (0–9,200)	205.00 (0–5,000)	$U = 196.00$[e]		0.538

*Significant p-values are shown in bold. Means and standard deviation of means in parenthesis. ADHD-SR, ADHD self-rating scale; BDI, Beck Depression Inventory. [a]χ^2 test (across all groups/cocaine users only) for frequency data. [b]ANOVA (across all groups, with Sidak post-hoc tests vs. controls: †$p < 0.10$). [c]Welch's ANOVA (across all groups, with Games-Howell post-hoc tests vs. controls: *$p < 0.05$; **$p < 0.01$; vs. NoSoM: ‡$p < 0.10$). [d]Independent t-test (cocaine users only). [e]Mann–Whitney U test (cocaine users only). [f]Welch's t-test (cocaine users only). [g]Average use during the last six months. [h]Median (range) is reported. [i]$Cocaine_{total}$ (= cocaine + benzoylecgonine + norcocaine) as a more robust parameter (45).*

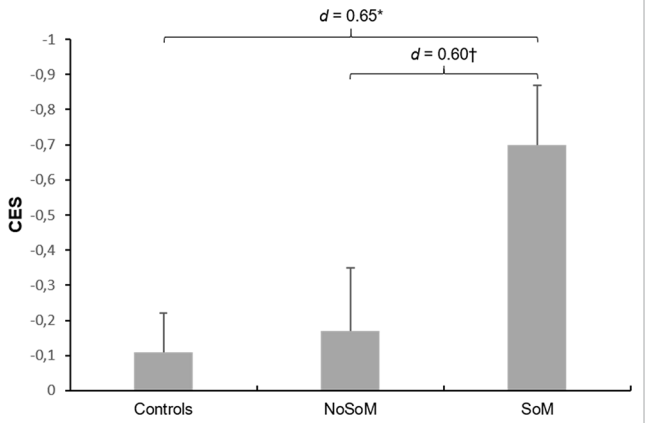

FIGURE 1 | Mean z-scores and standard errors for the Cognitive Empathy Score (CES) in controls and cocaine users with (SoM) and without a social enhancement motive (NoSoM). Values adjusted for verbal IQ and age. Sidak post-hoc tests vs. controls: *p < 0.05; vs. NoSoM: †p < 0.10. Cohen's d effect sizes for group comparisons are shown on top of the bars.

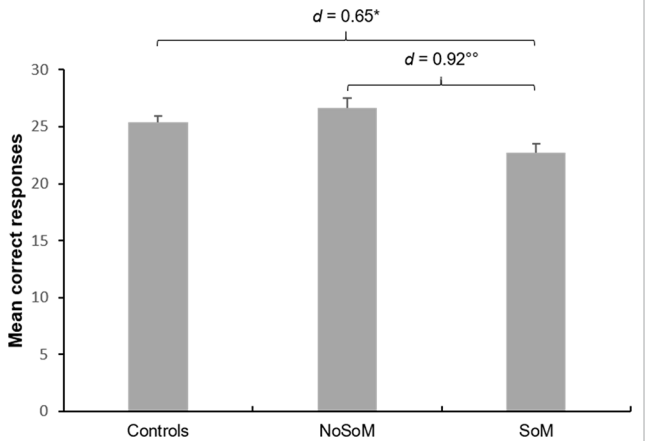

FIGURE 2 | Mean correct responses and standard errors for cognitive empathy in the Multifaceted Empathy Test (MET) of controls and cocaine users with (SoM) and without a social enhancement motive (NoSoM). Values adjusted for verbal IQ and age. Sidak post-hoc tests vs. controls: *p < 0.05; vs. NoSoM: °°p < 0.01. Cohen's d effect sizes for group comparisons are shown on top of the bars.

of CU with ADHD altered the result for the global CES as this effect no longer remained significant. However, the effect for CE in the MET persisted even after exclusion of subjects with ADHD. Furthermore, to exclude the possibility that our findings were driven by more cumulated lifetime cocaine consumption (2, 15, 16) in the SoM group, we repeated the ANCOVAs adjusted for age and verbal IQ for the domain, the MET, and the MASC scores only comparing CU groups and additionally included ln-transformed cumulated lifetime dose of cocaine. This did not change the results. In an exploratory analysis, we additionally investigated the performance in the neurocognitive domains in the social cognitive enhancement groups. These results can be found in **Table S2** in the **Supplementary Material**.

Non-Social Cognitive Enhancement

Demographic Characteristics and Substance Use

Controls and CU of the NoCoM and CoM group did not significantly differ in age, sex distribution, and years of education (**Table 2**). However, the groups were significantly different in verbal IQ, indicating a marginally lower IQ for the CoM group compared to controls. Both CU groups scored significantly higher on the BDI and ADHD-SR than controls but did not differ from each other concerning their craving for cocaine.

The CU groups showed similar patterns of cocaine use (**Table 2**). However, the CoM group indicated higher consumption frequency per week. Drug reports and hair analyses for both CU groups again confirmed a clear preference for cocaine over other substances. For more details see **Table S3**.

Cognition

ANCOVAs controlled for age and verbal IQ revealed significant group effects in the GCI ($F(2, 85) = 4.63$, $p = .012$, **Figure 3**) and the domains working memory ($F(2, 85) = 6.76$, $p = .002$), declarative memory ($F(2, 85) = 3.18$, $p = .047$), and executive functions ($F(2, 85) = 4.13$, $p = .002$). No significant effect was found for attention ($F(2, 85) = 0.73$, $p = .485$). Sidak-corrected post-hoc comparisons for the GCI demonstrated that only the CoM group performed significantly worse than controls ($p = .034$; $d = 0.60$). The effect for the NoCoM group was only marginally significant ($p = .059$; $d = 0.52$). However, both effects had moderate effect sizes indicating cognitive deficits in CU in general. Regarding the working memory domain, both, the CoM ($p = .004$; $d = 0.84$) and NoCoM group ($p = .037$; $d = 0.61$), performed worse than controls, with the CoM group showing a strong, and the NoCoM group showing a moderate effect size. Concerning declarative memory, only the CoM group showed inferior performance compared to controls ($p = .048$, $d = 0.60$), whereas the NoCoM group showed weaker performance in executive functions ($p = .015$; $d = 0.67$). Both effects had a moderate effect size. Analyses of the individual test parameters underlying the cognitive domains are presented in **Table S4**.

We again excluded subjects with a suspected ADHD and repeated ANCOVAs on the GCI and the cognitive domains. However, this did not change the overall results. We also repeated the analyses only with CU and included ln-transformed cumulated lifetime dose of cocaine. This again did not change the results. In an exploratory analysis, we analyzed social cognition in the non-social cognitive enhancement groups. Results can be found in **Table S5** in the **Supplementary Material**.

DISCUSSION

We investigated the cognitive profile of CU with a social motive who occasionally take cocaine to enhance their performance in social situations and CU with a cognitive motive who at least

TABLE 2 | Demographic data and cocaine use information for controls and cocaine users in the analysis of non-social cognitive enhancement.

	Controls (n = 48)	NoCoM (n = 23)	CoM (n = 19)	Value	df/df_{err}	p
Sex (m/f) (n)	32/16	18/5	15/4	χ^2 = 1.59[a]	2	0.453
Age	31.35 (8.73)	34.61 (9.89)	30.58 (5.79)	F = 1.48[b]	2/87	0.234
Verbal IQ	107.58 (10.04)	103.04 (7.83)	101.84 (10.84)†	F = 3.15[b]	2/87	**0.048**
Years of education	10.76 (1.83)	10.04 (1.72)	10.26 (1.66)	F = 1.45[b]	2/87	0.240
ADHD-SR sum score	7.69 (5.19)	13.83 (6.64)**	13.84 (10.00)*	F = 9.42[c]	2/34.38	**0.001**
BDI sum score	2.33 (3.27)	8.57 (9.43)*	7.84 (8.82)*	F = 7.68[c]	2/29.20	**0.002**
Narcissistic PD	2.07 (1.68)	3.96 (2.51)**	4.29 (3.41)*	F = 7.58[c]	2/30.71	**0.002**
Antisocial PD	2.76 (2.06)	4.61 (3.45)†	4.41 (3.64)	F = 3.82[c]	2/30.78	**0.033**
Cocaine						
Dependence (y/n) (n)	–	6/17	8/11	χ^2 = 1.20[a]	1	0.273
Times/week[g,h]	–	0.46 (0.04–1.50)	0.69 (0.00–2.83)	U = 302.00[e]		**0.034**
Grams/week[g,h]	–	0.46 (0.06–2.00)	0.81 (0.00–11.25)	U = 283.50[e]		0.100
Years of use	–	11.17 (5.96)	7.86 (5.38)	t = 1.87[f]	40	0.069
Age of onset	–	23.95 (7.12)	22.61 (4.79)	t = 0.70[f]	40	0.489
Last consumption (days)[h]	–	8.00 (2.00–121.60)	5.00 (2.50–182.40)	U = 161.00[e]		0.145
Cumulative lifetime dose (grams)[h]	–	633.26 (30.42–28,103.25)	360.20 (36.41–6,603.22)	U = 208.00[e]		0.791
Cocaine craving	–	15.26 (5.60)	21.58 (12.46)	t = -2.05[f]	23.967	0.052
Urine toxicology (neg/pos)	48/0	16/7	11/8	χ^2 = 21.59[a]	2	**<0.001**
Hair sample (pg/mg)						
$Cocaine_{total}$[h,i]	–	5,340.00 (953–290,250)	7,390.00 (908–202,035)	U = 235.00[e]		0.677
Cocaine[h]	–	4,500.00 (790–200,000)	6,000.00 (790–170,000)	U = 241.00[e]		0.570
Benzoylecgonine[h]	–	1,050.00 (115–84,000)	875.00 (100–31,000)	U = 224.00[e]		0.889
Norcocaine[h]	–	135.00 (13–6,250)	150.00 (15–1,035)	U = 208.50[e]		0.800
Cocaethylene[h]	–	305.00 (0–9,200)	170.00 (0–8,550)	U = 178.00[e]		0.306

*Significant p-values are shown in bold. Means and standard deviation of means in parenthesis. ADHD-SR, ADHD self-rating scale; BDI, Beck Depression Inventory. [a]χ^2 test (across all groups/cocaine users only) for frequency data. [b]ANOVA (across all groups, with Sidak post-hoc tests vs. controls: †p < 0.10). [c]Welch's ANOVA (across all groups, with Games–Howell post-hoc tests vs. controls: *p < 0.05; **p < 0.01). [d]Welch's t-test (cocaine users only). [e]Mann–Whitney U test (cocaine users only). [f]Independent t-test (cocaine users only). [g]Average use during the last six months. [h]Median (range) is reported. [i]$Cocaine_{total}$ (= cocaine + benzoylecgonine + norcocaine) as a more robust parameter (45).*

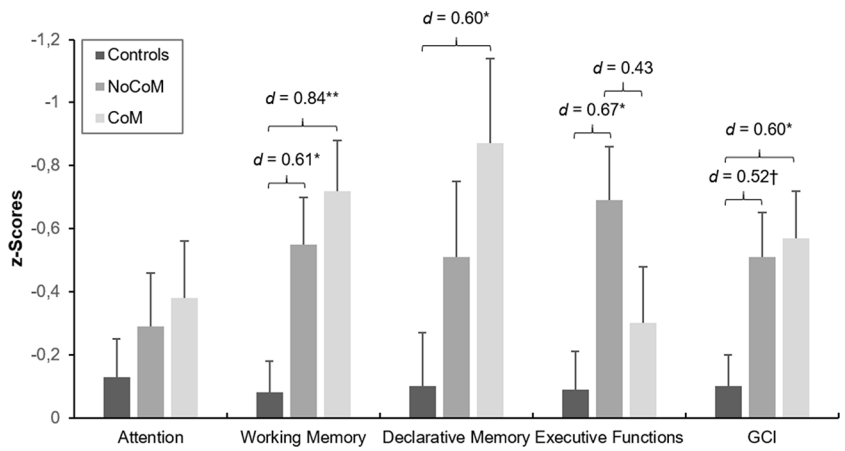

FIGURE 3 | Mean z-scores and standard errors for the four cognitive domains and the Global Cognitive Index (GCI) of controls and cocaine users with (CoM) and without a cognitive enhancement motive (NoCoM). Values adjusted for verbal IQ and age. Sidak post-hoc tests vs. controls: †p < 0.10; *p < 0.05; **p < 0.01. Cohen's d effect sizes for group comparisons are shown on top of the bars.

sometimes take cocaine to perform better in demanding cognitive situations, e.g., at work.

First, socially motivated CU showed lower cognitive empathy (as reflected by the CES) compared to controls (d = 0.65) and, on a trend-level, also compared to CU of the NoSoM group (d = 0.60). The lower score in the CES for the SoM group was mainly driven by reduced cognitive empathy in the MET. We therefore propose that CU with a social motive for cocaine consumption use cocaine partially to counteract deficits in the cognitive aspect of empathy. Contrary to the baseline measurement of this sample, we did not find impairments in emotional empathy in the same test (4). Notably, cocaine hair concentrations indicate that the follow-up sample (analyzed here) did not include as many severe users as the baseline sample [compare with (2, 4)]

due to a higher drop-out rate within the more severe users. Moreover, although we excluded abstinent (n = 7) and non-chronic CU (cocaine hair concentration <500 pg/mg, n = 14) at follow-up, the sample still included CU who decreased their cocaine consumption over one year accompanied with improved cognition at follow-up (15, 16). This might explain a lack of findings regarding emotional empathy. Emotional empathy deficits seem to be at least partially drug-induced (16). However, this does not seem to be the case for cognitive empathy and socially motivated CU. Within CU, the inclusion of self-reported cumulated lifetime dose of cocaine did not change the results in social cognition suggesting that these deficits might precede stimulant use. Moreover, the SoM group reported significantly less (Mdn = 244.2 g) cumulated lifetime dose of cocaine than the NoSoM group (Mdn = 1,076.1 g), additionally supporting that the effect found for cognitive empathy is maybe not induced by previous cocaine use. However, this needs to be verified in further longitudinal studies. Interestingly, Maier et al. (26) examined methylphenidate users that took methylphenidate for PCE and found reduced cognitive empathy on the MET as well, which points to a potential common underlying factor in stimulant users that use the substances for PCE.

Second, we found non-social cognitive impairments in both CU groups as indicated by the GCI, although the comparison between controls and the NoCoM group was only marginally significant (d = 0.52). This replicates results from previous studies (1, 5–7) and the baseline measurement (2), although effects were somewhat stronger at the baseline assessment. Both CU groups showed impairments in working memory. However, only CU of the CoM group had additional deficits in declarative memory, whereas only CU of the NoCoM group demonstrated deficits in executive functions. In both cases, the respective other CU group displayed intermediate performance but was not significantly different from either controls or the other CU group. Surprisingly, no differences were found for attention. However, as mentioned before, the follow-up sample was—in the mean—less severely addicted compared to the baseline sample. Given the significant correlation between cognition and cocaine use intensity (2), this likely explains the overall smaller effects in cognition in the present sample of CU. Based on our findings, we propose that CU with a cognitive motive for cocaine consumption use cocaine at least sometimes to counteract deficits, e.g., in working memory functions. Interestingly, they show intermediate performance in executive functions, suggesting that they are likely not (yet) as impaired in this domain as CU without a cognitive motive. This is not surprising as PCE is considered a complex goal-oriented behavior (46). In order to use a substance for PCE, one needs to be able to plan this behavior to get the best outcome. Remarkably, Maier et al. (26) actually found superior functioning of PCE motivated methylphenidate users in executive functions and goal-directed decision-making which points in the same direction. Of note, this study used exactly the same cognitive test battery as applied here.

Additional analyses after exclusion of subjects with a putative diagnosis of ADHD did not change the overall results in cognition whereas some changes occurred for social cognition as the effect in the CES did not remain significant. This is not surprising as we did not observe strong effects in the MASC at baseline (4) where the effect was, additionally, partially driven by individuals with a suspected ADHD diagnosis (41). However, the effect on the cognitive empathy score of the MET persisted. After exclusion of subjects with ADHD, the respective effects in the MET and MASC canceled each other out leading to a non-significant result in the composite score. Nevertheless, we believe that our main results are still valid and meaningful even without considering ADHD, as the motive to enhance social and non-social cognitive performance through cocaine consumption needs to be considered within the entire profile of the CU and often, cocaine use is associated with an ADHD diagnosis (2, 15, 41, 47–49). Notably, CU with ADHD (n = 8) appeared more frequently in the enhancement groups with seven CU with ADHD in the SoM (p < .001, Fisher's exact test) and six in the CoM group (p < .001, Fisher's exact test) indicating the use of cocaine as a form of self-medication especially for those CU with a putative comorbid ADHD.

The findings need to be interpreted with the following limitations in mind. First, controls, NoSoM and SoM groups differed with regard to verbal IQ and years of education and controls and CoM group differed with regard to verbal IQ. However, groups were matched for age and sex and we included age and verbal IQ as covariates in the statistical models. We did not include years of education as a covariate as only verbal IQ differed in both investigations and verbal IQ and years of education were moderately correlated with each other (r = 0.31, p < .01). Second, sample sizes of the CU groups were small and only a few CU utilized cocaine intensively as a social or cognitive enhancer. Therefore, the results need to be replicated in larger samples of CU who instrumentalize cocaine for PCE more regularly.

This study demonstrates that a subgroup of CU who sometimes employ PCE strategies also show social and non-social cognitive deficits. It is therefore conceivable, that these subgroups try to compensate cognitive deficits with cocaine use. This instrumentalization of cocaine use can be considered as a self-medication of pre-existing or cocaine-induced cognitive impairments (or both), which seems to be especially true for CU with a co-morbid ADHD diagnosis. Consequently, existing PCE strategies have important implications for treatment outcomes as these strategies need to be addressed and alternatives to satisfy the motive need to be found. In general, social and non-social cognitive impairments have been proposed to diminish the efficacy of therapeutic interventions (50, 51). Thus, psychotherapeutic but also psychopharmacological approaches were recently suggested to alleviate cognitive deficits in CU in order to improve addiction therapy success (51–53). For instance, cognitive enhancement with ADHD (or other) medications has been proposed as a treatment target for cognitive disturbances in cocaine use disorder in the past (53–55). However, contrary to opioid or nicotine dependence, substitution in cocaine use disorder is not yet approved due to unclear evidence from clinical studies (56–58). Nevertheless, substitution with methylphenidate has been proposed to be a safe and effective treatment in CU with comorbid ADHD (57).

As our findings indicate that especially CU with comorbid ADHD employ PCE strategies and that cognitive impairments in CU with ADHD are amplified (41), we assume that substitution could be beneficial in these patients. We therefore suggest that attending physicians discuss putative PCE strategies and cognitive impairments with their patients in general, explain the negative long-term consequences of cocaine use (15, 16, 18) and additionally offer PCE with medical drugs as an alternative to CU with comorbid ADHD. This could foster treatment compliance as patients are signaled that their personal goals in using cocaine are respected and met. However, the use of medical stimulants might delay recovery that can be observed after longer periods of abstinence as the reversibility of cocaine-induced cognitive dysfunctions has been proposed to reflect re-adaptation of brain functions and neurotransmitter systems (15).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Canton Zurich. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BQ and A-KK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. BQ developed the study concept and design. MV, KP, and LH contributed to the acquisition of the data, A-KK and BQ analyzed and interpreted the data. A-KK and BQ drafted the manuscript. All authors contributed to the article and approved the submitted version. ES and BQ obtained funding. MV, KP, LH, and ES contributed to the administrative, technical, or material support. ES and BQ were in charge of supervision.

FUNDING

The study was supported by grants from the Swiss National Science Foundation (Grant Nos. PP00P1-123516/1 and PP00P1-146326/1) and the Olga Mayenfisch Foundation. A-KK was financed by a grant of the Swiss National Science Foundation (105319_162639) to BQ. The funders had no role in study design; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript, and the decision to submit the manuscript for publication.

ACKNOWLEDGMENTS

We are grateful to Daniela Jenni, Kathrin Küpel, and Franziska Minder for their excellent support with recruitment and assessment of the participants.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00618/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 07 July 2020
doi: 10.3389/fpsyt.2020.00569

Prevalence of Novel Psychoactive Substance (NPS) Use in Patients Admitted to Drug Detoxification Treatment

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Edited by:
Aviv M. Weinstein, Ariel University, Israel

Reviewed by:
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Jolanta B. Zawilska, Medical University of Lodz, Poland

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *04 April 2020*
Accepted: *03 June 2020*
Published: *07 July 2020*

Citation:
Specka M, Kuhlmann T, Sawazki J, Bonnet U, Steinert R, Cybulska-Rycicki M, Eich H, Zeiske B, Niedersteberg A, Schaaf L and Scherbaum N (2020) Prevalence of Novel Psychoactive Substance (NPS) Use in Patients Admitted to Drug Detoxification Treatment. Front. Psychiatry 11:569. doi: 10.3389/fpsyt.2020.00569

Background: About 15 years ago, a diverse group of new recreational psychotropic substances began to emerge, which were marketed for example as "legal highs," "research chemicals," or "designer drugs." These substances were later subsumed under the label "Novel Psychoactive Substances" (NPS). Important NPS classes are cathinones, synthetic cannabimimetics, phenethylamines, and herbal drugs. The health care system for psychotropic substance use disorders (SUDs) traditionally focused on a few substances, such as alcohol, heroin, cocaine, amphetamines, or cannabis. Users of illicit substances often engage in polydrug use. However little is known about the prevalence of NPS use within the group of "classical" illicit substance users.

Objective: We investigated lifetime and recent use of NPS and other drugs in patients who underwent in-patient detoxification treatment from illicit drugs in Germany.

Methods: In a multicenter study with eight participating facilities, patients admitted to treatment underwent a standardized interview at admission, concerning their past and current substance use. The interview comprised classical substances of abuse, NPS, and rarely used substances such as LSD. In addition, participating sites had the opportunity to analyze their patients' routine drug screenings by means of gas chromatography/mass spectrometry (GC/MS), which permitted detection of NPS.

Results: Interviews from 295 patients could be analyzed. Most patients were opiate dependent and multiple substance users. About 32% reported use of synthetic cannabimimetics during lifetime, but usually only a few times. An important reason for their use was that NPS were not detected by drug testing in prisons or drug treatment facilities. Cathinones, herbal drugs or other NPS had rarely been used during lifetime. NPS use during the last 30 days before admission was nearly zero. This was confirmed by urine analysis results. In contrast, lifetime and current use of opiates, alcohol, cocaine,

benzodiazepines, and cannabis was high. In addition, 18% reported of regular unprescribed pregabalin use during lifetime, and 20% had recently used pregabalin.

Conclusion: Patients admitted to drug detoxification treatment showed multiple substance use, but this did not include NPS use. The diversion of legal medications such as pregabalin in this group is a serious concern.

Keywords: novel psychoactive substances, pregabalin abuse, multiple substance use, drug dependence, drug detoxification, opiate dependents

INTRODUCTION

The health care system for substance related disorders has traditionally been concerned with a limited number of psychoactive drugs, for example alcohol, opiates, cocaine, cannabis, and amphetamines, and to a much lesser degree with hallucinogenic drugs such as LSD, psilocybin, and others (1). About 15 years ago, the market for psychotropic substances saw the advent of a range of diverse substances, designed as legal alternatives to legally controlled drugs (2). These substances first gained prominence under labels such as "legal highs," "herbal highs," "research chemicals," or "spice." The term Novel Psychoactive Substances (NPS) which is used to describe these substances is not descriptive of their intrinsic properties. NPS is a label for substances imitating the effects of known psychotropic substances. Effects can resemble those of cannabis, of hallucinogens, or even of opioids.

The term NPS denotes, amongst other, synthetic cannabimimetics (agonists at the cannabinoid receptors), synthetic cathinones, which chemically resemble amphetamines or methamphetamine (for example mephedrone), phenetylamines as stimulants or hallucinogens. In addition, some authors also include ketamine and herbal products such as salvia divinorum. The early warning system of the European Union has documented the emergence of several hundred new NPS over the years (3).

NPS were initially not regulated by the law so that their possession and sale was legal. If a certain NPS substance was prohibited, it could be re-introduced after small chemical changes had been made. Legal regulations in response to this were introduced in several countries during the last few years. For example, the German "Neue psychoaktive-Stoffe-Gesetz" (NpSG) from November 2016 meant a far-reaching prohibition of complete groups of NPS and no longer of only singular substances. In the UK, the Psychoactive Substances Act (2016) was imposed, which criminalizes any NPS (4).

The most frequent NPS classes are associated with medical risks (1). The scientific literature has documented fatalities associated with or even attributable to the use of NPS. An analysis from 2015 of hospital emergency data by the European Drug Emergencies Network found that 9% of all drug-related emergencies involved new psychoactive substances (5). Substances involved are often synthetic cannabinoids (e.g., "spice") and synthetic cathinones (e.g., "bath salts") (6). Synthetic cannabinoids can cause agitation, tachycardia, and arterial hypertension. There were emergency admissions with myocardial infarction, epileptic seizures, unconsciousness, aggressiveness, and psychiatric symptoms. Tryptamines, as 5-HT2A-receptor-agonists, have a hallucinogenic effect. Tryptamines have a low potential for being addictive, but there is a risk for the development of tolerance, and of cross tolerance with serotonergic substances. Phenetylamines can cause cardiovascular and psychiatric symptoms. There were documented emergency admissions with panic and agitation (1).

Prevalence of NPS use in the general population is seemingly low. In Germany, a general population survey on 18 to 64 year olds in 2015 estimated a 2.8% prevalence of lifetime NPS use, defined as "legal highs, research chemicals, bath salts, spice, or novel psychoactive substances, which could be available for example as herbal mixtures, powder, crystals, or pills." The 12-month prevalence was 0.9%, and prevalence during the last 30 days was nearly zero (7, 8). Prevalence in the younger age groups of the general population is higher. Estimates from Europe suggest between 1% and 8% of school students have used NPS at some point (2). In an online survey, 6.7% of Dutch university students reported of NPS use (9). Even higher consumption rates were found in young attendees of electronic dance music events or nightclubs (10–12). Relevant rates of cathinone use have been found in several studies on adolescents and young adults (13).

It is yet unclear how much users of "classical" illicit psychotropic substances are attracted by NPS. In that population, multiple substance use is frequent and can include cocaine, opiates, cannabis, benzodiazepines, alcohol, and/or amphetamines. Use of NPS is not routinely assessed, for example in drug screenings. This could make NPS use attractive during detention, in residential homes or therapeutic facilities, while on parole, or in association with driving license issues.

Although administration of NPS is mainly *via* non-injecting routes (14), data from Hungary (15) and Scotland (16) suggest that persons who inject drugs might also inject NPS. In a sample of drug dependent and/or acutely intoxicated patients from hospitals in Paris and its suburbs (17), prevalence of NPS use was 29%, according to hair analysis. In that study, ketamine was subsumed under NPS and constituted more than half of the consumed substances. Users had used more than one NPS in about half of cases, mostly in combination with conventional drugs of abuse. In a study from Scotland, about 24% of patients with a substance use disorder (including alcohol) reported that they had consumed NPS before admission (4). By analysis of hair sampled from confirmed amphetamine users in Switzerland, a 37% rate of NPS users was found (18). In an interview study with clients from drug counseling centers in Germany, 6 out of 33 clients with opiate problems (18.2%), and 21 out of 48 polysubstance users (43.8%) reported of past NPS use, in the

vast majority cannabimimetics like "spice" (19). In addition, NPS were detected in 13% of urine samples from opiate substituted patients in Sweden, but patients were rarely sure about which substances they had consumed (20).

Thus, studies suggest that consumers of long-known substances of abuse might also be prone to NPS use. In the present multicenter study, we examined lifetime and recent NPS use in patients admitted to in-patient drug detoxification treatment for illicit drugs. NPS use was therefore investigated in the context of "classical" drug use, including the main substances used by members of the drug scene, as well as other long known substances such as LSD, Khat or psilocybin, etc.

METHODS

Study Design

The present study used a prospective, cross-sectional design. Included were patients admitted to in-patient drug detoxification treatment in the German state of Nordrhein-Westfalen. Participating institutions were members of an association of facilities and professionals in the field of drug treatment and drug detoxification (Fachverband Qualifizierte stationäre Entzugsbehandlung Opiatabhängiger). In-patients undergo an anamnestic interview at admission to treatment, including questions concerning past and present drug use. For study purposes, the interview was standardized with regard to questions and answering formats, and specific questions about NPS use were included. Also basic socio-demographic characteristics were recorded (age, gender, migrant background, current relationship status, living with children, current employment). The laboratory analysis of the drug screenings routinely taken at treatment admission was expanded to include NPS. This required an additional transfer of urine samples to an external laboratory and was not carried out by all participating facilities (see below). The study was reviewed and agreed upon by the ethics board of the Medical Faculty, University Duisburg Essen. Data were collected during years 2018 and 2019.

Sample Recruitment, Inclusion and Exclusion Criteria

All eligible patients admitted to drug detoxification treatment during a specified period (2 or 3 months, depending on the respective facility) were invited to participate. If patients agreed into participation, they were informed about the study aims and procedures and about data protection measures. In particular, patients were informed that their data were stored and analyzed in pseudonymous form only. Patients then gave their written informed consent.

Patients could be included into the study if they received a diagnosis of dependence from cannabis, opiates, cocaine or amphetamines. Exclusion criteria were: a patient did not understand German well enough to fully comprehend the study information and/or the interview questions; a patient showed cognitive impairments, including severe symptoms of intoxication or withdrawal, which prevented understanding of study information and/or the interview questions; a patient showed symptoms of a psychiatric disorder (e.g., acute psychosis) which cast doubt upon that s/he could fully understand the study information or could act freely; or a patient did not give informed consent.

Patients were informed that they could object to study participation at any time and without negative consequences, and that they could withdraw a given consent.

Assessments

Patients were interviewed for consumption of psychotropic substances using a standardized questionnaire. It included names of substances or of types of substances, for example heroin, substances used in opioid agonist maintenance treatment (methadone, buprenorphine), cocaine, cannabis, alcohol, but also of substances with an assumed lower prevalence, such as opioid analgesics, gabapentin/pregabalin, muscarin, khat, ketamine, etc. For each substance or substance class, patients should indicate if they had ever used it at least once during lifetime. If yes, they were then asked about its consumption during the previous 30 days: on how many days, in which daily dose, and by which application route (intravenous, oral, nasal, by smoking/inhaling). Regarding lifetime consumption, patients were asked for lifetime frequency (< 5 times, 5 to 50 times, more than 50 times), historical years of regular consumption (defined here as at least weekly, e.g., every weekend), and historical years of daily or almost daily consumption.

Within the list of psychotropic substances, NPS were introduced as substances also known as "Legal Highs," "Herbal Highs," or "Research Chemicals." In particular, four classes were listed: synthetic cannabinoids ("spice" etc.), i.e., substances which act like cannabis; synthetical stimulants (bath salts, mephedrone, etc.); Herbal Drugs (herbal ecstasy, etc.); and any other, not previously mentioned NPS. Patients were asked to give the name of consumed substances. In addition, they were asked whether there were particular reasons or circumstances when they consumed the respective NPS, for example because it could not be detected by urine tests, or served as a substitute for unavailable substances.

Comprehensiveness and practicability of the interview were tested in a pilot study with 12 patients, and questions and answering options were improved where necessary. The interviews were carried out by a resident from the respective ward.

Analytical Testing

In addition to the interview, urine specimens routinely sampled at admission were sent to an external laboratory (LVR Klinik Viersen, head: Jürgen Sawazki). The determination of NPS as well as of common drugs out of a urine matrix was performed utilizing Solide-Phase-Extraction (SPE) and followed by a screening on a Gas Chromatography system coupled to a Time-of-Flight Mass spectrometer (GC-ToF-MS) (21). Acetate buffer and beta-Glucuronidase/Aryl Sulfatase were added to 3 ml urine and incubated for 30 min at 56°C. Afterwards the extraction of the basic drugs and Drugs-of-Abuse (DOA) was performed according to a validated method on a SPE cartridge. This step was followed by the injection of 1 µl of the extract into the GC-ToF-MS.

To perform a sensitive analysis the data were collected at a high detector voltage. A ToF system allows detecting every eluting analyte on a very high data rate. This allows the sensitive detection of very small amounts of psycho active substances. This is mandatory, since the NPS are excreted out of the body in small concentrations, the metabolites are excreted in an even smaller concentration however metabolites provide an important information on when the drug was abused and which drug was consumed. The separation of the mixture is performed in 14 min, followed with an automated deconvolution, which allows determining even coeluting substances.

In a library search the spectra of the drugs in the current analysis were then compared to the spectra of already entered drugs. Such libraries are commercial and for free available, but own spectra of relevant substances can be added. Such libraries contain hundreds of spectra of NPS and their metabolites (SWGDRUG.ORG). Possible structural modification of analytes can be determined, if the probability (match with the spectra in the library) is reduced. Additional research could be done for an unknown substance with the suspicion for NPS.

Data Analyses

Completed interview forms and printouts of the urine analyses were pseudonymized using a code based on letters from a patient's given name and his birthday. The documents were sent to the LVR Klinik Essen for data entry and statistical analyses.

RESULTS

Self-Reports of NPS and Other Drug Use

Recruitment data refer to only 7 out of 8 participating sites; in one hospital, documentation of recruitment failed. During recruitment, 475 patients in the 7 hospitals were admitted to treatment with a dependence diagnosis for one or more illicit substances; 10.1% of these patients were excluded because of language problems, 10.7% because of or cognitive, psychiatric or substance related problems, and 22.1% refused participation or failed to give written consent. In addition, 2.7% did not complete the interview. Therefore based on 7 out of 8 participating sites, it is estimated that 54.3% of patients were finally included in the analysis.

In total, the eight study sites investigated n = 295 patients which could finally be analyzed. More than 4 out of 5 patients had an opiate related diagnosis (**Table 1**), and about half were transitions from opioid maintenance treatment, either for detoxification from concomitant substance use, or for detoxification from the maintenance drug. There were also high rates for diagnoses related to other substances of abuse. Rates of employment, living with partner, or living with children were low in this generally male sample.

In accordance with the substance related diagnoses, the vast majority of patients reported of lifetime use of heroin, but also alcohol, cannabis, cocaine, and amphetamines (**Figure 1**). These substances had also been used during 30 days before admission to detoxification treatment. Not counting nicotine, prescribed medications and maintenance drugs, more than one psychotropic substance during the last 30 days had been used by 86.0% of patients. The mean number of recently used substances was 3.3 (SD 1.8). Some substances with high lifetime prevalence (MDA/MDMA "Ecstasy," LSD, and Psilocybin) had low or nearly zero prevalence during the last 30 days. Gabapentinoids, namely pregabalin, also belonged to the 10 substances with highest lifetime prevalence, and also had been used recently (20.0%) by a substantial proportion of patients. Note that the prescription of pregabalin for substance abusers is considered a malpractice in Germany.

The proportion of patients with any self-reported lifetime NPS use was 32.6%. Almost all NPS users had consumed synthetic cannabinoids such as "spice" (32.1% of the total sample, **Figure 2**), synthetic stimulants had been used by 4.4%, other NPS (reported as "synthetic angel dust," "synthetic ketamine," 2CB, "micros," "Armageddon," or DMT) by 3.1%, and herbal drugs by 2.0%. The rate for synthetic cannabinoid use during the last 30 days was 2.0%, and 0.3% (1 patient) for each of the other NPS categories.

The total number of reports about consumed NPS was 126. Sixty-seven of these (53.2%) consisted of less than 5 episodes, 29 (23.1%) of 5- to 50, and 20 (15.9%) of more than 50 episodes. In 10 cases (7.9%) the number of episodes was not clear. There were 42 different patients (14.3% of the total sample) who had consumed NPS 5 times or more or for an unclear number of times during lifetime.

Patients reported whether they had ever used a psychotropic substance regularly, i.e., at least weekly. Cannabis, heroin cocaine, alcohol, and heroin were the substances with the highest lifetime prevalence of regular consumption (**Figure 3**). Only a small proportion of patients reported of regular NPS consumption during lifetime (**Figure 4**); the most important type in this respect were synthetic cannabinoids (5.6%).

There were 77 statements about specific reasons or circumstances of NPS use. In only one case a pleasant

TABLE 1 | Sociodemographic characteristics and substance use diagnoses of the study sample (n = 295).

Female	21.2%
Male	88.8%
Age	Range, 19–64 years Mean, 39.0 years; SD, 8.4 years
Migrant background[1]	42.1%
Living with partner	16.9%
Living with children	13.1%
Employed full-time or part time	13.4%
Daily cigarette smoker	95.9%
Substance use diagnoses (abuse or dependence)	
Opiates	81.8%
Alcohol	38.7%
Cannabis	38.4%
Cocaine	34.0%
Benzodiazepines	25.9%
Amphetamines	12.1%

[1]*Patient and/or at least one parent was foreign born.*

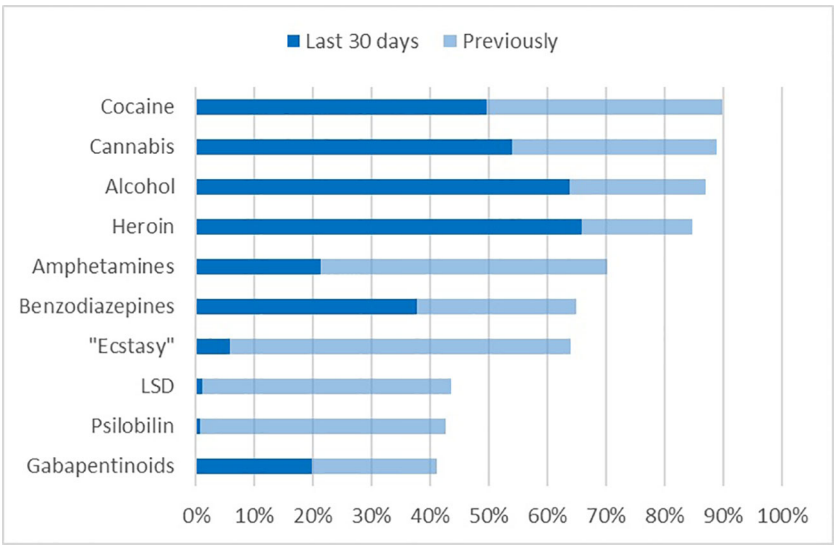

FIGURE 1 | Top 10 of lifetime prevalence of substances of abuse, and their recent use.

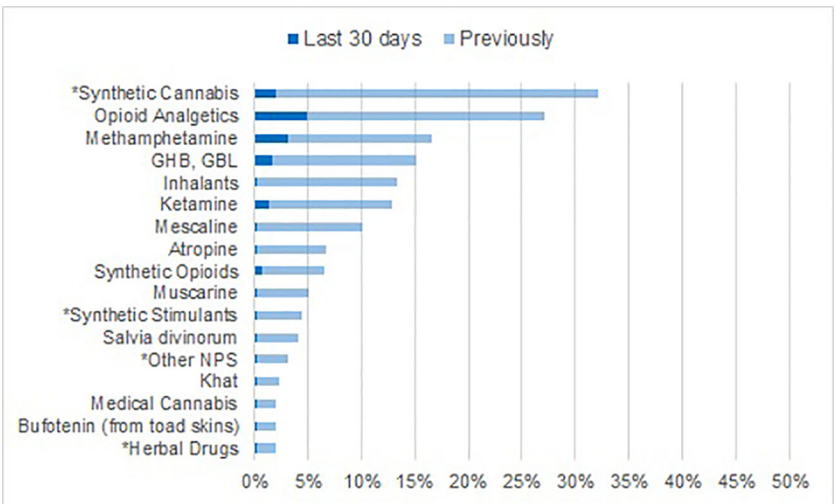

FIGURE 2 | Lifetime prevalence and recent use of other substances including *NPS.

psychotropic effect of the substance was mentioned as reason for consumption. Curiosity, exploration or an accidental offering were mentioned in 29 cases (37.6%). In 27 cases (35.1%), NPS were used in supervised surroundings, i.e prison (19 times, including 10 statements that the substance could not be detected by drug screenings there) or therapeutic settings (8 times). According to 5 statements (6.5%), NPS served as substitute for other drugs, and 4 statements (5.2%) were about non-detectability in drug screening, without further specification of the circumstances.

Urine Analyses

Additional urine analyses using a broadband GC/MS approach were carried out for patients from 5 of the participating sites (n = 181). Patient characteristics were very similar to the total group (mean age 39.1 years, 20.9% females, 39.2% migrant background, 82.3% with a diagnosis related to opioid use, 52.5% from opioid maintenance treatment). The pattern of results closely resembles that of self-reported substance use during the last 30 days (**Figure 5**). The substance class most frequently found was opiates (excluding opioids, i.e., maintenance drugs), followed

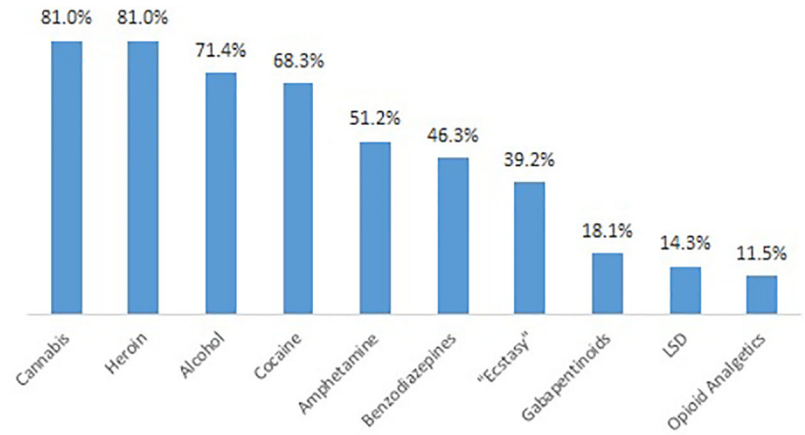

FIGURE 3 | Top 10 of substances used regularly during lifetime.

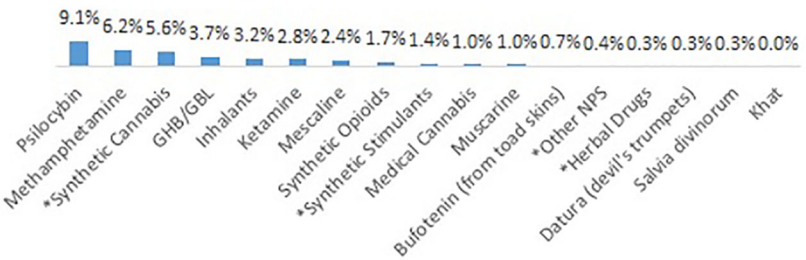

FIGURE 4 | Other substances used regularly during ifetime, including *NPS.

by cannabis. NPS were found in none of the 181 samples. In addition, pregabalin was found in 20.1% of the samples. If an NPS had been used in the past, this was in more.

DISCUSSION

To our knowledge, the present study is the first to investigate the NPS use history of "classical" drug users in detoxification treatment. The present sample consisted of mainly male patients, mostly older than 30 years, and with a low employment rate. The vast majority was opiate dependent, and especially the rate of recent heroin use was high.

About one third of the sample reported of NPS lifetime use, but recent use was extremely rare. Moreover, more than half of NPS lifetime consumption consisted of less than 5 episodes, and about three fourth consisted of 1 to 50 episodes. Accordingly, rates for lifetime regular use (at least weekly) were very low. In accordance with self-reports, the GC/MS urine analyses did not produce any result positive for NPS.

The vast majority of used NPS were cannabimimetics, while synthetic stimulants and hallucinogens were infrequent. That

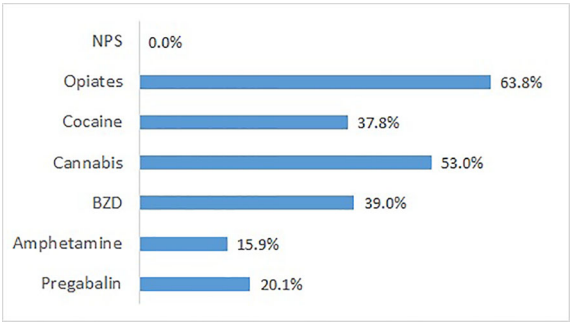

FIGURE 5 | Substances found by GC/MS analysis of urines sampled at admission, except prescribed medication (n = 181 patients from five detoxification wards).

does not mean that patients generally did not try out substances with such effects, as documented by the high rates of lifetime use of longer known substances, for example LSD, psilocybin, or MDMA ("ecstasy"). The markedly different lifetime use of these substances compared with NPS might in part be explained by the birth cohort of the present sample. When NPS appeared on the market, patients were mostly past their early 20s and perhaps beyond the age of experimenting with different substance classes. Nevertheless, according to patient reports, one third of NPS had been consumed out of curiosity, or to try out an unknown substance. In addition, nearly half of reported NPS were used in an institution (prison, or treatment facility) where drug use was sanctioned and NPS were not included into drug testing, and/or because it temporarily served as a substitute for other drugs.

The prevalence rate for recent NPS use in the present study was lower than in previous studies with other drug using groups, i.e., injecting drug users from Hungary and Scotland (15, 16), drug using patients in France (17), patients with substance use disorders in Scotland (4), or Swedish patients in opioid maintenance treatment (20). Moreover, cathinones are more prevalent in other studies (17). Regional or national differences between drug markets, including legal regulations, might play a role here. For example, in Switzerland NPS were rarely found in presentations to emergency rooms due to acute toxicity of psychoactive substances (21, 22) and were therefore considered not to be an important health issue, in contrast to other countries (23). Generally, members of a traditional drug scene dominated by opiate use in combination with cocaine, alcohol, cannabis, and/or benzodiazepines do not seem to prefer substances with hallucigenic properties. With regard to cannabimimetics, it could be argued that there is little reason for their continued use outside of prisons or treatment facilities, if cannabis, although controlled by the law, is easily available and its synthetic NPS versions are legally sanctioned. Moreover, many users experience psychological or health problems (9, 24), for example panic attacks, nausea, or circulatory problems (19), a fact that could further reduce demand for these substances.

So NPS had not been added to the range of "classical" substances of abuse in the investigated group. Instead, interview and urine data indicated an important role of pregabalin. In the last ten years, pregabalin has been extensively prescribed off-label for psychiatric conditions such as bipolar disorder, alcohol/narcotic withdrawal states, and ADHD, and it has entered the black market (25, 26). The principal population at risk consists of patients with other current or past substance use disorders, mostly opioid and multi-drug users who consume pregabalin in high dosages to achieve euphoria and also to reduce withdrawal symptoms, or to potentiate the effects of methadone (27). Pregabalin use was detected for example in 10.7% (28) and 14% (27) of hair specimens from of opioid maintenance patients in Italy, and in 4 to 17.7% of urine samples from opioid maintenance patients in Switzerland (29), Ireland (30), Sweden (20), and Israel (31), while one other study found zero prevalence in hair samples (32). The present finding indicates a constant or even increasing problem concerning pregabalin in the population of illicit drug users.

Limitations

For determination of NPS use through face-to-face interviews we included several types and examples of NPS, and included the category "other NPS." Such a combination of checklist and generic questions were found to reduce underestimation of NPS use (33). Still, it is conceivable that the actual prevalence of lifetime NPS use is higher than here determined, for example because patients are not always precisely aware about which novel substances they consume (20). Nevertheless, we assume that patients are aware of whether those substances which they consume frequently or regularly are NPS or not, so that we consider the very low rates for regular use and for frequent use as valid.

Another concern is the selection and self-selection of patients for this study. Findings only refer to patients who were not prevented from participation by language, psychiatric, cognitive, or drug-related problems (in total, more than one fifth of the patients admitted to drug detoxification), and who did not refuse to participate (also more than one fifth). It is unknown to us whether these groups of patients might show a distinct pattern of NPS (non-)use.

CONCLUSIONS

NPS use in the studied population was mainly restricted to trial use or to temporary use in restricted contexts such as prisons. If such a consumption is considered worrisome, inclusion of NPS into urine drug screenings would probably further decrease consumption rate. It is possible that future cohorts of classic drug users will show higher rates of NPS, since the majority of the current sample had been in their late twenties or older when NPS emerged on the market and they were already used to other types of substances. Nevertheless, the profile of NPS, apart from cannabimimetics, seems not meet the preferences of the here studied patient group, e.g., drugs with hallucigenic properties are rarely used.

The high rate of pregabalin abuse in the current sample resembles findings in other countries with similar patient samples. This reminds us that legally prescribed drugs need to

be closely monitored for their abuse potential. Other examples for this phenomenon are nonmedical use of benzodiazepines or of opiate analgesics.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethik-Kommission, Medizinische Fakultät der Universität Duisburg-Essen, Robert-Koch-Straße 9-11, D-45147 Essen, ethikkommission@uk-essen.de (file number 18-8580-BO). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS and NS designed the study, carried out the data analysis and interpreted the results. MS wrote the manuscript. JS and LS designed and carried out analyses of biological samples and wrote a description of the technical details. UB, MC-R, RS, HE, TK, BZ, and AN discussed the study design, organized the acquisition of data and contributed to the interpretation of results. The authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

The study was conducted as part of project JUSTSO, funded by the European Union's Justice Programme — Drugs Policy Initiatives (number 806996 — JUSTSO — JUST-2017-AG-DRUG). The urine analyses were financially supported by Fachverband Qualifizierte stationäre Akutbehandlung Drogenabhängiger e.V.

ACKNOWLEDGMENTS

The authors wish to thank all the colleagues involved in the data collection, among them Meruyert Akhmedyarova (Paderborn), Doris Wagner (Krefeld), Laura Pohlmann (Castrop-Rauxel), and Torsten Grigoleit (Langenfeld).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

OPINION
published: 16 July 2020
doi: 10.3389/fpsyt.2020.00700

New Trends of Substance Abuse During COVID-19 Pandemic: An International Perspective

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Keywords: substance abuse, COVID-19 pandemic, opioids, new benzodiazepines, new psychoactive substances

OPEN ACCESS

Edited by:
Fabrizio Schifano, University of Hertfordshire, United Kingdom

Reviewed by:
Laura Orsolini, University of Hertfordshire, United Kingdom
Stefania Chiappini, University of Hertfordshire, United Kingdom

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *10 May 2020*
Accepted: *03 July 2020*
Published: *16 July 2020*

Citation:
Zaami S, Marinelli E and Varì MR (2020) New Trends of Substance Abuse During COVID-19 Pandemic: An International Perspective. Front. Psychiatry 11:700. doi: 10.3389/fpsyt.2020.00700

INTRODUCTION

In the late 2019, an epidemic of cases with severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) has spread from China to the rest of the world, resulting in a global pandemic (COronaVIrus Disease 19, COVID-19 pandemic). Starting from the first months of 2020, several restrictions have been imposed by governments to face the public health threat, impacting the usual patterns of drug abuse throughout the world (1). The temporary border closure affected the usual illicit drug route of shipping from country to country, resulting in scarcity of classic street drugs (2). Moreover, restrictive measures internationally adopted by several countries made necessary to close all the usual recreational settings in which stimulants drugs are commonly abused. On the contrary, since in house drugs abuse became the most feasible option, other private encounters might have caught on, such as chemsex (3). In particular this phenomenon, which originated mainly in the large cities of Northern Europe, has gradually spread across the continent and is now a worrying reality in western European countries. Other rising trends of substance abuse include cognitive enhancers and new psychoactive substances (4, 5). Furthermore, the consequent social isolation and the likely limited access to detoxification centers caused additional psychological distress, pushing drug addicts toward alternative psychotropic drugs, possibly through illegal online marketplaces. An international overview of the new trends of drug abuse during the current COVID-19 pandemic and the related health risks are hereby discussed, taking into consideration different points of view.

Can New Trends of Substance Abuse Be Identified During COVID-19 Pandemic?

As we write this opinion paper, the social and economic restrictions due to the coronavirus pandemic have already seriously impacted health and social fields. COVID-19 outbreak has led to the implementation of social distancing to contain the spread of the disease, changing people's lifestyle. People have been going through a moment of anxiety and fear for their health and their jobs, and they are forced to live an unfamiliar lifestyle, deprived of relationships. Furthermore, the condition of people with psychological troubles may have worsened during the pandemic as a result of the unconsciously mirroring of others feelings (6). This peculiar situation may have pushed more people toward a deviant behavior linked to licit or illicit substance use, and it may have been a good opportunity for drug dealers to attract new customers. However, global issues have not favored the usual trade business. Indeed, social distancing has substantially reduced drug trafficking on the streets, pushing consumers toward illegal markets on the dark web or through messaging applications (7).

Furthermore, the paucity of classic drugs, together with the impossibility to go out to look for those, might have induced addicts to misuse psychoactive prescription drugs such as benzodiazepines (8–10). In this concern, although there is limited scientific evidence, the impact of the COVID-19 pandemic could lead to substantial modifications in substance use patterns, and an increased risk of substitution, adulteration, contamination, and dilution with a potentially harmful substance. As such, reports from forensic science and toxicology laboratories are crucial for the early detection and response to such events (11, 12). Moreover, in this period of home confinement, users might no longer be looking for "socializing" substances to be used in recreational settings, but for psychotropic drugs to be consumed in solitude.

Even short periods of isolation and loneliness can have negative consequences on physical and mental well-being. The feeling of isolation can lead to anxiety and anger, and even sleep disorders, depression, and post-traumatic stress disorders, which may be underestimated due to the lack of specific screening tools (13, 14). Moreover, psychiatric assistance from health professionals is not assured due to the temporary monopolization of psychiatric facilities for COVID-19 treatment (15). In addition to drug addicts using prescription sedatives available at home, some may have shifted to narcotics such as new synthetic opioids or designer benzodiazepines, available online. Indeed, these two classes of new psychoactive substances showed the highest consumption increase in 2019 (16–19).

COVID-19 Health Risks Associated to Psychotropic Drug Use

The European Monitoring Centre for Drugs and Drug Addiction (18), in Europe, and the National Institute on Drug Abuse (20), in US, first sounded the alarm, raising concerns about the vulnerability of people with substance use disorders to COVID-19, especially because of opiates (e.g. heroin), synthetic opioids, and methamphetamine effects on the respiratory system and pulmonary health (21–23). Comorbidities, including cardiovascular and other respiratory diseases, have proven to worsen prognosis in patients with other coronaviruses affecting the respiratory system, such as SARS-CoV and MERS-CoV (24).

COVID-19 affects the respiratory tract and has a high mortality rate among elderlies and people with comorbidities such as diabetes, cancer, and breathing difficulties. Given the high prevalence of chronic diseases among drug users, many may have been at risk of respiratory distress and death if infected with COVID-19 (20). It is also worth mentioning that smoking heroin or crack cocaine addicts may undergo asthma and chronic obstructive pulmonary disease (COPD) (24). Moreover, people using high doses of prescription opioids or presenting opioid use disorder experience additional challenges for their respiratory health. Indeed, opioids act on the central nervous system with respiratory-depressant effects, and high doses may cause severe hypoxemia, which may lead to irreversible brain damage. Chronic respiratory diseases are already known to increase overdose mortality in opioid users, and reduced lung function due to COVID-19 could similarly threaten this population. There is also a high incidence of cardiovascular diseases among opiates, opioids, and cocaine users (25, 26).

DISCUSSION

At this time of crisis, the rapid implementation of extraordinary changes is not something "obvious" and "automatic", but requires a strong effort of adaptation and the active participation of all people, including drug users. Some may be better at withstanding a quarantine for many reasons, including people's personality. However, being in quarantine can be challenging for addicts, especially substance addicts. Forced isolation and difficulties to move around and obtain illegal substances can impact the behavior of drug abusers. As an example, reports of people violating the quarantine in search of drugs have multiplied in several Italian cities (27). Moreover, the psychological impact of quarantine may have exacerbated a number of mental health problems. Addictions are already a manifestation of psychological discomfort and these circumstances may have worsened psychophysical well-being. In terms of public mental health, the main psychological risk is high stress and anxiety (28). However, due to new and increasingly stringent measures and their effects on many people's lifestyle and wellness, an increase in alcohol and drug abuse is expected. Depression and self-harm behaviors leading to suicide have been also anticipated. Additionally, new obstacles for obtaining drugs will emerge, worsening the troubles of drug addicts. The current crisis prevents illicit drug trafficking on the streets and imposes the use of alternative methods for obtaining drugs *via* the Internet through specialized websites, and their subsequent shipment by private couriers. Hence, an increase in cannabis product online sales was recorded during the first 3 months of 2020 (29). In the authors' opinion, a straightening of postal police controls should prevent the spread of this phenomenon. As already mentioned, since recreational drug use usually occurs in groups or crowded environments, the implementation of social distancing in response to the COVID-19 crisis may have modified drug use patterns: a shift to substances that can be consumed in solitude and have a relaxing effect, such as opioids, new synthetic opioids, or new benzodiazepines, is expected (18, 20, 25). In addition, a potentially reduced access to legal substitution treatments is of concern to drug addicts and drug addicts services pushed for an easier access to drugs such as methadone and buprenorphine to help alleviate withdrawal symptoms, reduce drug craving, and prevent opioid overdose (30). In fact, social distancing could also increase the likelihood of isolated overdose and subsequent failure to administer naloxone by health services, potentially causing more deaths. During the pandemic, it may be necessary to suspend or reduce the number of face-to-face meetings and implement alternatives. In our opinion, the continuous operation of drug treatment services, including the continuous supply of substitute therapies and other essential drugs and the implementation of contingency plans to address any shortage of therapies and tools, should be ensured. Before the pandemic, patients receiving methadone had to follow an approved treatment program for opioid addicts, under which the drug could only be administered daily and under supervision. This may not be possible at this time. Patients under opioid addiction treatment with a reasonable degree of stabilization should obtain several doses of methadone in sufficient quantity for several days or refill their buprenorphine prescription over the phone (26). In the opinion of the authors, the public health community should also

focus efforts on the development of virtual support meetings for people with psychiatric disorders or undergoing addiction therapy and the possibility to take home medication (31, 32). In addition, it is worth noting that there is a high prevalence of HIV infections, viral hepatitis infections, and liver cancer among intravenous drug users, leading to a weakened immune system. Therefore, the current health crisis could limit access to healthcare, putting this population at risk for many diseases, as hospitals and clinics are already stretched to their maximum capacity (15). These people, who are already stigmatized and underserved by the health system, could therefore face even greater barriers to treatment, increasing their chances of falling ill and being rejected by charities, forcing them to live on the streets or in squats. Self-isolation, required by lockdown and subsequent movements limitation, for homeless drug addicts can be problematic, as they have no choice but to spend time in public spaces with limited personal hygiene, increasing the risk of infection with COVID-19. Addressing the needs of homeless or unstable drug users is important. The efforts of not-for-profit organizations and associations could help in the short term, but they also must address the increasingly stringent measures dictated by governments and closely monitor the safety of their workers.

To conclude, as suggested by the US National Institute on Drug Abuse and the European Monitoring Centre for Drugs and Drug Addiction, a range of resources has to be developed to support situational awareness and inform relevant and timely actions for preparedness and response activities at national and international level related to the impact of the pandemic on the drug situation and eventual new trends of drug abuse. Psychiatric and psychological assistance to addicts undergoing substitution therapy should be implemented through any possible alternative mean during COVID-19 pandemic.

AUTHOR CONTRIBUTIONS

SZ provided initial idea and construct of the opinion. EM and MV co-authored and edited the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 22 July 2020
doi: 10.3389/fpsyt.2020.00705

Cathinone Use Disorder in the Context of Slam Practice: New Pharmacological and Clinical Challenges

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OPEN ACCESS

Edited by:
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Reviewed by:
M. Foster Olive, Arizona State University, United States
Francesco Paolo Busardò, Sapienza University of Rome, Italy

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: 04 June 2020
Accepted: 06 July 2020
Published: 22 July 2020

Citation:
Schreck B, Guerlais M, Laforgue E, Bichon C, Grall-Bronnec M and Victorri-Vigneau C (2020) Cathinone Use Disorder in the Context of Slam Practice: New Pharmacological and Clinical Challenges. Front. Psychiatry 11:705. doi: 10.3389/fpsyt.2020.00705

Background: "Slam" has emerged since 2008 as a new international phenomenon among men who have sex with men (MSM); it consists of the intravenous injection of drugs before or during planned sexual activity. The practice of slam is associated with the use of psychostimulants, including synthetic cathinones.

Methods: All spontaneous notifications (Nots) of slam practice reported between January 2012 and October 2019 at the Nantes addictovigilance center in France were collected and analyzed. The purpose of this work was to analyze cases of slam to characterize cathinone use disorder according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and to further our knowledge of slam practice based on data on drug use, risk taking and harmful consequences.

Results: We collected 39 slam Nots. The severity of cathinone use disorder was mild, moderate and severe for 18%, 12%, and 58% of the patients, respectively. "Much time spent using cathinone" was the diagnostic criterion most often cited (82%).

Conclusions: To the best of our knowledge, our study is the first to evaluate the presence of a cathinone use disorder. Cathinone use disorder seems particularly important in this population of users, and negative consequences of slam practice appear quickly.

Keywords: slam, slamming, chemsex, party and play, new psychoactive substances, cathinones, cathinone use disorder

INTRODUCTION

Slam has emerged as a new phenomenon in Western Europe (1, 2) among men who have sex with men (MSM) since 2008 and has also emerged in Southeast Asia (3–5), North America (6, 7), and Australia (8, 9), where it is called "party and play" or "intensive sex partying". According to the French Monitoring Centre for Drugs and Drug Addiction (OFDT), slam is a form of chemsex defined by (i) the use of psychostimulants (ii) through the intravenous route of administration (iii) in a sexual context (10). For several years, there has been emerging evidence focusing on high-risk

sexual practices and infectious harms (11–15) but not on the substances used in this specific context. In Europe, and more particularly in France, this practice is associated with the use of specific psychostimulant substances in the synthetic cathinone family. Synthetic cathinones are a large group of stimulants chemically related to cathinone, a phenethylamine that is the most potent amphetamine-like compound naturally present in the khat plant (*Catha edulis*, Peter Forsskål, 1775) (16). The molecular structure of cathinone can be modified in various ways to produce a series of compounds chemically related to it, and this technique has been used to circumvent international drug laws (17). The pharmacological properties of synthetic cathinones differ from molecule to molecule, but they exert their effects by increasing the concentration of catecholamines such as dopamine, serotonin, and norepinephrine in the synaptic cleft (16). Animal studies have shown that synthetic cathinones have reinforcing properties and abuse liability (18). Synthetic cathinones are used for their stimulant and entactogenic effects; desired effects include euphoria, intensification of sensory perceptions, increase in sociability, increase in energy, and increase in sexual performance, which is precisely why they are used in slam (16). In fact, Weatherburn et al. (19) identified motivations for combining sex and these drugs; they increase libido, confidence, disinhibition, and stamina, enhance qualities of the sex, and make other men seem more attractive, increase physical sensations, intensify perceptions of intimacy, and facilitate a sense of sexual adventure. Nevertheless, cathinone use is not without risks, since fatalities have been associated with the consumption of various cathinones (20). Mephedrone, 3-methylmethcathinone (3-MMC), and 4-methylethcathinone (4-MEC) are the most commonly substances used in slam (10, 21), but new synthetic cathinones appear monthly on the illicit drug market, making knowledge of these substances and their impact on users even more complex. In 2018, 130 different cathinones were identified by the European Monitoring Centre for Drugs and Drug Addiction (21). No accurate data are available in the literature about the specific effects of synthetic cathinones in the context of slam, how they are used, and if they induce substance use disorder, negative consequences, withdrawal syndrome, tolerance, or craving.

France is the only European country with a national system dedicated to observing and assessing the abuse and dependence potential of psychoactive substances, medicines and drugs (22). The addictovigilance centers are responsible for the collection of cases of drug dependence, abuse, and misuse related to the taking of psychoactive substances through notifications (Nots) by health professionals. These centers are organized in a network, and there are thirteen centers spread throughout France. The missions of the addictovigilance centers are defined in the public health code (23). The three major ones are (i) to collect data and evaluate the dependence potential of the identified psychoactive drugs; French regulations make it mandatory to report all cases of serious abuse and drug dependence related to the intake of psychoactive substances or herbs as well as any other drug or product (24, 25); (ii) to provide information on the risk of abuse or dependence on psychoactive substances; and (iii) to carry out scientific research.

Since 2012, the addictovigilance center of Nantes has been notified of several cases of the use of psychoactive substances, including synthetic cathinones, in the context of slam practice. It is therefore within the framework of its missions that the Nantes addictovigilance center has been able to obtain data on the slam practice in the Pays de la Loire region.

The purpose of the present study was to analyze cases of slam reported to the Nantes addictovigilance center to characterize cathinone use disorder and to further our knowledge of slam practice based on data on drug use, risk taking, and harmful consequences.

MATERIALS AND METHODS

Those Who Notify

The Pays de la Loire addictovigilance center is located in the Nantes University Hospital. Notifications of psychoactive substance use in a sexual context come from general practitioners, specialists working in hospitals or in private offices, and other health professionals. The AIDES association, which is particularly involved in prevention and risk reduction, also participates in Nots. In fact, AIDES works with people with sexually transmitted infections (STIs) [including human immunodeficiency virus (HIV) and hepatitis C virus (HCV)] and aims to reduce risky practices. All healthcare professionals (regardless of their field of expertise) are required to anonymously report cases of serious drug abuse and dependence associated with the use of substances or plants with psychoactive effects (26, 27). These spontaneous Not reports by healthcare professionals are key for determining "real life" drug misuse and abuse and for identifying new nonmedicinal drugs that present a risk to public health.

The Collected Data

The addictovigilance center in Nantes has sensitized practitioners concerned with slam practice to collect, in the course of notification, important data related to drug risk evaluation in this particular context. According to the French National Agency for Medicines and Health Products Safety (ANSM) notification form, the three types of information collected regarded sociodemographic characteristics, medical history, and drug use; drug use was defined according to the substance disorder diagnostic criteria of the DSM-IV (28) for the Nots before 2013 and the criteria of the DSM-5 (29) for all other Nots. In this context of the analysis of mandatory Nots, which is one of the main duties of the French addictovigilance centers, no permission to use a database was required (23).

Nots collected at the addictovigilance center of Nantes between January 2012 and October 2019 were extracted using the keyword "slam" in the center's database. The data were as follows:

- Sociodemographic characteristics (age, family status, employment status);
- Medical history (HIV status, HCV status, lifetime and current substance use disorder, lifetime, and current psychiatric disorder);

- Information related to drug use (drug name and family drug name, dose by intake and frequency of administration, routes of administration, effects sought, effects felt, unpleasant symptoms felt after taking drug, perceived negative consequences on health and in the socioprofessional environment, tolerance, weaning, craving, desire to stop, and risk taking related to use).

The data were collected and analyzed with Microsoft® Excel software.

RESULTS

Characteristics of the Nots

In total, the Nantes addictovigilance center collected 39 slam Nots. The first notification was reported at the Nantes addictovigilance center in 2012. The number of reports varied across the years, but we observed the maximum number of cases in 2017. The results are shown in **Figure 1**.

Characteristics of the Subjects

We found that 34 slammers were the subject of 39 Nots corresponding to different slam sequences. Over the 2012–2019 period, two slammers were the subject of two Nots, and one slammer was the subject of four Nots. Sociodemographic and medical history data are shown in **Table 1**. The median age was 38 years (min–max: 23–63), and the median duration of slam practice was 3 years (1–5). More than four-fifths of the sample were HIV positive (82%, 18/22), 27% (6/22) were infected with HCV, and 18% (4/22) were coinfected with HIV and HCV. More than two-thirds of the subjects (69%, 22/32) reported a history of substance use disorder.

Characteristics of the Slam Practice

Psychoactive Substances

During slam sessions, all the subjects used drugs in the cathinone family: 4-MEC (20/34 users), 3-MMC (22), mephedrone or 4-methylmethcathinone (4-MMC) (8), pentedrone (8), NRG3 (a combination of cathinones) (7), 3-methylethcathinone (3-MEC) (5), methylone (3), α-pyrrolidinovalerophenone (α-PVP) (1), and 4-P (1). Some slammers used cathinones in combination with other psychoactive substances; among the 18 drugs used during slam sessions, nine substances did not belong to the cathinone family: γ-butyrolactone GBL (11), γ-hydroxybutyrate (GHB) (5), cocaine (4), poppers (5), cannabis (3), methamphetamine (2), methylenedioxymethamphetamine (MDMA) (1), ketamine (1), and alcohol (1). The set of psychoactive substances used according to the number of citations is shown in **Figure 2**.

Routes of Administration and Frequency

For all users, the administration of cathinones was intravenous. The frequency of the intake varied according to each user, ranging from two per session to one administration every hour, until the exhaustion of the availability of the drugs. The frequency of slam practice was monthly for 29% (10/34 users) of the users, multimonthly for 21% (7) of the users, weekly for 12% (11), and multiweekly for 6% (2); this information had not been entered for four slammers.

Polydrug Use

The median number of drugs used when practicing slam was 3 (1–9). Polydrug use occurred in 85% (29/34) of the subjects; nevertheless, we did not have the information to say that the polydrug use took place during the same session or during different sessions. However, the users reported never mixing drugs within a syringe.

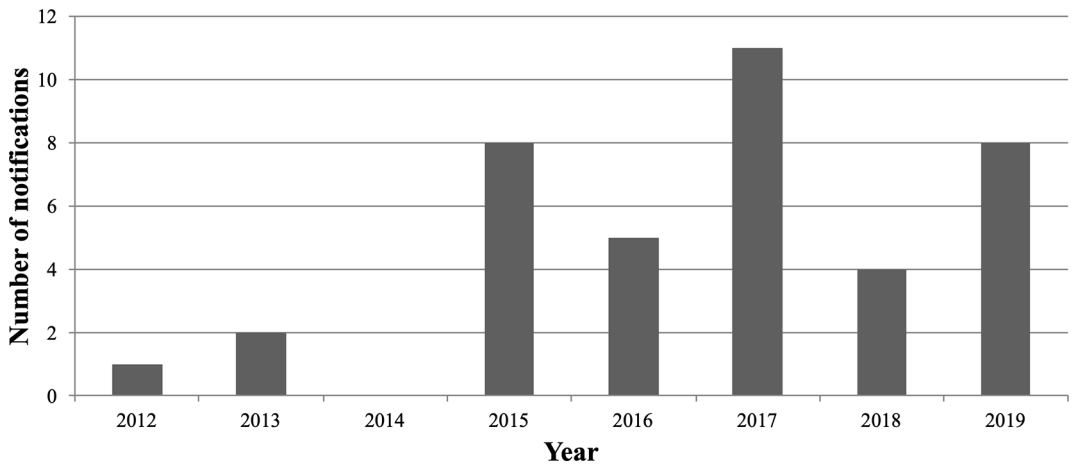

FIGURE 1 | Number of notifications to Nantes addictovigilance center per year.

TABLE 1 | Sociodemographic and medical history of the sample.

	N	Median (Min–Max) Percent (N)
Age (years)	34	38 (23–63)
Duration of slam practice (years)	30	3 (1–5)
Marital status: couple	29	62% (18)
Employment	29	62% (18)
Substance use disorder	32	69% (22)
Mood disorder	22	18% (4)
HIV-positive	22	82% (18)
HCV-positive	22	27% (6)
Syphilis	22	27% (6)

Characteristics of Cathinone Use

Cathinone Use Disorder Diagnosis

Only one Not was reported in 2012, before the publication of the DSM-5. The slammer described in this Not presented with cathinone dependence according to the DSM-IV (28). From 2013, 29 slammers out of 33 presented with cathinone use disorder according to the DSM-5 criteria (29). The severity of cathinone use disorder was mild, moderate and severe for 18%, 12%, and 58% of the patients, respectively. The median number of diagnostic criteria met was 6 (0–11).

Cathinone Use in the Context of Slam

The percentage of the 33 slammers presenting with each DSM-5 Substance Use Disorder criterion is shown in **Figure 3**. "*Much time spent using cathinone*" was the diagnostic criterion most often cited (82%). Then, the "*hazardous use*" criterion ("*recurrent substance use in situations in which it is physically hazardous*") and the "*physical/psychological problems*" criterion ("*substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance*") were cited in 73% and 70% of the cases, respectively. The criteria on craving, tolerance and withdrawal, at 45%, 42%, and 27%, respectively, were less present among the slammers.

Health consequences (physical or psychological), with the exception of those experienced during the "comedown" period, and social consequences were entered in the Nots for some users and are shown in **Table 2**. Unpleasant symptoms were reported by the users in the "comedown" phase in the days following the use of the psychoactive substances in the sexual session. Several users described intense asthenia (24%, 8/34), anxiety with sadness (24%, 8/34), hallucinations (9%, 3/34), depersonalization (6%, 2/34), and paresthesia (6%, 2/34).

The desired effects reported by the subjects during the administration of synthetic cathinones were the following:

- Letting go: "well-being, relaxation, hovering" (62%, 21/34);
- Stimulation: "sexual arousal, increased endurance, increased alertness" (50%, 17/34);
- Disinhibition (35%, 12/34);
- Anesthesia and analgesia: "performing hard sexual practices, decreasing the sensation of pain" (18%, 6/34);
- Increased sensations (12%, 4/34);

Evolution of Drug Use

Among the 39 Nots, five involved the same three users over the 2012–2018 period, which allowed us to identify an evolution in terms of drug use. For the first slammer, Nots were reported in 2015, 2017, 2018, and 2019. In 2015, this subject reported using mephedrone, GBL, and poppers during slam sessions. In 2017, he reported using 3-MMC, pentedrone, and α-PVP. In 2018 and 2019, he reported only using 3-MMC. There was also a change in drug use patterns: in 2015, he began to use monthly by the intravenous and intranasal routes. Then, the route of administration became exclusively intravenous and he began using weekly in 2017 and 2018. He tried several times to cut down or stop participating in the slam practice but quickly relapsed; nevertheless, the Nots of 2019 informed us about a decrease in frequency with a multimonthly slam practice. For the

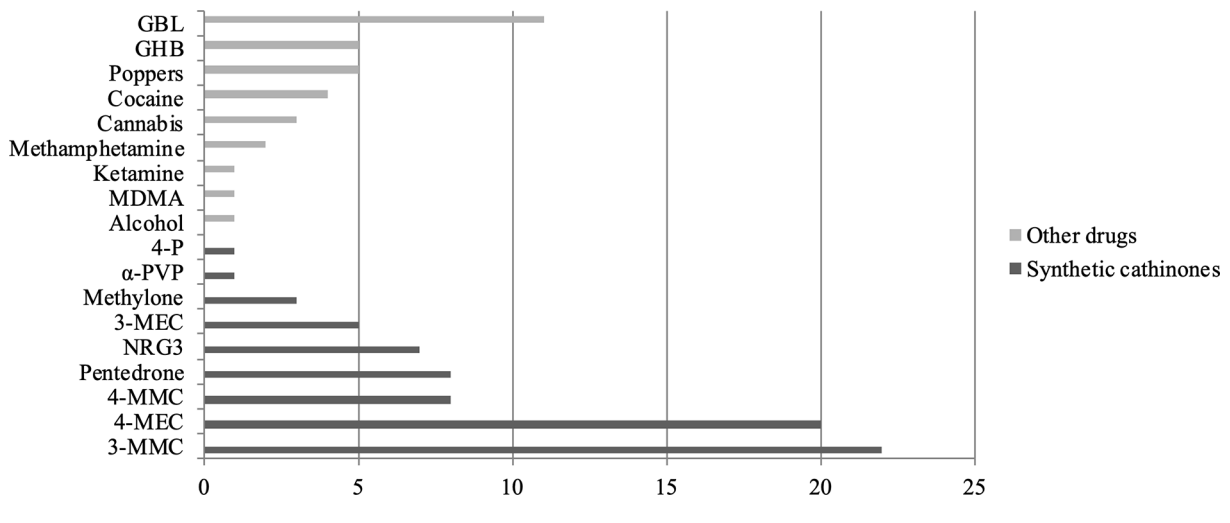

FIGURE 2 | Number of psychoactive substances used.

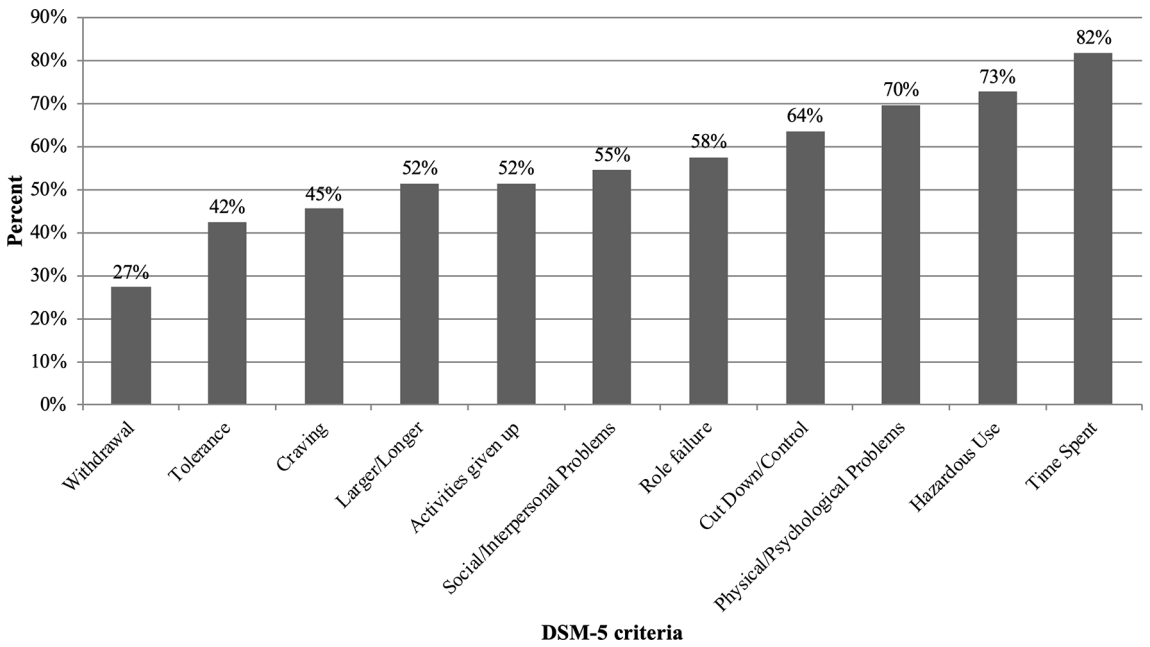

FIGURE 3 | Percentage of 33 slammers meeting the DSM-5 substance use disorder criteria.

TABLE 2 | Health and social consequences of cathinone use in the context of slam practice.

Health consequences	65% (22/34)
Psychological	26% (9/34)
Sadness	56% (5/9)
Asthenia	33% (3/9)
Anxiety	33% (3/9)
Loss of self-confidence	33% (3/9)
Apathy	22% (2/9)
Amnesia	11% (1/9)
Sleep disorder	11% (1/9)
Hallucinations	11% (1/9)
Suicidal ideation	11% (1/9)
Loss of appetite	11% (1/9)
Physical	38% (13/34)
Pain	31% (4/13)
Injection site injury	23% (3/13)
Syphilis infection	15% (2/13)
Anal lesion	8% (1/13)
Tachycardia	15% (2/13)
Weight loss	8% (1/13)
Sweating	15% (2/13)
Urinary retention	8% (1/13)
Tremor	8% (1/13)
Low blood pressure	8% (1/13)
HCV infection	8% (1/13)
HIV infection	8% (1/13)
Social consequences	53% (18/34)
Separation	44% (15/34)
Loss of work	24% (8/34)

second slammer whose Nots were reported across an 8-month interval in 2017 and 2018, there was no notable difference in the substances used and the modalities of use during the slam sessions. For the third slammer, two Nots were reported at a 1-month interval in 2016. He reported using cathinones multiweekly in a slam context. Strong cravings were reported in both Nots.

DISCUSSION

Comparison With National Cases and International Literature

Batisse et al. (30) synthesized all cases of chemsex practice reported to the French addictovigilance network for the period from 2008 to 2017. This analysis concerned chemsex practice without specifying the proportion of slam. We observed similarities between the national analysis and our regional slam analysis regarding (i) age, (ii) frequency of HIV, HCV and other STIs, (iii) psychiatric history, and (iv) substances most commonly consumed (3-MMC and 4-MEC). Polydrug use was high in both groups but was higher among the regional cases (national cases: 64%, regional cases: 85%), which might be related to the systematic inquiry in these cases, resulting from the regional awareness of the professionals involved and therefore the specific selection of slam cases. In contrast, differences emerged between the national chemsex analysis and the regional slam analysis. A history of substance use disorder was clearly more prevalent in our sample (national cases: 16%, regional cases: 69%); this difference may be explained by the systematic nature of the Nots inquiry in our sample. Finally, the mean duration of the practice was on average more than 1 year in the national cases and more than two and a half years (m=2.7, sd=±1.5) in the regional cases.

Thus, our cases appeared to be similar to those identified in the rest of France, except regarding drug use, which appeared to be more severe in this regional sample (substance use disorder and polydrug use background). This difference can be explained by the more complete data obtained in our sample relative to those in the routine spontaneous Nots usually performed in addictovigilance centers, i.e., those analyzed in Batisse et al. (30).

The median age of the slammers was similar to those found in international articles (4, 8, 31, 32). We also found that the slammers tended to have a job, which has been previously reported (8). The frequency of HIV infection has been very variable in the literature, ranging from 0.6% (33) to 100% (34), but our sample of slammers was in the upper range (4, 8, 15, 31, 33–37). In contrast, HCV infection was less common in our sample than in the literature (8, 15, 31, 35–38). There were similar findings regarding STIs (38). According to the international literature, slammers mostly use methamphetamine (8, 31, 34, 37), a psychostimulant substance about which we have much pharmacological data (39). Our entire sample reported using synthetic cathinones, about which we have very little data regarding their effects and toxicities (40, 41). Methamphetamine is known for its effects on sexual activity (42–44) through the activation of neurons in brain regions of the mesolimbic system that are involved in the regulation of sexual behavior (43, 44). This drug provides sexual disinhibition, endurance and sexual arousal (4, 31, 32),which is probably why it is used in slam. Methamphetamine is widely available in the United States of America (6), the United Kingdom (21), and Australia (31) but is almost absent in France or sold only in Paris at very high prices, explaining the preferential use of cathinones in the practice of slam in our sample. Considering the extremely high percentage of cathinone use disorder in our sample (88%), we can assume that the synthetic cathinones used by slammers seem as addictogenic as methamphetamine, which is a very potent amphetamine derivative (39). As in our sample of slammers, the literature has also noted the strong representation of poppers and GHB–GBL use in the context of slam practice (8). Risk behaviors associated with substance use, such as sharing of syringes or small equipment, were present at a higher level in our sample of slammers than in the literature, where they seldom occurred in more than 10% of slammers (31, 33, 34). The motivations of slammers to practice slam were the same as those found in the article of Bui et al. (31), that is, seeking disinhibition, endurance, sexual stimulation, and increased sensations.

Finally, the regional sample also seemed to have the same characteristics as those found in the international literature in terms of risk of STIs and motivations for slam practice. Nevertheless, the substances used were not the same, and risk behaviors associated with substance use were more severe in our sample.

Cathinone Use Disorder

Our study on slamming explored the synthetic cathinone use and related disorder. To the best of our knowledge, our study is the first to address the existence of a cathinone use disorder, both among slammers and the general population. This is an aspect of slam practice that is crucial to explore, considering that we have demonstrated that a cathinone use disorder was screened among 88% of the slammers; this result highlights the highly addictive nature of synthetic cathinone when used in this specific context. We did not find any articles describing cathinone use disorder. Nevertheless, it is interesting to take a closer look at khat, a plant that contains mainly cathinone, and although khat use disorder is not still recognized as a diagnostic entity, disorders related to khat use are being more frequently described in the literature. In fact, Duresso et al. (45) reported a prevalence of 73.8% of "khat use disorder" in a sample of 400 frequent Ethiopian chewers aged 16 and above. In a 2019 systematic review by Mihretu et al. (46), the prevalence of problematic khat use ranged from 20.6% to 80.7% in khat-chewing communities in Ethiopia, Saudi Arabia, and Somalia. Thus, it is clear that khat, which contains a derivative of amphetamine, can induce substance use disorder and that by their chemical proximity, synthetic cathinones are potentially capable of inducing substance use disorder. Cathinone use disorder seems to be an actual diagnostic entity that has not been clearly explored; therefore, our data are unlike previously published data, especially as they relate to a specific population with a particular practice.

In our sample, the three most prevalent criteria for cathinone use disorder were the time spent, hazardous use, and physical/psychological problems. The criteria on physical dependence (tolerance and withdrawal) were the two least represented criteria in our sample. As previously described by many authors and initially by Goodman (47), the key symptoms of addiction are the loss of control and the continuation of the use despite the negative consequences. We demonstrated that is also the case for cathinone use disorder. This is consistent with the international literature regarding khat use. For example, in the article by Duresso et al. (45), the criterion "continuation use despite physical/psychological problems" was the most prevalent; "tolerance" and "withdrawal" were among the least represented. The systematic review by Mihretu et al. highlighted the psychological dependence that complicates the use of khat (46). The results regarding stimulant use disorder are more nuanced. The most represented diagnostic criteria among methamphetamine and cocaine users were "withdrawal", "much time spent" and "social/interpersonal problems" according to Gilder et al. (48), and "quit/control", "hazardous use", and "social/interpersonal problems" according to Saha et al. (49).

Furthermore, the very high prevalence of cathinone use disorder is even more noteworthy when we consider the low duration of the slam practice in our sample. We can see how the use of cathinones can quickly become invasive in all aspects of life, with harmful consequences and loss of control. The presence of cathinone use disorder seemed obvious and impacted the majority of slammers in our sample, but it is necessary to consider the polydrug use and sexual context playing a large role in the practice of slam. Indeed, almost all slammers declared polydrug use during slam sessions, which can disrupt their perception of cathinone's effects or reinforce the addictive nature of cathinones, leading to overreporting a cathinone use

disorder. Thus, polydrug use can make it difficult to analyze and understand substance use in the context of slamming.

Pharmacological and Toxicological Aspects

Some data are available on the pharmacodynamics, pharmacokinetics, and toxicological properties of synthetic cathinones; these are studies using animals (40, 50, 51) and humans (52, 53), like clinical trials (54, 55). Moreover, we have seen that polydrug use affects the majority of subjects (85%). Polydrug use is more the rule than the exception in slam practice, and the use of combinations of substances can lead to pharmacodynamic and pharmacokinetic interactions. For example, the combination of synthetic cathinones, substances with high adrenergic potency, with sildenafil (phosphodiesterase type 5 inhibitor) and a vasodilator (such as poppers) would increase cardiovascular risk. Therefore, practicing slam exposes individuals to a high risk of pharmacodynamic interactions as well as pharmacokinetic interactions. Indeed, some antiretrovirals used in the treatment of HIV (such as ritonavir) are powerful enzymatic inhibitors likely to increase the toxicity of synthetic cathinones (56, 57); as a reminder, 82% of the users in our sample were infected with HIV. Thus, polydrug use in slam leads to increased physical (mainly cardiovascular) and neuropsychiatric risks, especially if the user suffers from preexisting illnesses. Moreover, high and frequent doses of drugs are often being used in long sessions of slam (4, 8, 31, 32, 58, 59), which increases the risk of toxicity of each product. The Nots did not provide the frequency and the number of injections and therefore the total quantity of drugs administered per session. Another important element concerns the drugs used as reported by the slammers. We have no certainty that what they used actually corresponded to what they had bought. Since 1999, in France, the National Detection System of Drugs and Toxic Substances (SINTES) scheme has intended to document the toxicological composition of illegal substances in circulation in France. The information incorporated in this system comes from two sources: the submission to the OFDT of the toxicology test results performed on seizures by law enforcement laboratories (French National Forensic Science Institute, Forensic Sciences Institute of the French gendarmerie and Customs laboratories) and investigations conducted by the OFDT on samples of substances obtained directly from users. Collection of these data is governed by a strict regulatory framework and conducted by specifically trained survey workers. The analysis of substances by SINTES makes it possible to know the scams being used, which are of three types: different products, unexpected quantities, and adulterations by cutting agents. In 2018, synthetic cathinones were the third most scammed products (60); this was particularly true with 3-MMC, which has been the subject of a large number of substitutions, especially ephylone. Moreover, at the European level (21), we know that a large proportion of the new psychoactive substances come from the Internet drug market, and a 2016 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) report (61) mentioned frequent scams on websites. Because of these scams, the risks of intoxication are high; depending on the particular molecule, there can be extreme variations in the doses that cause an effect as well as the toxicity thresholds. Thus, slam practice, beyond the risks of infection and risks related to sexual acts, poses a real pharmacological danger.

Strengths and Weaknesses

Our study has some limitations. First, health professionals and workers primarily report the most severe cases, which could have led to a selection bias. Moreover, our sample size was also relatively small, which limits the representativeness of this population of slammers; however, we must be careful not to stigmatize slammers (4, 15), as many users do not have problematic behavior and do not seek help from health professionals. In addition, the Nantes area differs from other areas in terms of its sexual networks and patterns of drug use, and it may not be possible to extrapolate our findings to other geographical areas. We assume that concerns about the disclosure of sensitive issues, such as sexual behavior and drug use, might still persist and that socially desirable answers could have been given to health professionals. Furthermore, this was a cross-sectional study that makes it very difficult to measure changes in the practices of slam users. Unfortunately, the notification form of the ANSM does not capture information relevant to behavioral addictions because it was designed to contribute to a pharmacological database. However, slamming is a complex behavior because it involves both substance use and sexual activity at the same time, with the drug use being at the service of the sexual behavior; sex and drugs are strongly entangled. Psychostimulant drugs make sexual practice more intense, more compulsive, and less controllable (4, 32, 59). These elements are also strongly suggestive of hypersexuality or sex addiction in slammers, but there are no data in the international literature regarding sex addiction in slammers (or chemsexers), probably because it can be difficult to distinguish between substance use disorder and sex addiction. In fact, we can assume that sex addiction could be a confounding factor in the detection of a cathinone use disorder in our sample; the desire to cut down, control, or stop the behavior, the craving, the persistence of behavior despite psychic, physical, or social consequences can also be connected to sex addiction. Unfortunately, the sexual aspect has not been explored in the Nots because this notification form was made to highlight new psychoactive substances, new patterns of use behavior or new types of harm related to substance use and was not made to characterize sex addiction or a hypersexuality disorder.

However, these limitations are compensated for by the strengths of the study. Our results are original, and there is no similar published work in the literature that provides a detailed analysis of intravenous substance use in a sexual context. All Nots were made by health professionals or workers in the health sector who had accurate data on each patient in their care; we have exhaustive data on substances used in the practice of slam, and screening for a substance use disorder was done according to the DSM-5 benchmarks.

Future Directions

Our work contributes to a better understanding of slam practice. We have seen that substance use disorder seems particularly important in this population of users, and negative consequences of slam practice quickly appear. This work partially addresses the lack of pharmacological knowledge on cathinone and associated substances that are usually used in slam; the goal is to better understand the effects of substances used in the slam practice to develop effective medical management and risk reduction counseling. Future work should focus particularly on the issues of hypersexuality/sex addiction, motivations, repercussions, and precipitating and maintaining factors in these practices among slammers. It is essential to maintain vigilance regarding slam practice, to try to analyze user trajectories in the evolution of their practice and not to stigmatize this community but rather to develop future relevant prevention messages.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

BS, MG-B, CV-V, CB, EL, and MG collected the data. BS, MG, and CB performed the analysis. BS, MG-B, and CV-V wrote the paper. MG and CB helped to draft the manuscript and participated in the discussion. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We are grateful to all of the people who took part in the notifications and especially Jeremy and Laurent from the AIDES association.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

BRIEF RESEARCH REPORT
published: 25 August 2020
doi: 10.3389/fpsyt.2020.00862

Reinforcing Effects of the Synthetic Cathinone α-Pyrrolidinopropiophenone (α-PPP) in a Repeated Extended Access Binge Paradigm

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Synthetic cathinones are designer psychostimulants that are derivatives of the natural alkaloid cathinone, and produce effects similar to more traditional illicit stimulants such as cocaine and methamphetamine. The pyrovalerone cathinones methylenedioxypyrovalerone (MDPV) and α-pyrrolidinopropiophenone (α-PPP) exert their effects *via* inhibition of presynaptic dopamine and norepinephrine reuptake transporters. While the reinforcing effects of MDPV in rodents are well-established, very few studies have examined self-administration patterns of α-PPP. Users of synthetic cathinones often engage in repeated binge episodes of drug intake that last several days. We therefore sought to determine the reinforcing effects of three doses of α-PPP (0.05, 0.1 and 0.32 mg/kg/infusion) under conditions of prolonged binge-like access conditions, with three 96-h periods of drug access interspersed with 72 h of abstinence. MDPV (0.05 mg/kg/infusion) was used as a comparison drug. Our results show that both MDPV and the high (0.32 mg/kg/infusion) dose of α-PPP are readily self-administered at high levels across all three extended access periods, whereas lower doses of α-PPP produce variable and less robust levels of self-administration. These results indicate that higher doses of α-PPP have reinforcing effects under conditions of extended access, suggesting the potential for abuse and a need for consideration in drug control policies.

Keywords: synthetic cathinone derivative, alpha-pyrrolidinopropiophenone, methylenedioxypyrovalerone, psychostimulant, self-administration, binge, extended access, rat

OPEN ACCESS

Edited by:
Simona Zaami,
Sapienza University of Rome, Italy

Reviewed by:
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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *25 May 2020*
Accepted: *07 August 2020*
Published: *25 August 2020*

Citation:
Nagy EK, Overby PF and Olive MF (2020) Reinforcing Effects of the Synthetic Cathinone α-Pyrrolidinopropiophenone (α-PPP) in a Repeated Extended Access Binge Paradigm. Front. Psychiatry 11:862. doi: 10.3389/fpsyt.2020.00862

INTRODUCTION

Frequently referred to as "bath salts", synthetic cathinones are psychostimulants with neurochemical actions similar to those of cocaine and methamphetamine (1). As derivatives of the naturally occurring alkaloid cathinone isolated from *Catha edulis*, these drugs carry a high risk of adverse reactions such as agitated delirium, seizures, psychosis, organ failure, and death (2). Among the first cathinone derivatives to infiltrate drug markets in the 21st century were the so-called "first generation" synthetic cathinones that included 3,4-methylenedioxypyrovalerone (MDPV), 4-methylmethcathinone (mephedrone), and methylone. However, due to the ease at which their chemical structures are modified,

numerous other cathinone derivatives have emerged, including pyrovalerone cathinones (α-pyrrolidinophenones) such as α-pyrrolidinopentiophenone (α-PVP), α-pyrrolidinopropiophenone (α-PPP), amongst many others (3–5).

The pharmacological mechanisms of action of synthetic cathinones are similar in nature to those exerted by traditional psychostimulants (4, 6). For example, 4-methylmethcathinone (mephedrone) produces amphetamine-like monoamine releasing effects *via* inhibition and reversal of presynaptic transporters for norepinephrine and dopamine (NET and DAT, respectively) as well as the type 2 vesicular monoamine transporter ($VMAT_2$). In contrast, MDPV, α-PVP and α-PPP produce cocaine-like inhibition of DAT and NET, with up to 100 times greater potency than cocaine and with longer durations of action (7, 8).

Studies in rodents support the notion that synthetic cathinones possess a high potential for abuse and dependence. For example, in line with their pharmacological actions, MDPV and α-PPP induce discriminative stimulus effects similar to those of cocaine and methylenedioxymethamphetamine (MDMA) (9–12) and are intravenously self-administered under conditions of limited drug access (13–15). However, detailed case reports have revealed that users of synthetic cathinones often engage in binge-like intake patterns that last 3-5 consecutive days or longer (16, 17). We recently characterized self-administration patterns of MDPV in rats using a prolonged binge-like intake paradigm, where several extended (96 h) drug access periods are separated by 72 h of abstinence in the home cage (18). This paradigm was originally developed to model multi-day binge-like intake of methamphetamine in rodents (19). The present study was designed to assess intake patterns of α-PPP under similar conditions of repeated periods of extended access to the drug.

MATERIALS AND METHODS

Animals

Adult male Sprague-Dawley rats (300-350 g, Envigo, Placentia, CA) were used as subjects. Prior to surgical procedures, animals were housed in pairs in a vivarium on a reversed light-dark cycle (12:12; lights off at 0700 h), with temperature and humidity within guidelines of the National Institutes of Health. Following catheter implantation and recovery from surgery, rats were singly housed to prevent cagemate chewing and damage to vascular access ports. Food and water were available ad libitum at all times.

Drugs

MDPV (Laboratory Supply USA, San Diego, CA) was verified to be >95% purity by liquid chromatography/mass spectrometry as we have previously reported (13). The same was true for initial experiments utilizing α-PPP, although additional amounts of this drug were purchased from Cayman Chemical (Ann Arbor, MI) in order to complete the study, as the original source was no longer available. Drugs were dissolved in 0.9% w/v sodium chloride for intravenous self-administration.

Surgical Procedures

Rats were placed under anesthesia with isoflurane (5% induction, 2-3% maintenance) that was vaporized in O_2 at a flow rate of 2 L/min. An incision was made on the neck to expose the jugular vein, and polyurethane catheters (Access Technologies, Skokie, IL) were inserted ~3.0 cm and secured with silk sutures. The other end of the catheter was routed subcutaneously to the dorsum, where it exited the skin *via* a 3-mm incision between the scapulae. This end of the catheter was connected to a vascular access port (Instech Laboratories, Plymouth Meeting, PA) that was secured to the surrounding skin with sutures. Following implantation, access ports were flushed with 0.2 ml of a Timentin solution (66.6 mg/ml, dissolved in saline containing 70 U/ml heparin). During postoperative care (5 days), rats received daily infusions of the heparinized Timentin solution to maintain catheter patency. During the first 3 days of operative care, rats were administered meloxicam (2 mg/kg s.c.) and buprenorphine (0.03 mg/kg s.c.) daily to reduce post-surgical discomfort. Animals then were randomly assigned to commence training for self-administration of either α-PPP, MDPV, or saline.

Apparatus

Self-administration procedures were performed in operant conditioning chambers (Med Associates, Model ENV-007, St. Albans, VT) interfaced to a PC computer. Located at one end of each chamber was a 2.5-cm diameter active nosepoke aperture and a similarly sized inactive aperture. Within both apertures, a small LED provided visual cues during each drug infusion. Located at the top of the chamber was a speaker that provided a tone (~65 dB, 2900 Hz) during each drug delivery. Each conditioning chamber also contained a water bottle, and food pellets were placed on the floor of the chamber every morning of each 96-h session. Above each chamber was a liquid swivel that was connected to a PC-controlled syringe pump (Med Associates) for intravenous drug infusions. Drug solutions were delivered through polyethylene tubing housed within a metal tether that was connected to the vascular access port. Each operant chamber was located in a separate sound-attenuating cubicle that was equipped with a house light (programmed to match the light-dark cycle of the colony room), and a ventilation fan to mask external noise and odors.

Self-Administration Procedures

Following surgical recovery, rats were allowed to spontaneously acquire self-administration of α-PPP, MDPV, or saline in 96-h sessions. Doses of 0.05, 0.1, and 0.32 mg/kg/infusion of α-PPP were selected based on a similar doses recently demonstrated to support self-administration in limited daily access sessions in rats (15). A dose of 0.05 mg/kg/infusion of MDPV was selected based on our prior findings of binge-like intake of this drug in the 96-h paradigm (18). After the first 96-h session, animals were removed from the operant chamber and returned to the home cage for 72 h of abstinence. This procedure of 96 h of drug access followed by 72 h of abstinence was repeated twice, so that each animal underwent a total of three 96-h self-administration sessions, each separated by 72 h of abstinence in the home cage. All reinforcers

were available on a fixed-ratio 1 (FR1) schedule of reinforcement, where nosepokes into the active aperture lever resulted in reinforcer delivery in a volume of 0.06 ml over a 1-s period. Each reinforcer delivery was accompanied by a 1-s illumination of LED light within the nosepoke aperture and 1-s presentation of a tone. Following each infusion, a 20-s timeout period was enacted where additional active nosepokes were recorded but had no consequences. Nosepokes into the designated inactive aperture had no consequences at any time during the experiment. Prior to and following each 96-h session, catheters were flushed with 0.1 ml of heparinized Timentin as described above. Criteria for acquisition of α-PPP or MDPV self-administration were defined as the subject obtaining at least 50 infusions during the first 96-h session. The use of yoked administration of either drug or saline as a control was not employed, since yoked infusions have been shown to have aversive properties, as well as reduce the motivation for intake of psychostimulants (20, 21).

Statistical Analyses

GraphPad Prism v.8.4 (GraphPad Software, La Jolla, CA) was utilized for statistical analyses. P-values <0.05 were considered statistically significant. A two-way mixed model analysis of variance (ANOVA) was used to analyze the number of α-PPP, MDPV or saline infusions obtained across each 96-h session, followed by Holm-Sidak corrections for multiple comparisons. We also analyzed the number of infusions obtained during this session in 8-h blocks to obtain a temporal profile of drug intake.

RESULTS

A total of n = 40 animals were implanted with intravenous catheters. Of these, data from n = 4 rats were excluded from analysis due to loss of catheter patency, and data from n = 5 rats were excluded from analysis due to failure to meet acquisition criteria (>100 infusions obtained during the first 96-h period, and/or failure to discriminate active vs. inactive nosepoke hole by a ratio of >1:1). Additionally, data from n = 2 rats were excluded from analyses due to the development of severe health problems, and one rat was found dead in the operant conditioning chamber during one of 96-h sessions. As a result, final group sizes were as follows: α-PPP 0.05 mg/kg/infusion (n = 8), α-PPP 0.1 mg/kg/infusion (n = 4), α-PPP 0.32 mg/kg/infusion (n = 4), MDPV (n = 6), and saline (n = 6).

Analysis of the number of infusions earned across each of the three 96-h sessions revealed a significant effect of reinforcer (saline, MDPV or one of the 3 doses of α-PPP, $F_{4,23} = 12.05$, $p<0.0001$), session ($F_{1.61,\ 36.25} = 4.29$, $p<0.05$, and an interaction between these factors ($F_{8,45} = 4.53$, $p<0.0005$). Post hoc analyses revealed that the number of MDPV infusions obtained was greater than the number of saline infusions across all three 96-h sessions (p-values <0.0005, 0.005, and 0.05 during the first, second and third 96-h sessions, respectively). In animals self-administering the low (0.05 mg/kg/infusion) dose of α-PPP, the number of infusions obtained was greater than the number of saline infusions obtained only during the first 96-h session ($p<0.05$, **Figure 1A**). In animals self-administering the 0.1 mg/kg/infusion dose of α-PPP, increased variability of responding was observed, and intake of the drug was not statistically different from that of saline (p-values = 0.15, 0.26, and 0.13 during the 1st, 2nd, and 3rd 96-h sessions, respectively). However, in animals self-administering the 0.32 mg/kg/infusion dose of α-PPP, the number of infusions obtained was greater than the number of saline infusions obtained during all three 96-h sessions (all p-values <0.05, **Figure 1A**).

To obtain a temporal profile of drug intake patterns, we analyzed the number of infusions obtained in 8-h bins during the first 96-h session (**Figure 1B**). We observed significant effects of reinforcer ($F_{4,23} = 9.81$, $p<0.0001$) and not session ($p>0.05$), but a significant interaction between these factors ($F_{44,253} = 1.63$, $p<0.05$). Multiple comparisons of the number of drug infusions obtained across each 8-h time bin are provided in **Table 1**. The number of MDPV reinforcers earned were significantly greater than those of saline during the 4th, 6th through 10th, and 12th time bins. The number of α-PPP (0.05 mg/kg/infusion) reinforcers earned were significantly greater than those of saline only during the 4th time bin, and the number of α-PPP (0.32 mg/kg/infusion) reinforcers earned were significantly greater than those of saline only during the 1st and 4th time bins. Temporal patterns of self-administration of the 0.1 mg/kg/infusion dose of α-PPP was highly variable (not shown in **Figure 1B** for clarity of presentation of the other doses), and significant differences with respect to levels of saline self-administration were not observed (**Table 1**).

DISCUSSION

The current study confirms our previous findings that MDPV is robustly self-administered under conditions of prolonged access in 96-h sessions (18). However, self-administration of α-PPP above levels observed for saline were variable and dose-dependent, as reliable self-administration was only observed at the highest dose tested (0.32 mg/kg/infusion). These findings are consistent with those of other investigators showing the reinforcing effects of this synthetic cathinone under conditions of limited (90 min/day) access (15). Self-administration of α-PPP has also been reported to occur in humans (22), although we note that it is difficult to extrapolate dose-related phenomena across species. We did not observe significant self-administration of α-PPP at a dose of 0.1 mg/kg/infusion. However, the lack of statistical significance may have resulted from a low sample size for this group, as two of the four animals tested in this group showed significant levels of α-PPP self-administration (individual subject data not shown).

Both MDPV and α-PPP can elicit cocaine-like locomotor stimulant and discriminative stimulus effects (9, 11, 23), and exhibit cocaine-like inhibitory effects on presynaptic DAT and NET transporters (7, 24). However, the potency of α-PPP as a DAT inhibitor is approximately 70 times less than that of MDPV (25), which is likely reflected in the higher doses of α-PPP required to support self-administration, as observed in

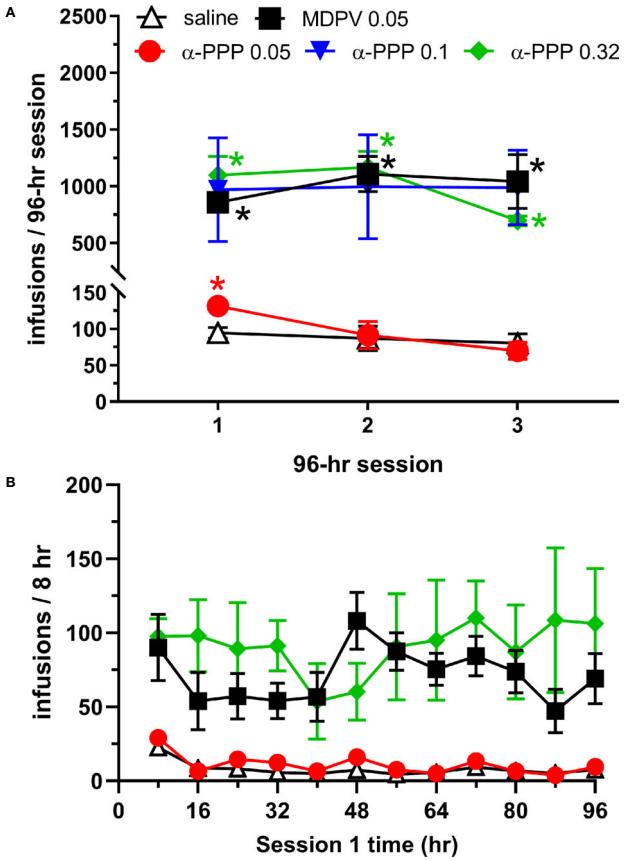

FIGURE 1 | (A) Total infusions of saline (n = 6), MDPV (n = 6), or one of the three doses of α-PPP (0.05, 0.1. or 0.32 mg/kg/infusion, n = 8, 4, and 4, respectively) during each of the three 96-h self-administration sessions. * indicates p<0.05 vs. the number of saline infusions obtained during the same 96-h session. **(B)** Total number of infusions of α-PPP (0.05 and 0.32 mg/kg/infusion), MDPV, or saline obtained in 8-h time bins during the first 96-h self-administration session. See **Table 1** for statistical significance of individual groups and time points. Data from the 0.1 mg/kg/infusion group are not shown to enhance clarity of the data presented, and as a result of lack of statistically significant overall intake observed. All data are presented as mean ± SEM.

TABLE 1 | Analysis of 8-h time bins for self-administration of MDPV or one of three doses of α-PPP vs. saline during the first 96-h session.

Time (h)	Comparison	P-value
0-8	saline vs. MDPV	0.0847
	saline vs. α-PPP 0.05 mg/kg/inf	0.1875
	saline vs. α-PPP 0.1 mg/kg/inf	0.1875
	saline vs. α-PPP 0.32 mg/kg/inf	0.0272*
9-16	saline vs. MDPV	0.1863
	saline vs. α-PPP 0.05 mg/kg/inf	0.5632
	saline vs. α-PPP 0.1 mg/kg/inf	0.2615
	saline vs. α-PPP 0.32 mg/kg/inf	0.1308
17-24	saline vs. MDPV	0.0955
	saline vs. α-PPP 0.05 mg/kg/inf	0.0958
	saline vs. α-PPP 0.1 mg/kg/inf	0.1587
	saline vs. α-PPP 0.32 mg/kg/inf	0.1540
25-32	saline vs. MDPV	0.0400*
	saline vs. α-PPP 0.05 mg/kg/inf	0.0400*
	saline vs. α-PPP 0.1 mg/kg/inf	0.3440
	saline vs. α-PPP 0.32 mg/kg/inf	0.0400*
33-40	saline vs. MDPV	0.0992
	saline vs. α-PPP 0.05 mg/kg/inf	0.3919
	saline vs. α-PPP 0.1 mg/kg/inf	0.3875
	saline vs. α-PPP 0.32 mg/kg/inf	0.3858
40-48	saline vs. MDPV	0.0128*
	saline vs. α-PPP 0.05 mg/kg/inf	0.0744
	saline vs. α-PPP 0.1 mg/kg/inf	0.1692
	saline vs. α-PPP 0.32 mg/kg/inf	0.1333
49-56	saline vs. MDPV	0.0052*
	saline vs. α-PPP 0.05 mg/kg/inf	0.2557
	saline vs. α-PPP 0.1 mg/kg/inf	0.2976
	saline vs. α-PPP 0.32 mg/kg/inf	0.2557
57-64	saline vs. MDPV	0.0052*
	saline vs. α-PPP 0.05 mg/kg/inf	0.7317
	saline vs. α-PPP 0.1 mg/kg/inf	0.3153
	saline vs. α-PPP 0.32 mg/kg/inf	0.3067
65-72	saline vs. MDPV	0.0096*
	saline vs. α-PPP 0.05 mg/kg/inf	0.0798
	saline vs. α-PPP 0.1 mg/kg/inf	0.3569
	saline vs. α-PPP 0.32 mg/kg/inf	0.0798
73-80	saline vs. MDPV	0.0210*
	saline vs. α-PPP 0.05 mg/kg/inf	0.9455
	saline vs. α-PPP 0.1 mg/kg/inf	0.5562
	saline vs. α-PPP 0.32 mg/kg/inf	0.2352
81-88	saline vs. MDPV	0.1349
	saline vs. α-PPP 0.05 mg/kg/inf	0.4373
	saline vs. α-PPP 0.1 mg/kg/inf	0.1349
	saline vs. α-PPP 0.32 mg/kg/inf	0.2346
89-96	saline vs. MDPV	0.0585
	saline vs. α-PPP 0.05 mg/kg/inf	0.5832
	saline vs. α-PPP 0.1 mg/kg/inf	0.5832
	saline vs. α-PPP 0.32 mg/kg/inf	0.2125

Asterisks indicate statistically significant differences vs. saline.

the present and previous studies (15). Interestingly, however, α-PPP does not show significant affinity for presynaptic serotonin transporters, but recent studies have revealed some MDMA-like discriminative stimulus effects of this cathinone derivative (12).

Additionally, it was recently reported that α-PPP exhibits antagonist and inverse agonist activity at type 2A serotonin (5-HT_{2A}) receptors at physiologically relevant (i.e., nanomolar) concentrations (26). This mechanism of action may limit some of the psychoactive and/or reinforcing effects of α-PPP, as pharmacological antagonism of 5-HT_{2A} receptors attenuates some of the behavioral and neurochemical effects of cocaine (27–29). It is therefore possible that in addition to its lower affinity for DAT and/or NET as compared to MDPV, inhibitory actions at 5-HT_{2A} receptors may reduce the relative reinforcing effects of α-PPP. However, this notion needs to be empirically tested prior to drawing any firm conclusions.

Upon examination of α-PPP self-administration in 8-h time bins across the first 96-h session, we observed no significant differences in temporal intake of the higher dose (0.32 mg/kg/infusion) of this drug with respect to those of MDPV. Possibly as a result of a greater degree of variability in drug intake for this dose of α-PPP, the number of infusions obtained per 8-h bin were significantly elevated during the 1st and 4th time bins as compared to saline, as opposed to being significantly increased during the 4th, 6th through 10th, and 12th time bins for MDPV relative to saline. For

the low dose of α-PPP tested (0.05 mg/kg/infusion), levels of intake were increased above those observed for saline only during the 4th 8-h time bin. Interestingly, however, during this 4th 8-h time bin, we observed robust self-administration of MDPV as well as two of the three doses of alpha-PPP tested (0.05 and 0.32 mg/kg/infusion). The reason why such effects were observed during this particular time period are currently unknown and require further investigation.

It is worth noting that both α-PPP and MDPV have metabolites with significant biological activity. For example, metabolites of α-PPP include 2′′-oxo-PPP, 4′-hydroxy-PPP, cathinone and norpseudoephedrine (30), some of which may accumulate and prolong the effects of the parent compound. Likewise, MDPV is metabolized to 3,4-dihydroxypyrovalerone and 4-hydroxy-3-methoxypyrovalerone among other biotransformation products, with the former metabolite showing significant (nanomolar) inhibitory activity at DAT and NET (6, 31). While specific drug metabolites were not measured in the present study during or after prolonged 96-h sessions, it is important to keep the potential contributions of such metabolites in mind when interpreting results from studies employing prolonged drug intake procedures.

In summary, the present study demonstrates that α-PPP possesses reinforcing effects in rats under conditions of extended drug access, albeit with lower potency and reinforcing efficacy as compared to those of MDPV. However, given that α-PPP is currently unscheduled by the U.S. Drug Enforcement Agency, and to our knowledge is not widely classified as a controlled substance in other countries worldwide, these findings suggest that this particular pyrovalerone cathinone derivative may have the potential for abuse.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Animal Care and Use Committee at Arizona State University.

AUTHOR CONTRIBUTIONS

EN and FO conceived and designed the experiments, and wrote the manuscript. EN and PO performed behavioral testing. FO performed the data analyses.

FUNDING

This work was supported by Public Health Service grant DA042172 from the National Institute on Drug Abuse.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 31 August 2020
doi: 10.3389/fpsyt.2020.00879

Club Drugs: Psychotropic Effects and Psychopathological Characteristics of a Sample of Inpatients

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OPEN ACCESS

Edited by:
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National Institute of Health (ISS), Italy

Reviewed by:
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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: 01 June 2020
Accepted: 11 August 2020
Published: 31 August 2020

Citation:
Martinotti G, Negri A, Schiavone S, Montemitro C, Vannini C, Baroni G, Pettorruso M, De Giorgio F, Giorgetti R, Verrastro V, Trabace L, Garcia A, Castro I, Iglesias Lopez J, Merino Del Villar C, Schifano F and di Giannantonio M (2020) Club Drugs: Psychotropic Effects and Psychopathological Characteristics of a Sample of Inpatients. Front. Psychiatry 11:879. doi: 10.3389/fpsyt.2020.00879

Background: Growing evidence supports the possibility of significant psychiatric consequences related to novel and traditional psychoactive substance consumption. The problem of differential diagnosis has hampered research on specific psychopathologies with unclear outcomes. The aim of our study was to report psychiatric and clinical features of subjects admitted to a psychiatric ward in Ibiza, Spain, with a clinical diagnosis of substance abuse or intoxication.

Methods: A survey was administered to a sample of inpatients hospitalized due to psychiatric symptoms related to recent use of psychoactive substances. The questionnaire investigated sociodemographic factors, familiar and personal anamnesis, substance use habits, general and psychopathological features. Urine samples were collected and analyzed in a toxicology laboratory using gas chromatography and mass spectrometry.

Results: A total of 110 patients were included in the study. Most patients (70%) declared multiple substance use, and 33% of patients reported more than two substances; nevertheless, it was possible to identify 17 (15%) depressor users, 44 (40%) stimulant users and 49 (45%) psychodysleptics users. A positive association with a lifetime diagnosis of bipolar disorder was found (two-tailed Fisher's exact test: $p = 0.013$). Psychomotor agitation, reference, and paranoid delusions, affective symptoms, consciousness disorders, and aggressiveness represented some of the most frequent symptoms at entry evaluation.

Conclusions: In this study, we described the acute psychiatric presentations related to recreational drug use in subjects on holiday in Ibiza. The use of psychoactive substances

was characterized by poly-use of both traditional and novel substances, with several psychopathological consequences. Future research should focus on a better understanding of the psychopathological effects of specific substances, defining signs and symptoms to help make a differential diagnosis and prospectively examine long-term effects.

Keywords: club drugs, novel psychoactive substances, psychopathology, psychosis, substance use disorder

BACKGROUND

Psychoactive substance use and related risks are considered a worldwide major public health issue, involving a variety of health and social consequences that require prompt sanitary policies as well as constantly updated responses from health professionals to promote harm reduction (1). In 2017, an estimated 271 million people worldwide had used psychoactive substances during the previous year—a number 30% higher than that in 2009 (2)—putting substance use disorders (SUDs) among the leading causes of disability worldwide (3). However, although consequences may be dramatic in terms of morbidity, mortality, and psychiatric load, such a widespread phenomenon is often defined as merely an aberrant behavior by modern society.

As shown by recent trends, the extent of problematic drug use is not limited to subjects with SUD or addiction; admissions to specific clinical settings, such as Emergency Rooms (ERs) and psychiatric wards, due to substance-related conditions involve a heterogeneous cohort of users with different motivations of intake. These range from traditional drug users to "psychonauts", clubgoers, students, athletes, marginalized populations, and individuals with patterns of non-habitual recreational drug consumption (4). Nevertheless, rates of SUD are significantly higher (up to 50%) among psychiatric patients than in the general population (5). In recent years, this rapidly evolving scenario has been further complicated by the rise of novel psychoactive substances (NPS). The United Nations Office on Drugs and Crime reports define 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" (2). Many of these substances were originally developed as research chemicals, as they often mimic the pharmacological effect of traditional drugs of abuse, such as cannabis or phenethylamines, and they were subsequently repurposed for recreational use. NPS are formulated in a variety of forms, both pure and in preparations with other substances. When smoked, ingested, snorted, or injected they may produce a plethora of psychotropic effects, of which some are not fully described. This, along with their often-unknown toxicological profile, their low traceability and the fast-moving and potentially limitless nature of their online market, initially raised significant concern among health professionals (6–8). Although a great effort has been made in the last decade by the scientific community to raise awareness and gain a better knowledge of such compounds and their related risks (9), the understanding of various features, including patterns of consumption, must be further developed (10).

Due to their diverse nature, various categorizations of NPS have been proposed, according to their origin, chemical structures or pharmacological action, among others. Based on their clinical effects on the central nervous system, NPS can be classified as stimulants, empathogens, entactogens, sedative-hypnotics/anxiolytics, dissociatives, and hallucinogens (11). In 2019, the total number of NPS identified worldwide was over 950, of which the vast majority (almost 800 different compounds) had been notified within the last decade (12). Although an increasing number of studies report the potential acute and chronic health dangers associated with such use, NPS and their clinical effects and related risks are often unknown to both users and health professionals, mainly due to a lack of evidence-based sources of information and to the ever-changing nature of their market (4, 9).

Nevertheless, growing evidence supports the possibility of significant psychiatric and physical consequences related to NPS consumption (13, 14). Recently, researchers have reported that NPS consumption may be associated with the onset of a variety of psychiatric symptoms and conditions, including confusion, paranoid thoughts, auditory and visual hallucinations, dissociation (e.g., derealization and somatopsychic depersonalization), insomnia, chronic cognitive impairment and delusions of reference, persecution, grandeur and jealousy, as well as hypomanic states, aggressiveness and irritability, violence, and suicidal thoughts (15–17). These symptoms are often due to the increased potency of NPS compared to traditional substances, as well as to their action on a number of different neural pathways, including dopamine (DA) and serotonin (5-HT) receptors for psychedelic phenethylamines, tryptamines and synthetic cathinones, cannabinoid (CB) receptors for synthetic cannabinoids, and N-methyl-D-aspartate (NMDA) receptors for some dissociatives (12). Such effects are particularly alarming for compounds that are frequently sold and advertised as natural and safer alternatives to other drugs. For example, observational research on a cohort of 594 synthetic cannabinoids users reported a higher prevalence of psychotic symptoms than in cannabis users (18). Furthermore, the study showed that psychotic disorders were usually more severe in synthetic cannabis users, and patients required higher doses of antipsychotic medications and were hospitalized for longer.

The growing prevalence of novel and traditional psychoactive substances, and their related risks, is further complicated by the phenomenon of "nightlife" and "clubbing" associated with international travels. Holiday periods, particularly in summer, appear to represent a time of risk, excess and experimentation, especially among young people (19). Substance use is a commonly reported habit among festivalgoers and clubgoers in

holiday resorts—environments in which hedonistic partying is socially accepted and drugs are typically readily available—which often involve practices such as polysubstance use (i.e., the consumption of two or more compounds simultaneously) (20, 21). Several studies reported the detection in such contexts of a variety of traditional drugs and NPS, such as synthetic cathinones, synthetic cannabinoids, opioids, and naturally derived drugs (e.g., psilocybin, and ayahuasca), by using different screening techniques that ranged from wastewater analysis to self-report surveys (22–24).

Although virtually any psychoactive substance may be used in such an environment for recreational purposes, the National Institute on Drug Abuse (NIDA) includes six compounds among the so-called "club drugs" or "rave drugs" (i.e., drugs commonly consumed during electronic music festivals, dance parties or raves from the 1970s to the present): flunitrazepam, ketamine, LSD, methylenedioxymethamphetamine (MDMA), methamphetamine, and gamma-hydroxybutyrate (GHB) (25). Users, especially young subjects who are often unaware of health-related risks and of the nature of such compounds, including potential contamination and adulteration (26), seek positive effects such as euphoria, improved psychomotor speed, alertness, sociability and talkativeness, amplification of sensory perceptions, alteration of space and time perception, loss of inhibition, increased libido, and improved sexual performance (27–29).

The current dynamic drugs scenario raises enormous concerns for public health at a national and international level. The risks posed by club drugs and related phenomena require adequate training for health professionals, effective harm reduction interventions and updated policies provided by local and supranational regulatory agencies (30). Addressing these challenges may be crucial for guiding the diagnostic and therapeutic options of healthcare professionals, as well as for counteracting related psychiatric and physical risks, such as acute toxicity. For this context, Ibiza and the Balearic Islands, one of the most popular nightlife resorts for summer holidays in Europe, appear as a crucial setting to explore psychopathological issues related to both traditional drugs and NPS. Previous studies available in literature confirmed a higher prevalence of risky behaviors for both residents and tourists in Ibiza, including problematic alcohol and substance use, and their connections with sexual disinhibition, casual sexual relationships and unprotected sex (19, 31–33). Furthermore, anecdotal cases of NPS intoxication have been reported in recent years in the Ibiza drug market; in such a dynamic setting, naive customers are frequently seen by traffickers and dealers as test subjects for trialling new and potentially dangerous compounds for the first time (33).

Our previous reports on this topic investigated substance-related fatalities and provided a first insight of traditional drug- and NPS-induced psychopathological symptoms, particularly regarding aggressiveness (30, 33). The aim of the present study was to analyze patients admitted to the psychiatric ward of the Can Misses Hospital in Ibiza for psychoactive substance intoxication, in order to (a) report the sociodemographic characteristics of the sample, (b) identify which drug is most involved; (c) assess psychopathological features associated with substance use, particularly regarding psychotic symptoms (referring to bipolar or schizophrenic spectrum disorder) and behavioral disturbances.

MATERIAL AND METHODS

Patient Recruitment

Subjects admitted to the Can Misses Hospital psychiatry ward during the summer nightclub opening periods between May 2015 and October 2018 were recruited for the study. This sample was derived from a larger sample of 223 subjects transferred to hospital ER from discotheques and other clubs around the island who were exhibiting intoxication and/or manifestations of psychiatric interest. All patients were evaluated according to the DSM-5 diagnostic classification. Inclusion criteria were being aged between 18 and 75 years and reporting the intake of psychoactive substances or more than five units of alcohol over the previous 24 hours. Patients with delirium tremens, epilepsy, liver encephalopathy, dementia and other neurological diseases, severe cardiac failure, diabetes mellitus, severe liver impairment, kidney failure, or neoplastic diseases were excluded after clinical evaluation.

Data Collection

Demographic (age, gender, family, and nationality) and socioeconomic data (living status, job status, and level of education) were collected in a structured interview administered during hospitalization, after the resolution of intoxication symptoms. The interview investigated recent and past medical and psychiatric history in addition to alcohol and substance use habits (tobacco, caffeine, cannabis, cocaine, and heroin), with a focus on NPS. Among these, recent and lifetime use of synthetic cannabinoids, synthetic cathinones [e.g., mephedrone, methylone, methylenedioxypyrovalerone (MDPV), alpha-pyrrolidinopentiophenone (α-PVP)], amphetamine and methamphetamine, plant-based substances (e.g., ayahuasca, kratom, Salvia divinorum), GHB and GBL (γ-butyrolactone), dissociative substances (e.g., ketamine and methoxetamine), and psychedelics (e.g., LSD, magic mushrooms) was investigated. Misuse of prescription drugs such as benzodiazepines, methylphenidate, and opioid painkillers was also explored. A urine sample was collected upon admission, stored at −30°C and subsequently analyzed at the laboratory of either the Department of Forensic Toxicology of the Università Politecnica delle Marche, Italy, or the National Institute of Toxicology and Forensic Sciences in Barcelona, Spain. Gas chromatography/mass spectrometry (GC/MS) was used to confirm the consumption of psychoactive substances and/or prescription drugs.

Psychodiagnostic Tests and Analysis

The following psychodiagnostic tests were administered to patients during their hospitalization: Timeline follow-back for psychoactive substances and alcohol (TLFB); Positive and Negative Symptoms Scale (PANSS); Brief Psychiatric Rating Scale (BPRS); Mania Rating Scale (MRS); Hamilton Depression Scale (HAM-D); Hamilton Anxiety Scale (HAM-A); Modified Overt Aggression Scale (MOAS). TLFB was used to identify the main substance of abuse for each patient. The other psychometrics

were used to explore different psychopathological aspects, such as depressive or manic symptoms, anxiety, psychosis negative or positive symptoms, somatic disorders, aggressiveness, and suicidality. The choice of psychometric instruments was derived from our previous studies on the topic (4, 33). Patients were divided into three main substance macro-categories according to the TLFB and the results of the urine analysis: Psychostimulants (e.g., cocaine, amphetamines, and synthetic cathinones), Psychodepressors (e.g., opioids, alcohol, and benzodiazepines) and Psychodysleptics (e.g., cannabinoids, psychedelics, dissociatives, empathogens, and entactogens). This classification was derived from our previous reports on the topic (4, 33). According to their pharmacological profiles (11), patients were also allocated to a specific group: Opioids, Stimulants, Empathogens-Entactogens, Psychedelics, Dissociatives, Cannabinoids, and Depressors. Urinalysis was performed in two separate laboratories (to enhance the level of sensitivity and specificity).

Ethics

Data collection was carried out anonymously and confidentially; all participants received a detailed explanation of the design of the study and written informed consent was systematically obtained from every subject, according to the Declaration of Helsinki. Ethical approval was granted by the University of Hertfordshire Health and Human Sciences ECDA, protocol no. aPHAEC1042(03); by the CEI Illes Balears, protocol no. IB 2561/15 PI ("Estimación y Evaluación de síntomas inducidos por Sustancias y Alcohol", Dr.a Cristina Merino del Villar, Area de Salud Mental de Eivissa y Formentera); and by the University "G.d'Annunzio" of Chieti-Pescara, no. 7/09 04-2015.

Data Analysis

Statistical analysis was performed by using IBM SPSS® Statistics software, version 20 and GraphPad 5.0 software for Windows (La Jolla, CA, USA). Independence between substance use and psychiatric diagnosis, as well as between substance use and symptoms at admission, was analyzed using a two-tailed Fisher's exact test. Correlation between substance categories or groups and psychiatric scales scores was analyzed by linear regression. Data concerning scale scores according to categories and groups of substances were analyzed by one-way analysis of variance (ANOVA), followed by Tukey's *post hoc* test. For all tests, a p value of <0.05 was considered statistically significant.

RESULTS

Sociodemographic Data

A total of 223 subjects showing a condition of intoxication and/or manifestation of psychiatric interest were transferred to the hospital ER from discotheques and other clubs around the island. Of this sample, 110 (49.3%) required subsequent psychiatric hospitalization and were enrolled in the study, whereas 50.7% of the sample only required a 2- to 36-hours stay in the emergency department before a rapid discharge. Sociodemographic information for the sample is reported in **Table 1**.

Categories and Groups of Abused Substances

All the subjects of the sample were diagnosed with substance intoxication at admission. Although the majority of patients declared multiple substance use (n = 77, 70.0%) and 33% of them reported more than two substance use, participants were divided into three macro groups according to their responses to the TLFB test and to the urinalysis in order to identify a category of substances "of choice" for each patient. This allowed to identify 17 (15%) depressors users, 44 (40%) stimulant users and 49 (45%) psychodysleptics users. When asked about lifetime use of specific groups of substances, stimulant use was disclosed by 74 patients and cannabis use by 68 patients. Categories of substances according to the TLFB and urinalysis, as well as prevalence for each substance group, are listed in **Table 2**. Cannabis and cannabinoids (40%) were the most common substances among patients who declared the use of only a single type of drug.

TABLE 1 | Sociodemographic characteristics of the sample.

Characteristic	n	%
Sample size	110	100
Gender	76	69.1
Male	34	30.9
Female		
Nationality	79	71.8
European	30	27.3
Other	1	0.9
Not available (NA)		
Education level	9	8.2
Primary education	18	16.3
Secondary education	42	38.2
Higher education/undergraduate	19	17.3
Higher education/postgraduate	22	20.0
NA		
Working status	52	47.3
Worker/professional	6	5.4
Student	3	2.7
Student and worker	40	36.4
Unemployed	1	0.9
Retired	8	7.3
NA		
Marital status	66	60.0
Single/never married	21	19.1
Divorced	13	11.8
Married	10	9.1
NA		
Living status	29	26.4
With parents	22	20.0
With a partner	27	24.5
Alone	13	11.8
With partner and child/children	10	9.1
With friends/flatmates	2	1.8
Other	7	6.4
NA		
Age subgroups	57	51.8
<30 years old	47	42.7
31–50 years old	6	5.5
>50 years old		
	Range (years)	Mean (SD)
Age	19–63	32.57 (9.15)
Total years of education	5–27	12.91 (4.48)

The most common symptom at admission was psychomotor agitation, which was observed in 43 patients, followed by reference ideation (n = 36) and paranoid delusional ideation (n = 30). Physical restraint was necessary for 14 patients (4%) in order to control symptoms (e.g., aggressiveness with concrete risk of harm to self or others). A detailed overview of symptoms detected upon evaluation in the ER is displayed in **Table 3**. The distribution of symptoms according to categories and specific groups of substances is highlighted in **Figure 1**.

A large majority of patients in our sample (83%, n = 91) reported to have a previous psychiatric history: 31% had received only one DSM-5 diagnosis, 30% had received two, 22% had received three, 14% had received four and 3% had received more than four. Among those who had previously received only one diagnosis according to DSM-5 criteria, bipolar disorder (21%), and psychotic episode (32%) were the most common. The psychiatric diagnoses associated with each group and category of substances are shown in **Figure 2**.

We investigated possible associations between psychoactive substance use and specific psychiatric diagnoses. In particular, we found a positive association between psychoactive substance use and lifetime diagnosis of bipolar disorder (two-tailed Fisher's exact test p = 0.013). Unsurprisingly, a positive correlation with a previous diagnosis of SUD was also reported (two-tailed Fisher's exact test p = 0.003). No significant association between substance use and the other psychiatric diagnoses was found (two-tailed Fisher's exact test p > 0.05).

Positive associations were also found with temporal disorientation at admission (two-tailed Fisher's exact test p = 0.022), although data were available for only 63 patients. No significant association between substance use and any other symptom at admission was found (two-tailed Fisher's exact test p > 0.05).

TABLE 2 | Categories and groups of abused substances.

Categories	n	%
Psychodysleptics	49	45
Psychostimulants	44	40
Psychodepressors	17	15
Groups	n	%
Stimulants	74	32
Cannabinoids	68	29
Depressors	32	14
Empathogens-Entactogens	28	12
Dissociatives	15	6
Opioids	9	4
Psychedelics	7	3

TABLE 3 | Symptoms observed at admission.

Entry Evaluation	n	%
Spatial disorientation	17	5
Temporal disorientation	23	7
Paranoid delusional ideation	30	9
Mystic delusional ideation	8	3
Reference delusional ideation	36	11
Grandeur delusional ideation	22	7
Mood elevation	21	7
Mood lowering	22	7
Psychomotor agitation	43	13
Sexual disinhibition	11	3
Anxiety and somatic anxiety	24	8
Aggressiveness towards others	24	8
Self-harm behaviour	14	4
Suicidality	25	8

Substance Use and Psychodiagnostics Scales

Severity of anxiety and depression symptoms according to HAM-A and HAM-D scales were comparable among different substance categories. The distribution of scores on the aforementioned scales is available in **Figure 3**.

Similarly, scores on the PANNS positive and negative subscales and total scores were equally distributed among categories of substances, as shown in **Figure 4**.

Presence and severity of mania and associated symptoms according to MRS were comparable among the different categories of substances. Finally, for general psychiatric symptoms assessed with the BPRS, no significant differences were found among depressor, stimulant and psychodysleptics users (**Figure 5**).

Severity of psychiatric symptoms according to HAM-D, HAM-A, BPRS, and MRS were comparable among specific groups of substances. However, it was possible to highlight a higher prevalence of psychotic symptoms, according to the PANSS Positive Scale, for psychedelic substances users compared to opioid users (**Figure 6B**).

Results of the linear regression analysis highlighted a weak positive correlation between psychedelics use and PANNS Positive Symptoms scores (R = 0.374) and BPRS scores (R = 0.324), as well as between depressors use and BPRS scores (R = 0.322).

Diagnoses Recorded at Discharge

Among the 110 participants, the most common psychiatric diagnosis at discharge was SUD (n = 44), followed by psychotic episode (n = 29). The main diagnoses assigned to patients after dismission from the psychiatric ward are described in **Table 4**.

DISCUSSION

In this study, we described the acute psychiatric presentations related to recreational drug use in an adult population of subjects on holiday in Ibiza. This region has the highest number of nights spent by EU residents in tourist accommodation establishments (34) and has a flourishing "substance market", which is frequently updated with newly developed recreational drugs. The characteristics of our sample, with high levels of education and good employment rates, differ from the typical profile of a substance abuser (35). An explanation for this phenomenon might be that the characteristics of substance-using clients have changed over recent years. In particular, clubbers and recreational drug users differ greatly from the "drug addicts" of the past (3, 36, 37). Moreover, Ibiza is a peculiar scenario in

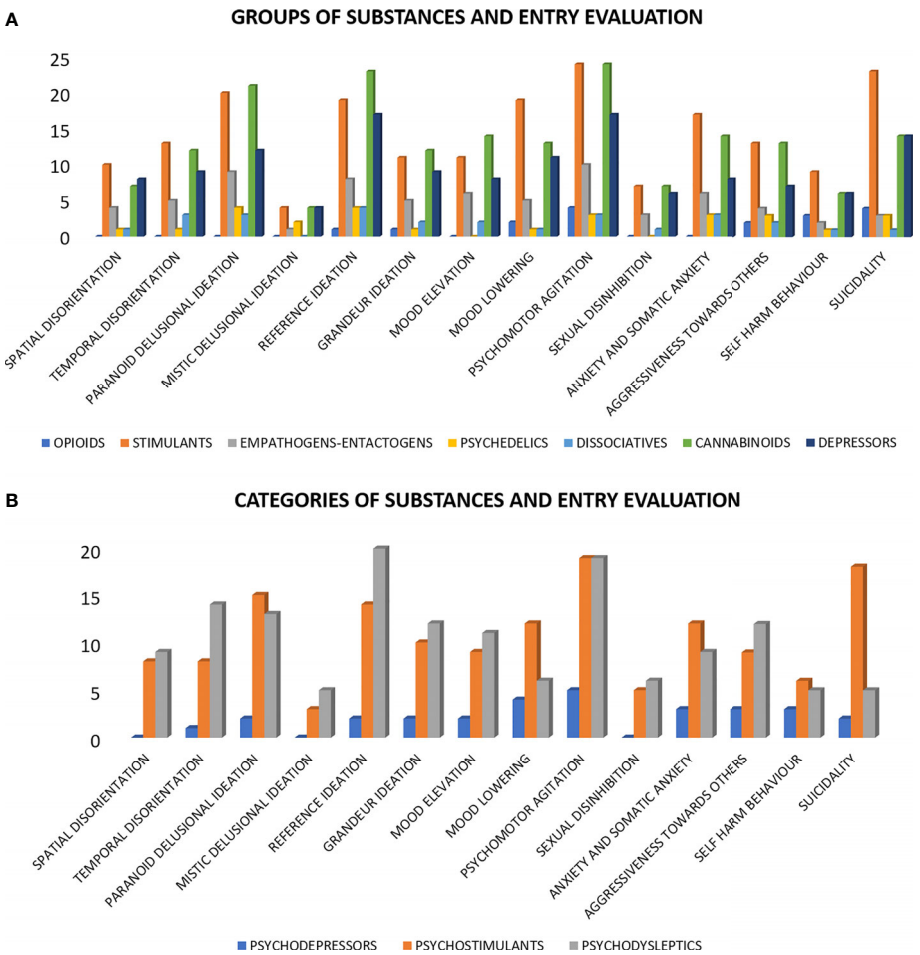

FIGURE 1 | Entry evaluation distribution according to groups and categories of substances. **(A)** Entry evaluation distribution according to the following groups of substances: opioids, stimulants, empathogens-entactogens, psychedelics, dissociatives, cannabinoids, and depressors. **(B)** Entry evaluation distribution according to the following categories of substances: psychodepressors, psychostimulants, and psychodyslpetics.

which subjects from low-income classes may not be able to find affordable facilities, while on the other hand, young tourists choose to spend most of their money earned during the winter period.

Cannabis and cocaine (in its different formulations, including crack) reported by users in the TLFB and by the urinalysis, were the most commonly referred substances, along with the presence of other traditional substances such as opiates, psychedelics, and entactogens. Alcohol was also commonly reported, mainly in association with other molecules. These findings have been confirmed by other studies that have demonstrated that most common emergency presentations related to acute recreational drug toxicity were associated with cocaine and cannabis use (38). NPSs represent a limited proportion (20%) of those reported. This data is of some interest, given that this is a real-life sample composed mostly of holidaymakers, among whom "2.0 online psychonauts" (39) do not represent the classical phenotype. Polysubstance abuse, including the use of two to six different substances during the same night, with alcohol as the substance most involved, followed by cannabis and cocaine, was showed to be a common behavior. The combination of psychoactive drugs may have numerous health implications (33, 40) and has been linked to increased levels of intoxication and possible fatality (41). Therefore, although a main "preferred" substance could be frequently identified with the structured interview and urinalysis data, the presence of polysubstance abuse appeared to be the relative norm.

Regarding the psychopathological evaluation upon admission, it is interesting to note the presence of spatial and temporal disorganization—an indication of qualitative alteration of consciousness. This phenomenon was evidenced mainly among users of psychostimulants and psychodysleptics. These types of manifestations are typical of the twilight state already described in SUDs (42) and are characterized by a state of clouded consciousness in which the individual is temporarily unaware of his or her surroundings. Our study confirms the importance of a

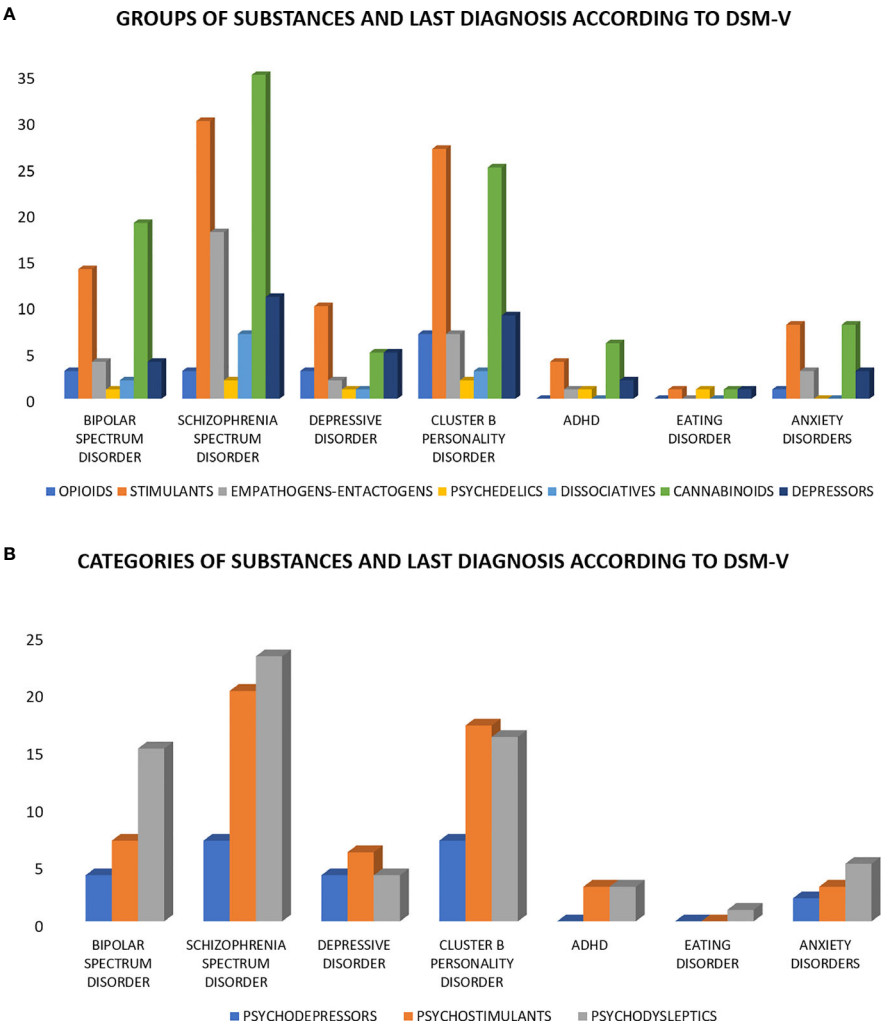

FIGURE 2 | Categories and groups of substances and last diagnosis according to DSM-V. **(A)** Last DSM-V diagnosis distribution according to the following groups of substances: opioids, stimulants, empathogens-entactogens, psychedelics, dissociatives, cannabinoids, and depressors. **(B)** Last DSM-V diagnosis distribution according to the following categories of substances: psychodepressors, psychostimulants, and psychodyslpetics.

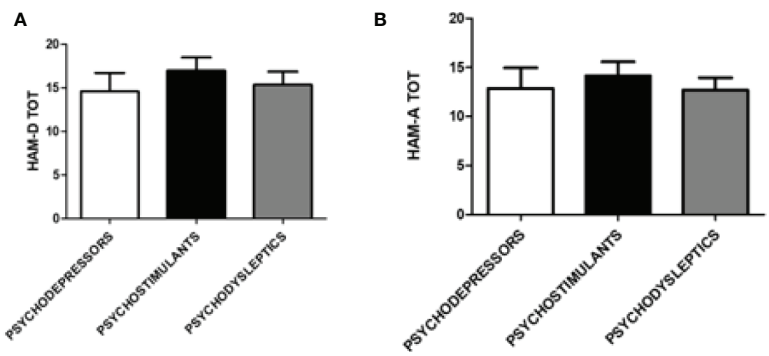

FIGURE 3 | Hamilton Depression (HAM-D) and Anxiety (HAM-A total) scales scores according to categories of substances. **(A)** HAM-D scale score according to the following categories of substances: psychodepressors, psychostimulants, and psychodyslpetics. **(B)** HAM-A total scale score according to the following categories of substances: psychodepressors, psychostimulants, and psychodyslpetics.

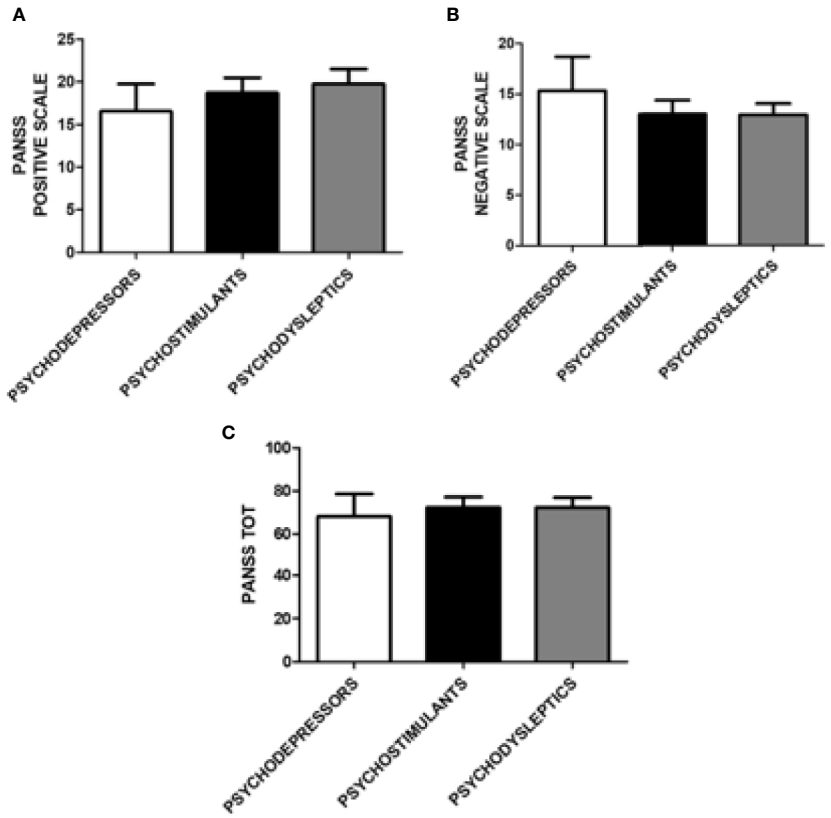

FIGURE 4 | Positive and Negative Syndrome Scale (PANSS) positive, negative, and total scores according to categories of substances. **(A)** PANSS positive score according to the following categories of substances: psychodepressors, psychostimulants, and psychodyslpetics. **(B)** PANSS negative score according to the following categories of substances: psychodepressors, psychostimulants, and psychodyslpetics. **(C)** PANSS total score according to the following categories of substances: psychodepressors, psychostimulants, and psychodyslpetics.

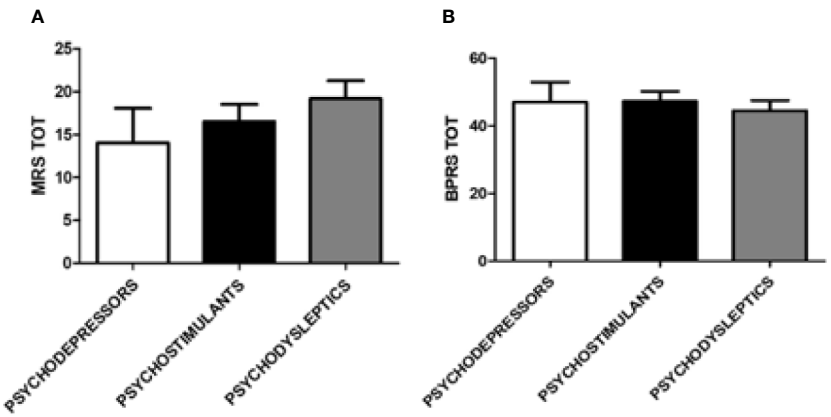

FIGURE 5 | Mania Rating Scale (MRS) and Brief Psychiatric Rating Scale (BPRS) scores according to categories of substances. **(A)** MRS score according to the following categories of substances: psychodepressors, psychostimulants, and psychodyslpetics. **(B)** BPRS score according to the following categories of substances: psychodepressors, psychostimulants, and psychodyslpetics.

correct assessment of the patient's state of consciousness. These transient cognitive disorders are quite unusual in psychiatric illnesses, with the exception of dissociative disorders, frequently described in the literature as substance-induced symptoms (43). The qualitative alterations of consciousness could, in fact, be characterized as distinguishing elements between a classic

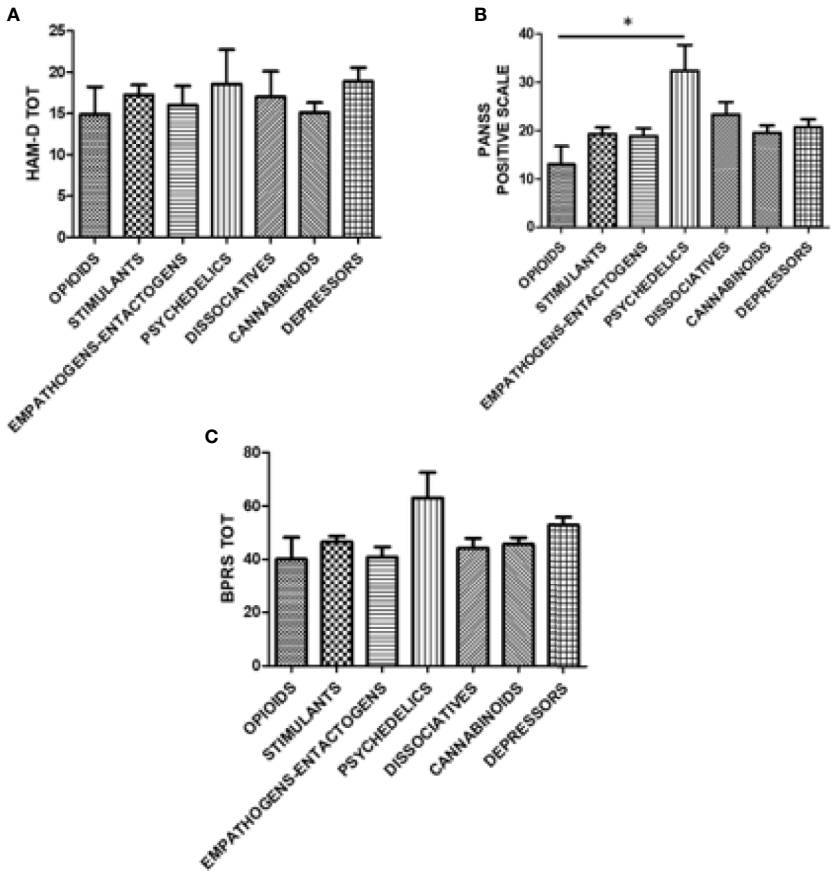

FIGURE 6 | Hamilton Depression (HAM-D) Scale, Positive Syndrome Scale (PANSS), and Brief Psychiatric Rating Scale (BPRS) scores according to groups of substances. **(A)** HAM-D scale score according to the following groups of substances: opioids, stimulants, empathogens-entactogens, psychedelics, dissociatives, cannabinoids, and depressors. **(B)** PANSS positive score according to the following groups of substances: opioids, stimulants, empathogens-entactogens, psychedelics, dissociatives, cannabinoids, and depressors; *$p < 0.05$. **(C)** BPRS score according to the following groups of substances: opioids, stimulants, empathogens-entactogens, psychedelics, dissociatives, cannabinoids, and depressors.

psychotic episode and an episode induced by substances. Moreover, it could become a predisposing factor facilitating the development of delusional thoughts. Among the other phenomena found in the initial evaluation of the patients, the presence of psychomotor agitation, aggression, self-harm and suicidality stand out, specifically in the group of psychodysleptics and psychostimulant users. This data still emphasizes that this type of patient represents a category at risk, also in terms of public health, as recently reported in other studies (44, 45). Reference and paranoid delusions were the most commonly described delusional phenomena, specifically in the category of psychostimulants and psychodysleptics users, in accordance with the literature (46). The substance- or alcohol-induced delirium is often characterized by confirmation and interpretation, rather than by revelation, and by imaginative contents. The delusions reported are similar to paraphrenic delusions, with a feeling of unreality, while the ability to analyze the feeling is preserved. In this regard, the model of the Lysergic Psychoma could be an interesting proposal (14). As already highlighted by previous studies (47), relevant symptoms were also inherent to the sphere of affectivity, both in the direction of positive and negative polarity. This data confirms how substance-induced phenomena often have a significant affective component

TABLE 4 | Discharge diagnoses.

Discharge Diagnosis	N	%
Bipolar disorder	9	6
Psychotic episode	29	19
Cluster B personality disorder	13	8
Substance use disorder	44	28
Alcohol abuse	16	10
Paranoid schizophrenia	4	2
Schizoaffective disorder	1	1
Manic Episode	9	6
Depression	6	4
Behavior Disorder	18	12
Adjustment Disorder	3	2
Anxiety Disorder	3	2

within them, probably deriving from the stimulation of both the dopaminergic and serotonergic systems (48).

Among the psychiatric manifestations observed in our sample, psychotic and mood symptoms predominated. Our findings have been confirmed by Acciavatti et al., who evidenced bipolar disorder and schizophrenia as the main psychiatric diagnostic frameworks within which the use of psychoactive substances is reported (47). Specifically, our study showed a significant association between a previous diagnosis of bipolar disorder and the use of substances. As regards the presence of the different diagnostic frameworks according to DSM-5 and the different types of substances, it should be emphasized that in the group of subjects with a diagnosis of schizophrenic spectrum disorder, a substantial number of subjects reported the use of entactogens/empathogens substances and dissociatives. This issue should be further investigated in future studies, given its relevance in terms of possible preventive strategies. Other diagnostic frameworks of greater response were those of depressive disorders, widely distributed among users of depressors and opiates, that of cluster B personality disorders, anxiety disorders, ADHD and eating behavior disorders. These data are in agreement with other studies in the literature with similar cases of substance abuse patients (49–51).

Mean scores of psychodiagnostic scales showed that psychiatric manifestations linked to psychoactive substances are characterized by a globally high level of psychopathology. As expected, PANSS Positive mean scores were higher than PANSS Negative mean scores, which is consistent with previous reports: a 2016 study demonstrated that patients with substance-induced psychosis had similar PANSS positive and significantly lower PANSS negative scores than patients with schizophrenia (4, 52). This data shows that the psychopathological potential of recreational substances is considerable, also in subjects without previous psychiatric symptoms of clinical relevance. We hypothesized that specific high potency substances, considerable amounts of a substance, and a high frequency of use may represent trigger factors. By differentiating between the groups of substances, it was possible to highlight how the use of psychedelics, compared to that of opiates, was more strongly associated with the presence of positive symptoms for PANSS. This data confirms that opiates can have an antipsychotic potential, or in any case, represent a group of substances with a low potential to induce positive symptoms (53).

In relation to the results for the other psychopathological scales of depression, anxiety, and mania, there is also evidence of high score levels. However, no significant differences are observed between the different groups (Opioids, Stimulants, Empathogens-Entactogens, Psychedelics, Dissociatives, Cannabinoids, and Depressors) or between the different categories of substances (Psychostimulants, Psychodysleptics, and Psychodepressors). This result could be explained by the high prevalence of poly-abuse, described in the majority of patients evaluated and also involving more than four substances together during the same night. For this reason, it is credible that possible intrinsic differences, with respect to the mechanism of action of the individual substances, have not resulted in fully manifesting themselves and, therefore, have not reached specific significance levels. If, on the one hand, this result may appear unsatisfactory, on the other, it should be emphasized that it represents a real-life population of abusers, in which the presence of a mono-substance user, always faithful to a single type of drug, represents an ideal scenario. This may also represent an important groundwork for harm reduction and prevention policies.

It is interesting to note the disparity between the diagnoses at discharge and the acute symptoms that have been observed upon admission. This data demonstrates how the psychoactive substance-induced phenomena often act as confounding factors for a correct diagnosis. At discharge from the hospital, the diagnosis of psychotic episode was reported in more than half of the participants. However, such a diagnosis is of an unclear nature, mostly in terms of future developments. Another relevant area of diagnosis was that of mood disorders (54% of the sample), with manic episodes in a high percentage of cases. Also, at discharge, multiple diagnoses still coexist, confirming the complexity of the field.

Limitations of the Study

This study presents limitations: 1) the possibility to identify new substances in urine samples remains both complex and limited, which also applies to post-mortem samples. We performed a professional urine drug screening but the comparison between the self-report and objective data is still far from being considered reliable; 2) in our analysis, we did not consider the intoxication cases managed at the emergency department and not admitted to the psychiatry unit. With this bias, we have probably excluded from our evaluation those subjects with acute and rapidly transient psychiatric reactions; 3) the long-term effects of novel and traditional substances are still a matter of discussion and are difficult to assess without follow-up examinations; and 4) differentiation according to groups (Opioids, Stimulants, Empathogens-Entactogens, Psychedelics, Dissociatives, Cannabinoids, and Depressors) and categories (Psychostimulants, Psychodysleptics, and Psychodepressors) is probably not ideal, as multiple substance abuse was the predominant behavior.

In future studies, the following points shall be addressed: 1) to better discriminate the psychopathological effects of specific substances, including NPS and select a common ground able to help in differential diagnosis, 2) to prospectively look at the long-term effects, 3) to retrospectively observe which pharmacological treatments show higher levels of effectiveness.

CONCLUSIONS

In a sample of subjects admitted to a psychiatric ward in a nightlife resort area, the use of psychoactive substances was notable and characterized by poly-use of both traditional and novel substances, with a relevant number of complex psychopathological consequences. Positive and manic symptoms and aggressiveness, including self-harm and suicidality, were highly represented, as well as state-of-consciousness alterations. These symptoms were not always transient in their nature and sometimes difficult to categorize *via* psychiatric diagnoses built

predominantly for subjects without current use of substances. All of the above-mentioned considerations should be investigated in further studies, together with careful monitoring of critical "hotspots" of substance misuse, in order to design better and targeted prevention strategies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Data collection was carried out in an anonymous and confidential way; all participants received a detailed explanation of the design of the study and written informed consent was systematically obtained from every subject, according to the Declaration of Helsinki. Ethics approval was granted by the University of Hertfordshire Health and Human Sciences ECDA, protocol no. aPHAEC1042(03); by the CEI Illes Balears, protocol no. IB 2561/15 PI; and by the University "G.d'Annunzio" of Chieti Pescara, no. 7/09 04-2015. Majorcan local ethics committee also gave approval to the study.

AUTHOR CONTRIBUTIONS

GM, MG, and FS organized the study. GM and AN wrote the paper. SS and LT made the statistics. All the other authors actively participated in patients recruitment and evaluation.

FUNDING

This study was partly found by the European Project entitled "Analysis, Knowledge dissemination, Justice implementation and Special Testing of Novel Synthetic Opioids" - JUST-2017-AG-DRUG.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer, SC, declared a shared affiliation, though no collaboration, with one of the authors, FS, to the handling editor.

frontiers in Psychiatry

PERSPECTIVE
published: 04 September 2020
doi: 10.3389/fpsyt.2020.567497

Neuroenhancement as Instrumental Drug Use: Putting the Debate in a Different Frame

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The use of performance-enhancing drugs to study or work better is often called "cognitive enhancement" or "neuroenhancement" and sparked a debate between scholars from many disciplines. I argue that such behavior can better be subsumed under the more general category of "instrumental drug use". This broader perspective allows understanding neuroenhancement better from the perspective of addiction medicine and public health and supports a more consistent drug policy. I also summarize the most important systematic reviews and individual surveys of nonmedical substance use to study or work better. Different definitions and methodologies limit the comparability of these studies. The unified approach of drug instrumentalization would partially solve such problems. Finally, prevalence studies from the 1960s to 1980s as well as anecdotal evidence since the late 19th century show that instrumental drug use is and has been for a long time a common phenomenon. It should thus also be investigated and treated accordingly.

Keywords: enhancement, addiction medicine, drug policy, stimulant drugs, drug instrumentalization

OPEN ACCESS

Edited by:
Simona Pichini,
National Institute of Health (ISS), Italy

Reviewed by:
Ornella Corazza,
University of Hertfordshire, United Kingdom
Francesco Paolo Busardò,
Sapienza University of Rome, Italy

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *29 May 2020*
Accepted: *17 August 2020*
Published: *04 September 2020*

Citation:
Schleim S (2020) Neuroenhancement as Instrumental Drug Use: Putting the Debate in a Different Frame. Front. Psychiatry 11:567497. doi: 10.3389/fpsyt.2020.567497

INTRODUCTION

Neuroenhancement received a lot of attention by ethicists, legal scholars, pharmacologists, and researchers from further disciplines since the beginning of the 21st century (1, 2).[1] According to the analysis of O'Connor, Rees, and Joffe, enhancement of the brain was also the most frequent neuroscience-related topic in general news media (3). It actually received so much attention that Lucke and colleagues spoke of a "neuroenhancement bubble" (4). The substances discussed most intensively are the stimulant drugs amphetamine, methylphenidate, and its analogs, also known as treatments for attention and impulsivity disorders, as well as the wakefulness promoter modafinil (5–7). Presently, questions like whether the use of performance enhancing drugs at universities should be seen as cheating (8) or psychiatrists' attitudes towards prescribing such substances in academic settings (9) are being discussed and investigated. The ethical and regulatory challenges of pharmacological enhancement were also addressed in this journal very recently (10).

The topic gained popularity with the rise of "neuroethics", a new discipline specifically intended to cover ethical, legal, and social challenges related to the neurosciences (11). Along with

[1] These publications in the high impact journals *Nature Reviews Neuroscience* and *Nature* received 772 and 973 Google Scholar citations (as of August 18, 2020), respectively, and are still being cited nowadays.

some academic scholars, news media soon reported that neuroenhancement is a common and increasing phenomenon, in some cases literally "as common as coffee" (12). But a colleague and I showed earlier that such claims are often exaggerated (13–16). Describing neuroenhancement as new and increasing lent and still lends much of the urgency to this discussion and related research. We reported evidence, though, that the phenomenon, particularly the use of stimulant drugs in academic settings, exists at least since the 1930s (14, 15).

That people use drugs to change their psychological state in order to study or work better has been associated with many terms before: cognitive, affective, or neuroenhancement, brain doping, smart drugs, non-medical drug use, recreational drug use, substance abuse, and probably many more. Publications in neuroethics particularly used the term "enhancement" and discussed it with respect to ethical issues such as freedom of choice, individual and social performance improvement, coercion, and fairness (1, 2). In this paper, I want to put it in a different perspective: that of *instrumental drug use*. Hitherto, the discussion of neuroenhancement in neuroethics on the one hand and research on addiction, substance abuse, drug diversion (17) and diffusion (18) on the other have been proceeding mostly separate from each other. For example, the previously mentioned seminal and influential publications don't even address the topic of addiction (1, 2). If we frame the phenomenon as instrumental drug use instead, we can easily integrate that which should never have been separate in the first place.

INSTRUMENTAL DRUG USE

It is a matter of fact: Many people are and have been using substances to achieve different kinds of aims. This is what characterizes such use as *instrumental*: People are doing it for a certain purpose; the substance thus becomes an instrument to get what people want to get. Note that this also introduces a notion of rationality, if people are justifiably convinced that doing something increases the likelihood of reaching a specific goal, and are then doing it. Substance use can imply irrational aspects, too; for example, when consumers are taking a substance to achieve a certain goal but at the same time damage themselves or others. This would conflict with the aim of being healthy and maintaining good relations.[2] People could also fail to stop using substances, even knowing that they harm themselves or others or that their use is getting out of control. This puts us into the domain of addiction, which has traditionally been discussed as an example for limiting human rationality and freedom. What I want to show here is that—at least within certain boundaries—substance use can be instrumental and thus rational. And substances affecting the nervous system on which our psychological functioning relies are in many instances called "drugs". In that sense, drugs can be understood as instruments, which has particularly been elaborated theoretically as well as practically by Christian P. Müller (19, 20).

Müller argues that instrumental drug use has ancient roots in human and actually also non-human history and that it can have an adaptive value in evolution. Thus, animals being able to use drugs to increase their chances of survival and procreation would have evolutionary benefits. Specifically and for humans in the present society, he distinguished nine different goals of drug instrumentalization: (1) improving social interaction; (2) facilitating sexual behavior; (3) improving cognitive performance or counteracting fatigue; (4) facilitating recovery or coping with stress; (5) self-medication for psychiatric disorders and mental problems; (6) sensory curiosity (*e.g.* "expanding" one's perceptions); (7) experiencing euphoria, hedonia, or a "high"; (8) improving physical appearance or attractiveness; and (9) facilitating spiritual or religious activities (19).

Note that just by distinguishing these nine goals one does not automatically approve of that behavior. In the debate, "enhancement" or "brain doping" might be positively or negatively biased concepts, respectively. In contrast to that, "instrumental drug use" seems a more neutral alternative, an alternative that provides us with a general analytical tool to make sense of people's drug consumption. In the context of the neuroenhancement debate, particularly Müller's first (social interaction), third (cognitive performance), and fourth (coping with stress) goal would be salient, as these are arguably relevant domains in present-day study and work environments. To demonstrate the usefulness of this analytical category, I shall discuss studies about the prevalence of instrumental drug use, from the past as well as the present, and then try to unify the different perspectives in the conclusion.

PREVALENCE STUDIES

Dozens of studies addressed the prevalence of instrumental drug use in study or work contexts. Already in 2011, Smith and Farah reviewed evidence from 28 individual articles investigating students' "nonmedical stimulant use" published between 2000 and 2009 (21). It is important to understand that methodologies varied widely: Most studies were based on self-reports from non-representative samples sized between N = 50 and N = 54,079 participants. The kinds of drugs included in the surveys differed (*e.g.* only prescription stimulants like methylphenidate or amphetamine or also illicit drugs like cocaine) as did the time spans (last month, last year, or lifetime use). Unsurprisingly, the outcomes then varied widely between 1.7 and 55%. The latter figure comes from a study investigating only fraternity members at a single location, a group that is notorious for its above-average drug use (22). Finally, not all studies asked for the motives of the nonmedical drug use and where they were surveyed answers also indicated recreational use like experiencing a "high" or partying better.

[2] It goes without saying that some consumers might simply not care about their own health or the wellbeing of others when trying to achieve their aims. Many athletes engaging in doping accept the possible—and in some cases even probable—health risks, perhaps even the risk of death, associated with performance-enhancing drug consumption. The philosophical discussion of which behaviors can be deemed rational and which not goes beyond the purview of this paper.

A very recent systematic review of nonmedical prescription stimulant use found already 111 studies meeting the inclusion criteria (23). But just like Smith and Farah before, Faraone and colleagues found much variance between the publications in terms of definitions used to investigate nonmedical use, methodologies, and samples, which made a formalized meta-analysis impossible. Similar to the earlier review, the prevalence of self-reported use varied between 2.1 and 58.7% and almost exclusively referred to student populations. The only population-based estimate, the US National Survey on Drug Use and Health 2015–2016, found that 2.1% adults had used stimulant drugs nonmedically at least once in the past year (24). Importantly, Faraone and colleagues discuss the reasons for which people had used the drugs in much detail. Academic motivations were mentioned most frequently. However, this may simply reflect that most participants were college students for whom this is particularly salient. The second most commonly mentioned reason was recreation (*e.g.* "getting high", enhancing the effects of other drugs, help with socializing). Weight loss was cited less frequently as motivation. Summarizing all the data, males, 18–25 year-olds, whites, fraternity/sorority members, students with worse grades, people who had been binge drinking in the last month, had used marijuana or nonprescription stimulants (*e.g.* MDMA or methamphetamine) in the past year, had had adverse childhood experiences, and have not grown up with both biological parents were most likely to use prescription stimulants (23). The authors conclude that this use is a significant public health problem, but that it has not reached epidemic proportions like nonmedical opioid use in the United States.

One survey deserving individual attention is the recent cross-sectional study of pharmacological cognitive enhancement among non-ADHD individuals in 15 countries by Maier and colleagues (25). Their data are based on the Global Drug Survey of 2015 and 2017, jointly comprising responses of more than N = 100,000 subjects who filled out questionnaires anonymously on the internet in response to advertisements in offline and online media. Remarkably, the authors report an almost threefold increase of the 12-month prevalence of prescription stimulant, modafinil, and/or illegal stimulant use to increase performance when studying or working from, on average, 4.9 to 13.7% in the 15 countries (United States, Netherlands, United Kingdom, Canada, Belgium, Ireland, France, Australia, Hungary, Brazil, Austria, Switzerland, Germany, Portugal, and New Zealand; in the order of the prevalence in 2017, from highest to lowest). In some countries, the increase would have been *sixfold* (France, from 2.7 to 16.2%) or almost sixfold (Ireland, from 3.4 to 18.8%) in only *two years*.

However, the authors concede that the wording of the questions was changed between the two cohorts and that, while their annual surveys on drug use always run from November to January, the new module on performance enhancing use for the 2017 cohort had to be removed after only one month because it had made the survey too long (25). Therefore, the second cohort is almost two thirds smaller than the first. The authors conclude that the differences still reflect a real increase of stimulant use for performance enhancement. Yet, as I see it, there is the possibility that drug consumers were more motivated to respond quickly and to complete the long version of the survey than non-consumers. This shows that it is difficult to make reliable statements about an increase even by studies from the same research team if the procedure is not repeated *exactly* and not based on a representative sample. An interesting finding of the second cohort, though, is that cannabis, alcohol, and benzodiazepines, which have been added in the 2017 survey, were also mentioned as performance enhancement drugs by many, particularly to increase relaxation such that one could study or work better at a later time.

To my knowledge, the hitherto most reliable evidence for an increase is reported by McCabe and colleagues, who repeated a survey at a North American college six times in the period from 2003 to 2013 (17). The non-representative samples reported an increase from 5.4 to 9.3% for the past-year and from 8.1 to 12.7% for the lifetime nonmedical use of stimulant drugs, respectively. Unfortunately, the researchers did not publish their results on the frequency of consumption. Students might thus simply have tried to find out what the media hype described in the *Introduction* above is about and used the substances only a few times.[3]

I would now like to compare these systematic reviews and essential surveys from the 21st century with studies published before 1990. To my knowledge, they have neither been addressed in the neuroethical debate nor in the studies summarized above. Smith and Blachly, for example, reported in 1966 that 92 (44%) of 208 medical students had used amphetamine at least once in their life (27). Of these consumers, 46% mentioned reduced fatigue, 11% reduced appetite, 10% improved alertness, 4% improved attention span, and also 4% increased motivation as benefits. Note that this is also instrumental drug use in the sense Müller described above (19, 20). In a much bigger sample of N = 7,170 New England college students, Wechsler and Rohman investigated, among other drugs, marijuana, stimulant, cocaine, tranquilizer, and hallucinogen consumption (28). The past-year prevalence reported in 1981 was 59.3, 16.2, 11.1, 9.6, and 7.8%, respectively. Of these consumers, 16% had used stimulants, 11% cocaine, and 10% tranquilizers to stay awake or study better, which we would nowadays often call "neuroenhancement".

The most relevant study I found from this period is by McAuliffe and colleagues who reviewed prevalence data on nonmedical drug use by present and future health professionals in no less than 21 individual studies published between 1966 and 1980 (29). Besides recreational use and self-treatment, they also defined instrumental use "to stay awake, to fall asleep, or to perform better on tests or in sports" as nonmedical use. The lifetime prevalence of amphetamine consumption, which was mostly instrumental, ranged between 11 and 54% in these samples. The authors discuss that the instrumental amphetamine use would be declining since the mid-1960s, while the recreational use of other drugs would be increasing. The same authors published a survey of N = 337 physicians, N = 312 pharmacists, N = 381 medical, and N = 278 pharmacy students two years after

[3] In personal correspondence, Sean McCabe referred to another study in which they addressed the frequency of consumption. There, indeed, 82.1% of past-year nonmedical users of prescription stimulants reported use on less than 10 occasions (26).

their review (30). For 19 drugs, including several stimulants, sedatives, and opioids, the groups had a self-reported 33.3, 19.3, 43.6, and 41.1% past-year prevalence, respectively, for recreational, instrumental use, and self-treatment combined. The professionals reported an average of 43.7 consumptions in their life and the students between 64.6 and 65.7. The lifetime prevalence for instrumental use in particular, thus to stay awake, facilitate work, or sports, was 16% for the physicians and 17% for the medical students.

These figures suggest that nonmedical drug use in general and instrumental consumption to study or work better was common, perhaps even more common in the 1960s to 1980s than it is now in the early 21st century. Anecdotal evidence for students consuming amphetamine to improve their academic performance can be traced back until the 1930s in the USA and the Netherlands (31–33). Instrumental stimulant drug use is likely even half a century older in Europe, where the German pharmacologist and military surgeon Theodor Aschenbrandt gave cocaine to Bavarian soldiers during a maneuver in 1883 and noted their increased capacity to endure hunger, strain, fatigue, and heavy burdens (34), which in turn inspired Sigmund Freud's research on the drug (35).[4]

CONCLUSION

A critical conclusion from the previous section is that the rationale of carrying out ever more surveys on consumption prevalence is questionable if they use such different definitions and methodologies that even after 60 years of research no clear picture emerges, not even on whether the substance use is increasing relevantly or not. A common view on drug instrumentalization could solve at least some of these issues. In any case, the evidence reviewed in this paper suggests that neuroenhancement, if one wants to use this term, was certainly not a new phenomenon in the early 2000s. That stimulant drugs and mostly amphetamine and methylphenidate, which are available since the 1930s to 1950s, still belong to the most frequently nonmedically used substances according to the studies summarized above supports that conclusion. Note that evidence that these drugs are actually enhancing the functioning of healthy people in real-life settings is scarce as the new meta-analysis by Roberts and colleagues demonstrates once more (7). Caviola and Faber argued earlier that the effects are probably not better than those of computer training, physical exercise, and healthy sleep (36). Additionally, the minor to modest effects of the drugs have to be balanced against their risks and side-effects.

Perhaps it was due to the enthusiasm of neuroethicists who emerged as a new profession in the early 2000s that such drug use was described as a new trend and framed first as "enhancement" and then as "neuroenhancement". But does it make sense to discuss the old phenomenon under a new label? I proposed here to apply Müller's general framework of instrumental drug use instead (19, 20). That a substantial amount of people use various kinds of substances to achieve certain goals is a fact. From a public health perspective, it appears to make no sense to treat the nine different aims distinguished by Müller differently, as the risks of the consumption of, say, amphetamine do not differ whether someone uses the drug to study longer or to party longer.[5] We have seen that, by contrast, framing substance use to study or work better as "enhancement" carried the risk of not addressing the problem of addiction at all (1, 2). Interestingly, the new survey by Maier and colleagues also found that about 28% of the stimulant consumers taking the substances to increase their cognitive performance would like to use less, but fewer than 2% reported to actually seek help (25). This suggests that this could be an important field for addiction medicine.

Treating Müller's nine goals differently on the legal or ethical level would require someone to take value judgments about which are morally better or worse aims. My considerations don't amount to a radical legalization of all substances, but rather to a more consistent treatment of them, in accordance with persistent calls for a more science-based drug policy (37). Concurring with a critique voiced against Müller's approach before by Wu, I would emphasize the importance to protect people from too much external pressure and coercion such that they are as autonomous as possible to choose for themselves (38, 39). The big difference between, for example, English- and German-speaking countries that came up in the survey by Maier and colleagues calls for follow-up studies investigating cultural, social, and economic factors explaining why so many more people take stimulant drugs in the former than in the latter. But also for this research the idea of drug instrumentalization would provide a viable and actually more fine-grained framework.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

FUNDING

This publication has been supported by the "History of Neuroethics" grant by the Dutch Research Foundation (NWO), grant number 451-15-042.

[4] I am indebted to my colleague Jeremy Burman for drawing my attention to Freud's early research on cocaine.

[5] Everything else being equal. Of course, it could be that common consumption patterns differ in that they are requiring higher doses or are combined with other risky behaviors for some purposes. But this rather seems to be a gradual than a principal difference.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 11 September 2020
doi: 10.3389/fpsyt.2020.546796

The Psychonauts' World of Cognitive Enhancers

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Background: There is growing availability of novel psychoactive substances (NPS), including cognitive enhancers (CEs) which can be used in the treatment of certain mental health disorders. While treating cognitive deficit symptoms in neuropsychiatric or neurodegenerative disorders using CEs might have significant benefits for patients, the increasing recreational use of these substances by healthy individuals raises many clinical, medico-legal, and ethical issues. Moreover, it has become very challenging for clinicians to keep up-to-date with CEs currently available as comprehensive official lists do not exist.

Methods: Using a web crawler (NPSfinder®), the present study aimed at assessing psychonaut fora/platforms to better understand the online situation regarding CEs. We compared NPSfinder® entries with those from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and from the United Nations Office on Drugs and Crime (UNODC) NPS databases up to spring 2019. Any substance that was identified by NPSfinder® was considered a CE if it was either described as having nootropic abilities by psychonauts or if it was listed among the known CEs by Froestl and colleagues.

Results: A total of 142 unique CEs were identified by NPSfinder®. They were divided into 10 categories, including plants/herbs/products (29%), prescribed drugs (17%), image and performance enhancing drugs (IPEDs) (15%), psychostimulants (15%), miscellaneous (8%), Phenethylamines (6%), GABAergic drugs (5%), cannabimimetic (4%), tryptamines derivatives (0.5%), and piperazine derivatives (0.5%). A total of 105 chemically different substances were uniquely identified by NPSfinder®. Only one CE was uniquely identified by the EMCDDA; no CE was uniquely identified by the UNODC.

Conclusions: These results show that NPSfinder® is helpful as part of an Early Warning System, which could update clinicians with the growing numbers and types of nootropics in the increasingly difficult-to-follow internet world. Improving clinicians' knowledge of NPS could promote more effective prevention and harm reduction measures in clinical settings.

Keywords: cognitive enhancers, nootropics, novel psychoactive substances, novel psychoactive substances, screening, early warning systems

OPEN ACCESS

Edited by:
Simona Pichini,
National Institute of Health (ISS), Italy

Reviewed by:
Stefania Chiappini,
University of Hertfordshire, United Kingdom
Jeremy Carlier,
Sapienza University of Rome, Italy

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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *29 March 2020*
Accepted: *17 August 2020*
Published: *11 September 2020*

Citation:
Napoletano F, Schifano F, Corkery JM, Guirguis A, Arillotta D, Zangani C and Vento A (2020) The Psychonauts' World of Cognitive Enhancers. Front. Psychiatry 11:546796. doi: 10.3389/fpsyt.2020.546796

INTRODUCTION

Cognitive enhancement may be defined as "the amplification or extension of core capacities of the mind through improvement or augmentation of internal or external information processing systems" (1). Both non-pharmacological and pharmacological enhancers are sought by the general public in order to improve performance during studying and at work by increasing concentration, motivation and accuracy, *via* physical, behavioral and biochemical activities (2).

Cognitive enhancer drugs (CEs) are also known as "nootropics" (from the Greek 'nous' meaning 'mind' and 'trepein' meaning 'turning/bending'), a term initially penned by Corneliu Giurgea when piracetam was found to exhibit memory-enhancing properties in clinical trials (3, 4). Cognitive enhancer drugs such as modafinil improve cognition in very specific ways such that it enhances "pattern recognition memory, digit span recall, and mental digit manipulation" (5).

Cognitive Enhancers, Historical Perspective and State of the Art

Historically, CEs have been used to treat conditions related to cognition deficits such as Alzheimer's disease, psychiatric disorders such as schizophrenia (6), stroke or attention deficit hyperactivity disorder (ADHD) (7–9). These phenomena commonly occur with aging (7–9). It was found that some CEs also improve cognitive functions in healthy subjects, such as memory, executive functions, creativity, and motivation (10). Their use has become more and more prevalent among college, high school, and university students as well as in the military (11–13).

The world of CEs is multifaceted and complex, with different molecules acting with different modes of actions and on different (and often multiple) receptors in the central nervous system (CNS). "Natural" enhancers such as nicotine (14–17) and caffeine (18) are generally accepted as substances that help us by improving focus, alertness, and productivity. Food-based antioxidants, herbal, and other food-derived nootropic agents have become increasingly popular in recent times after there have been suggestions of associations between cognition and diet (19). Prescription drugs, such as modafinil, amphetamine, and methylphenidate are used off-label by healthy people who do not have specific deficits but want to improve their standards of intellectual and cognitive performance (20). Cognitive enhancers also include many drugs which have never reached the market as they have been discontinued in Phase II or III clinical trials (7–9). The many dimensions of cognitive enhancement are described and disentangled in a recent review (2). Dresler and colleagues (2) pointed out how cognitive enhancement is not a monolithic phenomenon and how there are a great variety of interventions that can be classified and clustered into biochemical, physical, and behavioural enhancement strategies.

Misuse of Cognitive Enhancers

The most prevalent CEs that are currently abused/misused include diverted prescription medicines such as those used for the treatment of attention deficit hyperactivity disorder (ADHD) *i.e.* methylphenidate (MPH) and amphetamine/dextroamphetamine (Adderall—most common brand); "wakefulness-promoting agents" with psychostimulant effects such as modafinil (21–23); illicit psychostimulants such as amphetamine, and drugs that act on the glutamatergic AMPA receptors, the so-called ampakines or "glutamate activators" (24). While the benefits of medications, such as MPH or modafinil, in patients suffering from specific diagnosed conditions (such as ADHD or narcolepsy) have been studied and evaluated, the potential benefits of these substances in heathy individuals remain unclear. The use of CEs in healthy individuals poses significant concerns due to the lack of clinical evidence regarding their safety, effectiveness, and social consequences, especially with long-term use.

Urban and Gao (24) emphasized that these newly misused drugs, *i.e.* MPH, may in fact improve cognition by acting on the memory and learning circuits, thus exciting the dopamine/glutamate/noradrenergic neurons. The modulation of these neurotransmitters in healthy individuals seeks to enhance their cognitive functions beyond baseline levels, but may also lead to paradoxical effects, particularly in children's and adolescent's growing brains (25). In these cases, glutamate modulation may impair behavior flexibility, which may facilitate addictive behaviors. Conversely, dopamine and norepinephrine reuptake inhibition may lead to a hyperdopamin-/hypernoradrenalin-ergic state, which may induce a cognition decline because the relationship between the prefrontal cortex cognition enhancement and the levels of both dopamine and noradrenaline is non-linear and actually an inverted U-curve (25–27). Urban et al. (28) have also emphasized that the use of CEs such as MPH and modafinil can have short- and long-term impacts on plasticity in the pre-frontal cortex that may affect the potential for plastic learning especially in children and adolescents.

Like many other NPS, nootropics have become increasingly easily available on the internet over the last 20 years. According to the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA) on new psychoactive substances (NPS), NPS have been reported from over 100 countries and territories from all regions of the world (29–32). In addition, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has been monitoring more than 700 NPS that have appeared on Europe's drug market in the last 20 years, of which almost 90% have appeared in the last decade (33, 34). The European Database on New Drugs (EDND) of the EMCDDA records the notifications of new substances and the detection of NPS in Europe (35). Although many of these identified NPS might be used by healthy people as CEs, there are limited data on how many or which substance is, nor are CEs classified as a specific category. Despite being a challenging task in view of the pharmacological differences of CEs, producing a formal classification of these substances is crucial in order to further

Abbreviations: ADHD, attention deficit hyperactivity disorder; CEs, cognitive enhancers; EDND, European Database on New Drugs; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; EWA, Early Warning Advisory; GABA, gamma-aminobutyric acid; IPEDs, imaging and performance enhancing drugs; MPH, methylphenidate; NPS, novel psychoactive substances; SSRIs, Selective Serotonin Re-uptake Inhibitors; UNODC, United Nations Office on Drugs and Crime.

develop scientific research on the topic as well as regulate and monitor their use and effects.

Previous Findings and Current Challenges

Scientific data regarding NPS used or misused as CEs are lacking. Recent research papers mostly focus on the misuse of specific and well-known CEs such as methylphenidate analogs (36, 37), designer benzodiazepines, phenmetrazine, modafinil, novel synthetic opioids (37), and MPH (38). More literature is available on CEs which are potentially able to address cognitive deficits in specific patient groups. Froestl and Maitre (39) have classified these molecules into 19 categories based on their pharmacodynamics. Some of these molecules could not be classified based on their pharmacodynamics and hence were classified based on their chemical structure or their origin *i.e.* as natural products or endogenous molecules (39). Many of these drugs were clinically tested for their potential to improve cognitive function. Although they all might have a potential for being misused by the general public looking to enhance their cognitive abilities, the vast majority of these molecules have never reached the market as most of them have been discontinued in Phase II or III clinical trials (7–9).

A comprehensive literature review completed by Froestl et al. (7–9) proposed a description and a classification of 1,705 molecules as "nootropic agents or CEs" in the Thomson Reuters Pharma database, which were studied for their potential to counter cognitive deficits in Alzheimer's disease. The large number of CEs, reported in the latter review, is attributed to the fact that it contains a high proportion (42%) of molecules that were tested for the treatment of dementia and molecules which were discontinued. Many CEs were described as groups or families (*i.e.* beta-amyloid aggregation inhibitors). These CEs were not identified by either the EDND, EWA, or NPSfinder® as this is not part of the remit of any of the NPS early identification systems. In particular, many categories of CEs described by Froestl et al. (7–9) such as "Drugs interacting with Cytokines", "Drugs interacting with Gene Expression", "Drugs interacting with Heat Shock Proteins", "Drugs interacting with Hormones", "Drugs interacting with Ion Channels (different from receptors)", "Drugs interacting with Nerve Growth Factors", "Drugs interacting with Transcription Factors", "Metal Chelators", "Drugs preventing amyloid-beta aggregation", "Drugs preventing amyloid-beta aggregation", "Drugs interacting with tau", "Stem Cells" include molecules specifically targeted for Alzheimer's disease and, therefore, less likely to be relevant for the NPS early identification systems.

Apart from the known families of CEs (historically derivatives of MPH, modafinil, and racetams), psychonauts (subjects who experience intentionally drug-induced altered states of consciousness (40) have been experimenting with a variety of commonly prescribed drugs as well as illicit substances, often finding subjective evidence of cognitive enhancement and sharing their knowledge within the dark web sites and surface internet fora. At present, a comprehensive, up-to-date list of currently available CEs does not exist. Moreover, CEs are not described as a specific category/family within the EDND or EWA databases; this is because many substances, with many different (complex and, sometimes, not fully understood) pharmacological mechanisms, have the potential of improving aspects of cognition. Finally, some of these substances are not illegal (*i.e.* prescribed medication, food supplements, natural remedies *etc.*). For these reasons, it is difficult to create an early identification system which is able to keep professionals up-to-date with the CEs which are currently available to the general public *via* the online market.

Aims of the Study

In this study, the aims were to (a) identify and categorize the number of CEs collected by the NPSfinder® web crawler from a range of psychonaut, NPS-related, online sources; (b) compare the NPSfinder® cognitive enhancers' list with related findings from the UNODC's EWA and the EMCDDA's EDND.

MATERIALS AND METHODS

NPSfinder®, a Tool for the Early Recognition of NPS

NPSfinder® is a crawling/navigating software which was designed to facilitate the early recognition of the continuously growing amount of NPS that are available on the internet. At present, NPSfinder® is a password protected proprietary software, which allows registered researchers only to screen and classify the substances that are identified by the software. An open access part, which will allow the general public to have free access to the substances, is under development.

NPSfinder® automatically scans the web for new/novel/emerging NPS, including CEs, *via* the identification of psychonauts' websites/fora. Every time a new website is identified, all its items are scanned and compared with the online existing ones. When a novel substance is found, this is added to the growing NPSfinder® database. NPSfinder® screening process is tailored to each website, and no specific keywords are used by the software. This proprietary method, which was created by trained software engineers, allows to map, on a 24/7 basis, the large variety of psychoactive molecules mentioned/discussed within a range of representative online psychonauts' web sites/fora. This list is continuously growing (the current, full list of these sites is available upon request).

NPSfinder® was designed to extract a range of information regarding NPS, including: chemical and street names; chemical formulae; three-dimensional images and anecdotally reported clinical/psychoactive effects.

Identification of Cognitive Enhancers by NPSfinder®

NPSfinder® has been already successfully used to identify other types of NPS, including synthetic cathinones (41), novel psychedelics (42), and novel opioids (43). In each paper, the comparison with international or European NPS databases has shown that NPSfinder® is able to identify substances which were not previously described by the existent early detection systems. Raising awareness of novel substances has important implications from both a legislative and a clinical perspective.

Between 26 November 2017 and 31 May 2019, NPSfinder® carried out a range of open web crawling identification activities

focusing on a large range of psychonaut-based, specialized, multilingual sources with a specific focus on new/traditional psychoactive substances of likely recreational interest. Although the language most typically used in these websites was English, further languages analyzed by NPSfinder® included: Dutch, French, German, Italian, Russian, Spanish, Swedish, and Turkish. With the help of an *ad hoc* check control panel, all data were manually examined by four medically/psychiatrically-trained professionals (*i.e.* FN, DA, CZ, and LG). In this way, a full assessment and editing of each NPSfinder® data item were conducted, and the range of unique CEs presented here was identified.

The collection of further information was completed by consulting a range of open libraries and chemistry databases referring to the index item, if existing. These data were then stored in an online, restricted access/password-controlled database located within firewall protected, highly secure, and consistently performing servers.

When any new item was detected during the automated web scan, the system sent an e-mail notification/alert to the core researchers' mailing list. Data were then screened for relevance and possible duplications.

The identified psychoactive substances were classified as CEs when a cognitive enhancing ability of any kind (such as improved attention, concentration, alertness, and memory) was mentioned in the description and/or among the effects of the psychoactive substance. The used terms for the search were "nootropic", "cognitive enhancers", "cognition enhancement", "smart drugs", "memory enhancers", "concentration enhancers", "attention enhancers", "neuro enhancers", and "intelligence enhancers". Therefore, it is to be noted that these identified CEs are thought by psychonauts as having cognitive enhancing properties according to their subjective and anecdotical experience rather than due to any pharmacological analysis.

When a substance that was identified by NPSfinder® was not explicitly described as able to enhance cognitive abilities but was listed as a known CE within the comprehensive review by Froestl et al. (7–9), it was still included among the list of NPSfinder® CEs.

Identification and Classification of Cognitive Enhancers

The NPSfinder® CE results (updated to May 2019) were compared with those reported by the UNODC's EWA on NPS (updated by April 2019) and the EMCDDA's EDND (updated by April 2019).

Using chemical structure identification and other published information (*i.e.* published research papers and official databases), researchers assigned each molecule to its drug class, using the classification described by Schifano et al. (44, 45) for NPS. This classification includes the following families: synthetic cannabimimetics, synthetic cathinones, novel psychostimulants, novel derivatives of classic psychedelics phenethylamines/MDMA-like drugs, synthetic opioids, synthetic cocaine substitutes, novel tryptamines derivatives, GABAergic drugs, phencyclidine-like dissociative drugs, piperazine derivatives, herbs/plants, prescribed drugs, and image and performance enhancing drugs (IPEDs).

RESULTS

Identification and Classification of CEs

After about 18 months of operation, the number of substances identified by the web crawler activities was 5,922. By the time of writing (January 2020), 4,204 unique NPS substances were included in the database, and 1,718 out of 5,922 (29.0%) remaining substances were found to be false positives or duplicates. The most common NPS mentioned in psychonauts' fora included: psychedelic phenethylamines (30.1%); synthetic cannabimimetics (29.8%); and opioids (10.1%).

A total of 142 unique CEs was identified by NPSfinder® (**Table A1**). Of these, 35 were explicitly described as having nootropic properties by psychonauts; the remaining 107 molecules were classified as CEs as also present in the comprehensive review on CEs written by Froestl et al. (7–9).

Using the classification described by Schifano and colleagues (44, 45), the CEs identified by NPSfinder® (n = 142) were divided into 10 categories; the majority of these substances were classified as plants/herbs/products (29%), prescribed drugs (17%), image and performance enhancing drugs (IPEDs) (15%), and psychostimulants (15%); in addition, there were substances classified as miscellaneous (8%), phenethylamines (6%), GABAergic drugs (5%), cannabimimetic (4%), tryptamines derivatives (0.5%), and piperazine derivatives (0.5%) (**Table 1**).

Comparison of NPSfinder® Findings With EU and UN NPS-Related Databases

Current NPSfinder® results were compared with the EMCDDA and the UNODC databases in order to ascertain which molecules were also detected and listed by the official European and United Nation early identification systems.

Out of the 142 molecules identified as CEs by NPSfinder®, a total of 105 chemically different substances were uniquely identified by NPSfinder®; of the remaining 37 molecules, 22 were also listed in both the EDND and EWA databases, 15 of which were reported in both the NPSfinder® and in either the EMCDDA (n = 11) or the UN databases (n = 4) (**Table A1**).

Only one CE was uniquely identified by the EDND (*MIQ-001, also called meta-IQ*); no CE was uniquely identified by the EWA database.

TABLE 1 | CEs identified by NPSfinder® using Schifano et al.'s (44) classification (n=142).

Class (44)	N. of CEs
Plants/herbs/products	41 (29%)
Prescribed drugs	24 (17%)
Image and performance enhancing drugs (IPEDs)	21 (15%)
Psychostimulant drugs	21 (15%)
Miscellaneous	11 (8%)
Phenethylamines	9 (6%)
GABAergic drugs	7 (5%)
Cannabimimetic	6 (4%)
Tryptamines derivatives	1 (0.5%)
Piperazine derivatives	1 (0.5%)
TOTAL	**142**

CEs Identified According to Their Identification Source

Figure 1 shows the number of CEs identified by each source (including NPSfinder®, EDND and EWA database) as well as the ones identified by more than one source. A full list of the CEs is available upon request.

DISCUSSION

In this paper, we aimed to evaluate whether the innovative crawling software NPSfinder® can be employed as a helpful tool in the early identification and prediction of CEs. In order to achieve this goal, findings from NPSfinder® were cross-checked with two official sources (EMCDDA's EDND and UNODC's EWA). To the best of our knowledge, this is an unprecedented list of drugs which are described as CEs and, therefore, with a potential for recreational misuse by healthy individuals.

NPSfinder® identified 35 molecules (out of the total of 4,204) that were described by psychonauts as having cognitive enhancing effects, such as improved memory, alertness, attention, and concentration. A further 107 molecules were previously described as CE (7–9), although psychonauts did not explicitly describe them as CE. Since psychonauts experiment with novel substances in order to intentionally experience altered states of consciousness, it is to be expected that their interest also extends to the world of CEs. Among the CEs that they have been discussing online, there are mostly molecules that are known to have nootropic properties, are not illegal, and are likely to be easily available on the market (such as racetam compounds, modafinil and its derivatives, methylphenidate and its derivatives and food supplements).

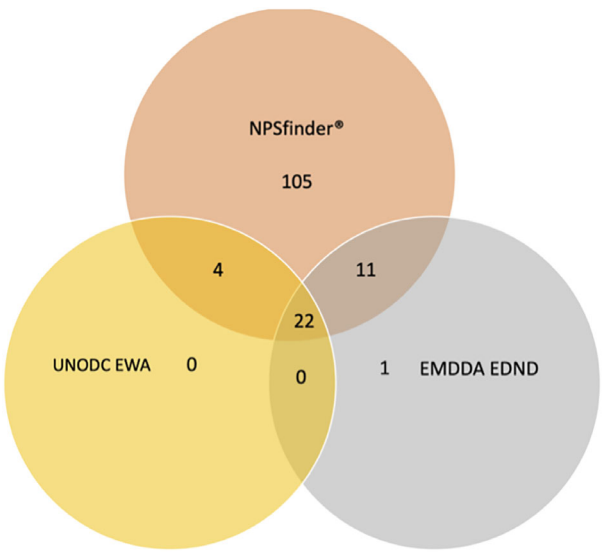

FIGURE 1 | Number of CEs identified by EMCDDA, UNODC, and NPSfinder® according to their identification source (n = 1,785).

Our results showed that NPSfinder® could be employed as an Early Warning System tool to help clinicians with keeping their knowledge up-to-date with the growing numbers and types of nootropics in the increasingly difficult-to-follow online market.

It is not surprising that the included sources (*i.e.* NPSfinder®, EDND, and EWA) have identified mis-matching numbers and types of CEs, as they differ in their methodology and purposes of CE identification. In fact, the EDND was created in order to allow the European Union to rapidly detect, assess, and respond to health and social threats caused by NPS (35). The UNODC EWA on NPS provides access to basic information on new psychoactive substances, including trend data, chemical details on individual substances, supporting documentation on laboratory analysis and legislative responses (30). Specifically, the EDND and EWA focus on illegal drugs and do not look at websites that contain patented medications, while NPSfinder® looks at websites whose contributors might have accessed sources containing patent medications.

NPSfinder® Findings

The large number of molecules that are both identified by NPSfinder® and described by Froestl et al. (7–9) leads us to believe that nowadays psychonauts are discussing (and likely using) substances that have been considered or used for the treatment of the Alzheimer's disease over seven years ago, and they are doing so in order to improve their cognitive performances in the absence of clinical reasons.

Among the CEs that have been subjectively identified by psychonauts as able to improve certain aspects of their cognition, there are molecules whose objective cognitive enhancing properties have not been established by research studies, such as the selective serotonin re-uptake inhibitors (SSRIs), melatonin and many others.

Comparison of NPSfinder® Findings With EDND or EWA Databases

The large number of unique molecules that were uniquely identified by NPSfinder® can be explained with the innovative methodology that NPSfinder® used for the early identification of all NPS, including CEs (41–43). Being a dynamic software, NPSfinder® is able to automatically scan the web for new/novel/emerging NPS on a 24/7 basis. This is indeed an effective mechanism for the early identification of (potential) NPS, which are being discussed on the psychonauts' websites and fora.

Description and Classification of CEs Identified by NPSfinder®

The CEs identified by NPSfinder® (n = 142) were divided into 10 categories as shown in **Table 1**.

Plants/herbs/product:

The NPSfinder® family of "Plants/herbs/product" contains a list of plant-based substances with a variety of psychoactive ingredients (**Table 2**).

TABLE 2 | Plants/herbs/product (n=41; 29%).

1	Acetyl-L-carnitine
2	Areca nut
3	Arecoline (transdermal patch)
4	Bacopa monnieri
5	Caffeine
6	Catechins
7	Celastrus paniculatus
8	Cinnamon extract
9	Coumarins
10	Curcumin
11	Flavonoids
12	Ginger root extracts
13	Gingko biloba
14	Ginseng
15	Harmaline
16	Harmalol
17	Icariin
18	Kaempferol
19	Kava kava
20	Kratom
21	Lemon balm
22	Lobeline
23	Maca
24	Marijuana
25	Menthol
26	Mucuna pruriens
27	Naringin
28	Nicotine (patch)
29	Peganum harmala
30	Periwinkle
31	Quercetin
32	R-alpha-lipoic acid
33	Sakae naa
34	St John's wort
35	Tannic acid
36	Vitamin A
37	Vitamin B12
38	Vitamin D
39	Withania somnifera
40	Yerba Mate
41	Yohimbine HCL

In this group, there are many well-known substances such as: caffeine, nicotine, cinnamon, ginger root extracts, curcumin, ginseng, coumarins, menthol, St John's wort, Yerba mate, Bacopa monnieri, Areca nut (and its main active ingredient arecoline), Lemon balm, Mucuna pruriens, Peganum harmala, harmaline, harmalol, and lobeline, some of which are commonly used by ayurvedic traditional medicine or in other branches of alternative medicine to improve memory and/or to treat various diseases. Flavonoids such as quercetin and naringin, as well as vitamins A, B, and D are also part of this group.

There are studies on the cognitive enhancing properties of *caffeine* (18), *nicotine* (14–17), *curcumin* (46–48), *St John's wort* (*Hypericum perforatum*) (49), *Bacopa monnieri* (50), and many others. Perry and Howes (51) completed an informative review on medicinal plants in dementia, pointing out the potential cognitive benefits of a significant variety of plants and herbs. A recent systematic review has found that *tyrosine* and *caffeine* could enhance cognitive performance when healthy young adults are sleep-deprived in a military context (52).

Prescribed drugs:

Methylphenidate is undoubtedly the most prescribed CE, and being indicated for the treatment of ADHD in many countries, it is described, in this paper, within the "prescribed drugs" group. The non-medical use of methylphenidate as a CE, which involves an attempt to improve memory, increase mental concentration, control anxiety, and stimulate motivation and creativity, is rising worldwide (38, 53). Many other prescribed drugs are being talked about in psychonauts' blogs and fora (**Table 3**).

Among the "prescribed drugs" family described by NPSfinder® the SSRIs are also listed as a class. Research studies have often failed to demonstrate that SSRIs can have cognitive enhancing properties (54, 55). For example, neither *sertraline* (54) nor *citalopram* (55) appeared to be superior to placebo in improving cognition in patients with Alzheimer's disease and comorbid depression. It was also suggested that any cognitive benefits of SSRIs were likely to be secondary to their effect on mood or behavioral disturbances. However, a more recent review on the topic concluded that the lack of evidence for SSRIs as CEs or disease modifiers in Alzheimer's disease is more the result of omissions in clinical trial design, as opposed to reports of negative evidence (56). Interestingly, both *fluoxetine* and *methylphenidate* potentiate gene regulation in the striatum, and their combination seems to mimic cocaine effects, with related increased risk for substance use disorder (57).

It is possible that many prescribed drugs are currently being misused by the general public but not picked up by the regulatory bodies because the vast majority of them are not classified as illegal. It is important that more studies and cross-sectional surveys are conducted as well as that the current pharmacovigilance systems focus on determining current patterns and quantifying current usage of these drugs by healthy people.

TABLE 3 | Prescribed drugs (n=24; 17%).

1	123I-Ioflupane
2	Amphetamine/dextroamphetamine (Adderal)
3	Armodafinil
4	Atomoxetine
5	Dextroamphetamine
6	DL-Phenylalanine
7	Galantamine
8	Hydergine
9	Lisdexamfetamine
10	Melatonin
11	Memantine
12	Memantine extended release
13	Methylphenidate
14	Modafinil
15	Modafinil suphone
16	NSI-189
17	Quetiapine
18	S-adenosyl-methionine
19	Selegiline
20	Sildenafil
21	Stablon
22	Tadalafil
23	Tropicamide
24	Vasopressin

Image and Performance Enhancing Drugs (IPEDs):

Racetam compounds, which are classically one of the major CE family (58), are identified by NPSfinder® and listed within the IPEDs sub-group (**Table 4**).

Piracetam enhances cognitive function without causing sedation or stimulation (3). This drug is also being used in clinical practice for the treatment of several diseases (59–62) although its mechanism of action remains not fully understood.

NPSfinder® identified *aniracetam, coluracetam, fasoracetam, nefiracetam, oxiracetam, phenylpiracetam, piracetam, and pramiracetam*. Although all these substances have been mentioned in the psychonauts' fora as having nootropic properties, research studies have not always succeeded in demonstrating their cognitive enhancing qualities. For example, recent studies failed in showing that *aniracetam* improves working memory in pigeons (63), learning and memory in rats (64), or cognitive and affective behavior in mice (65). Moreover, *nefiracetam* did not prove to be more efficacious than placebo in ameliorating apathy in stroke (66) despite some positive pre-clinical results (67, 68). One old study on *pramiracetam* has failed to demonstrate any cognitive benefit from its administration to patients suffering from Alzheimer's disease (69). There are no available studies on *coluracetam, fasoracetam*, and *phenylpiracetam.*

Psychostimulant drugs:

Among the psychostimulant CEs are described many derivatives of *methylphenidate* and *modafinil* (**Table 5**). These have been listed in this group when not licensed as prescribed drugs.

Methylphenidate is a prescription drug with medical restrictions in several countries, therefore, many illegal analogues have emerged on the internet and darknet drug markets during the last few years (53). The derivatives of methylphenidate that have been identified by NPSfinder® include: *3,4-dichloromethylphenidate, 4-fluoromethylphenidate, 4-methylmethylphenidate, dexmethylphenidate, ethylphenidate, methylmorphenate*, and *methylnaphthidate.*

The derivatives of modafinil include: adrafinil, fladrafinil, flmodafinil, and N-methyl-4,4′-difluoro-modafinil.

TABLE 4 | IPEDs (n=21; 15%).

1	Acetildenafil
2	Alpha GPC
3	Aminotadalafil
4	Aniracetam
5	Centrophenoxine
6	Choline Bitartrate
7	Citicoline
8	Creatine
9	Coluracetam
10	Dehydroepiandrosterone
11	Fasoracetam
12	Homosildenafil
13	Huperzine A
14	Lovegra
15	Nefiracetam
16	Noopept
17	Oxiracetam
18	Phenylpiracetam
19	Piracetam
20	Pramiracetam
21	Vardenafil

TABLE 5 | Psychostimulants drugs (n=21; 15%).

1	3,4-Dichloromethylphenidate
2	4 CTMP
3	4-fluoromethylphenidate
4	4-Mthylmethylphenidate
5	Adrafinil
6	Benzyl cyanide
7	Dexmethylphenidate
8	Dimethylaminoethanol
9	Ethylphenidate
10	Fladrafinil
11	Flmodafinil
12	L-655,708
13	Methylmorphenate
14	Methylnaphthidate
15	N-Methyl-4,4'-Difluoro-Modafinil
16	N-Methyl-cyclazodone
17	Pemoline
18	Prolintane
19	Razobazam
20	RO-4938581
21	Tyrosine

Miscellaneous:

The categories "miscellaneous" include amino-acids such as *tryptophan and L-tryptophan, 5-hydroxytryptophan, phenylalanine*, and *theanine*, as well as man-made chemicals such as *vinpocetine* and *sulbutiamine* and other various molecules such as *beta-asarone, PRE-084*, and *RO-4491533*. No research studies are available regarding the misuse of these molecules by healthy subjects in order to ameliorate their cognitive function (**Table 6**).

Phenethylamines:

The phenethylamines-related compounds that have been identified by NPSfinder® are listed in **Table 7**.

These are stimulant, entactogenic, and hallucinogenic substances that share similar chemical structures with amphetamine, catecholamines, synthetic cathinones, and other molecules (70).

Phenethylamines are known to enhance mood and empathy in healthy subjects. Substituted phenethylamines also include substituted amphetamines, which have been used as CEs to

TABLE 6 | Miscellaneous (n= 11; 8%).

1	5-HTP
2	Beta-asarone
3	L-Tryptophan
4	Phenylalanine
5	PRL-8-53
6	PRE-084
7	RO-4491533
8	Sulbutiamine
9	Theanine
10	TRP
11	Vinpocetine

TABLE 7 | Phenethylamines (n=9; 6%).

1	2C-D
2	B-HO-Hordenine
3	Desoxypipradrol
4	Ephedrine
5	Geranamine
6	Hordenine
7	Isopropylphenidate
8	Octopamine
9	Propylphenidate

promote learning and memory but can ultimately lead to addiction (20). Dolder et al. (20) found that MDMA-induced subjective, emotional, sexual, and endocrine effects that were clearly distinct from those of *methylphenidate* and *modafinil*. To the best of our knowledge, there are no research studies or case reports focusing on the misuse of specific phenethylamines as CEs by healthy subjects.

GABAergic drugs:

GABAergic drugs are chemicals that produce their effects *via* interactions with the GABA system, such as by stimulating or blocking neurotransmission (71).

Among these, *GABA*, *tolibut*, *picamilon*, *phenibut*, and *f-phenibut* were discussed in the psychonauts' fora as having tranquillizing as well as nootropic properties (**Table 8**). There is increasing evidence suggesting that *phenibut*, a potent psychoactive substance with GABA-B agonist properties which is often sold as a "dietary supplement", can induce withdrawal and physical dependence which makes its use dangerous (72–76). *f-phenibut*, which is closely related to *phenibut*, is a central nervous system depressant (72); *tolibut* is a GABA analog that was developed in Russia (77), similarly to *picamilon*, which is formed by a synthetic combination of niacin and γ-aminobutyric acid (GABA). *Picamilon* was developed in the Soviet Union in 1969 (78) and further studied in both Russia (79) and Japan (80) as a prodrug of GABA.

Cannabimimetic:

Among Cannabimimetic drugs there are the synthetic cannabimimetics that are designer drugs that target the same receptors to which cannabinoids in cannabis plants, tetrahydrocannabinol (THC) and cannabidiol (CBD) bind (81, 82). *dexanabinol*, *drinabant*, *Dronabinol*, *JZL-184*, *rimonabant*, and *URB-597* were the six CEs belonging to this group that were identified by the NPSfinder® (**Table 9**).

The use of cannabimimetics as CEs seems counter-intuitive as both pre-clinical and human studies have found a link between consumption of cannabinoids and long-term deficits of cognitive functions, especially high-order cognitive functions (83–88). However, recent pre-clinical studies have found that delta-9-THC can improve cognitive performances in rats (89) and mice (90). THC, in fact, appears to promote hippocampal neurogenesis to prevent neurodegenerative processes occurring in animal models of Alzheimer's disease, to protect from inflammation-induced cognitive damage, and to restore memory and cognitive function in old mice (91).

TABLE 8 | GABAergic drugs (n=7; 5%).

1	F-Phenibut
2	GABA
3	Phenibut
4	Picamilon
5	PWZ-029
6	SH-053-R-CH3-2′F
7	Tolibut

TABLE 9 | Cannabimimetic (n=6; 4%).

1	Dexanabinol
2	Drinabant
3	Dronabinol
4	JZL-184
5	Rimonabant
6	URB-597

Tryptamines derivatives:

5-Methoxytryptamine (*5-MT*, also called *mexamine*) (**Table 10**) was the only tryptamine derivative identified by NPSfinder® (as well as by the EWA). This is a tryptamine derivative closely related to both the serotonin and melatonin neurotransmitters (92). To the best of our knowledge, there are no studies, surveys, or case reports that identified 5-MT as a drug used by healthy people in order to improve their cognitive abilities. Jansen et al. (93) reviewed the efficacy of melatonin in addressing cognitive impairment in dementia but found the evidence for this to be inconclusive.

Piperazine derivatives:

Fipexide (also known as *attentil* and *vigilor*) (**Table 11**) is the only substitute piperazine that has been identified by NPSfinder® as a CE. This was initially developed in Italy in 1983 (94) and used as a CE in Italy and France for the treatment of dementia (95). *Fipexide* is no longer in use due to the occurrence of rare side-effects (96, 97). On psychonauts' fora it is described as a molecule able to improve short term memory, attention, learning, and cognition.

Ethical, Clinical and Legal Issues

Ethical issues raised by cognitive enhancement have been debated for over a decade (98), and many experts have identified multiple ethical concerns including risks to mental and health safety (99). While CEs hold significant benefits in improving cognitive impairments in several neuropsychiatric disorders such as Alzheimer's disease (7–9) and schizophrenia (100), the use of nootropics by healthy individuals clearly poses ethical, clinical,

TABLE 10 | Piperazine derivatives (n=1; 0.5%).

1	Fipexide

TABLE 11 | Tryptamine derivatives (n=1; 0.5%).

1	Mexamin

and legal issues, as well as the need to develop a practical policy framework.

Mohamed and Sahakian (101) pointed out that CEs' use in healthy people might have some advantages, such as: helping reduce disparity in society by mitigating the adverse environmental effects (like poverty) on the brain; improving the performances of people who need to perform at the best of their abilities in every situation (such as surgeons or pilots); finally CEs might also be used by people with undiagnosed disorders (such as ADHD) who might be therefore self-medicating with stimulant medications.

On the other hand, it is of concern that the safety and efficacy of these drugs in healthy individuals in the long-term are still unclear. While some CEs have been studied and research data on their mechanism of action and potential benefit are available, the action, the beneficial effects, and the potential side-effects of the majority of them have yet to be fully described and understood. Furthermore, CEs' effects (if present at all) seem to be temporary, lasting until their metabolism and elimination (102). Some of these drugs can cause dependence and have a significant range of harmful effects; they can be particularly dangerous to young people as their brains are not fully developed. Studies producing null results and some evidence of task-specific impairments should be also noted (103).

The limited evidence of effectiveness as well as the potential side-effects should be cautiously considered by relevant legislative and regulatory bodies. In 2015, the US Presidential Commission for the Study of Bioethical Issues (104) released a report on CE, reporting up-to-date findings and providing recommendations for clinicians (104). The Australian Alcohol and Drug Foundation has recently raised doubts about the actual cognitive benefits of most CEs, indicating that scientific studies showed only little to no benefits for cognitive enhancement in healthy individuals, while the associated side-effects do pose significant risks to health and safety of the general public (105).

While further research is needed on the topic, the early identification of CEs that are most commonly discussed on the internet will increase clinicians' awareness of this phenomenon and potentially help them make clinical decisions for patients presenting with psychiatric symptoms or physical health problems related to these substances. NPSfinder® could also be an important tool for analytical toxicologists to focus their efforts on the detection of the most recently misused substances (106, 107).

LIMITATIONS

In the online world, a significant variety of molecules/substances are described as CEs by anecdotal report or unofficial sources; it is important to note that the list of CEs is constantly evolving and changing. An official, up-to-date, comprehensive list of CEs is not currently available in the literature. The Early Warning Systems fail in the early detection of these substances as they are mostly legal products such as food supplements or prescribed medication, which are misused by healthy individuals to improve their cognitive abilities.

In addition, there is a lack of an official classification of CEs in families/categories. We based our classification on the one described by Schifano et al. (44). We noted that another type of classification, such as the one described by Froestl et al. (7–9) which is based on substances' pharmacodynamics properties, is also relevant and useful and could be used when further data on NPS pharmacological properties will be available.

In fact, many CEs do not have a fully understood mechanism of action, which makes it difficult to link them to a specific category; other CEs have multiple mechanisms of actions (*i.e.* might target several different receptors), and they could therefore belong to more than one category; for example, one CE might belong both to the "prescription drugs" and the "GABAergic drugs" groups. Some of the categories can themselves be very broad and have different types of molecules belonging to it, for example "IPEDs".

Furthermore, it is important to note that a limited number of languages were used for the screening of molecules on the web, and although many substances were first identified in seizures in Asia, only European languages are used. For all these reasons, forming a comprehensive and definite classification of CEs remains a complex challenge.

CONCLUSIONS

In this paper, three different databases, including the innovative crawling software (NPSfinder®) and two official sources (EMCDDA's EDND, UNODC's EWA) were cross-checked.

CEs are a wide and diverse group of molecules, constantly growing in terms of numbers as well as availability among the general public and especially *via* online platforms. CEs differ for pharmacological activity, time, and mode of action, targeted cognitive domain, pharmacodynamic and pharmacokinetic properties, as well as possible short- and long-term side-effects. The popularity of chemicals that are potentially able to augment brain functions is not surprising in a society which constantly demands for increasingly high cognitive performances.

For the current official Early Warning Systems, it is challenging to identify and monitor the use of CEs as they are often sold as legal food supplements or as prescribed medication for a number of medical conditions. Due to its innovative methodology, NPSfinder® has demonstrated its ability to identify a higher number of CEs than the official EMCDDA's EDND and UNODC's EWA (108). For this reason, NPSfinder® can be considered as a helpful systematic tool which could update clinicians with the growing numbers and types of nootropics in the increasingly difficult-to-follow internet world.

Previously, Arillotta and colleagues (43) have identified 176 novel opioids which were not listed in either international or European NPS databases, such as EMCDDA or UNODC. This information is useful to stakeholders such as enforcement agents, emergency department, scientific community, prevention program setters, and other regulatory agencies. The same applies to CEs; in particular, the early identification of substances that are misused as CEs and the discovery of novel CEs that were never reported or identified before are crucial to

raise the awareness of regulatory bodies. The identification of a drug is key to the treatment of its potential physical and psychiatric effects; if the drug is novel, its description may shed some light on its pharmacokinetics and toxicodynamics, which would in turn inform treatment decision-making in clinical settings.

Improving clinicians' knowledge of CEs is of paramount importance, and further research in order to clarify mechanism of actions, as well as short- and long-term effects of many CEs is also needed. The early identification and better understanding of the distribution and effects of CEs could promote both more effective prevention and harm reduction measures in clinical settings, including emergency departments, mental health and general practice clinics.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The current study involving human participants were reviewed and approved by the University of Hertfordshire Ethics' Committee; protocol number: aLMS/SF/UH/02951(3). Written informed consent from the patients/participants OR patients'/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FS and AV have conceived the idea of the manuscript and have coordinated the whole project. FN, CZ, DA, and LG have actually carried out the process of both data collection and systematization. FN performed the literature searching, the analysis of data and drafted the manuscript. FS, JC, and AG supervised the manuscript and contributed to the final version of the manuscript. FS approved the final content of the manuscript. JC provided data from the EMCDDA and UNODC databases for the purposes of this research. FS, JC, and AG have provided relevant epidemiological data and have contributed as well to the drafting and checking of the paper itself.

ACKNOWLEDGMENTS

The authors are grateful to Damicom srl, a small enterprise from Rome (Italy), whose professionals have developed the NPSfinder® web crawler and so generously have allowed here the testing of its potential.
The authors are also grateful to the EMCDDA and UNODC for being able to use their databases for the purposes of this research. Finally, we thank the European Commission for funding the EU-MADNESS and EPS/NPS projects.

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Conflict of Interest: None of the authors of this paper was directly involved with the website development. AV has conceived the idea of a new early detention software for NPS, which was developed by the professionals at Damicom srl, a small enterprise from Rome (Italy). FS and AV have coordinated the testing of the web crawler. FN, CZ, and DA have suggested minor changes to the software which have made the screening process more precise and efficient.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer, SC, declared a shared affiliation, though no collaboration, with several of the authors, FN, FS, JMC, AG, DA, CZ, and AV to the handling editor.

APPENDIX

TABLE A1 | Full list of CE identified by NPSfinder® (n=142).

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
1	123I-Ioflupane	Datscan; Ioflupane (FPCIT); [I-123] N-ω-fluoropropyl- 2β-carbomethoxy- 3β-(4-iodophenyl) nortropane	methyl (1R,2S,3S,5S)-8-(3-fluoropropyl)-3-(4-(123I)iodanylphenyl)-8-azabicyclo [3.2.1]octane-2-carboxylate	N	**N**	**Y**	Phenyltropane isotope used for as a solution to inject into living test subjects for neuroimaging in the diagnosis of Parkinson's Disease.
2	2C-D	2C-D, 2C-M; 2C-D; 2C-M; 2,5-Dimethoxy-4-methylphenethylamine; LE-25	1-(2,5-Dimethoxy-4-methylphenyl)-2-aminoethane	Y	Y	N	2C-D, or 2,5-dimethoxy-4-methylphenethylamine, is a substituted phenethylamine featuring a phenyl ring bound to an amino (NH2) group through an ethyl chain. 2C-D contains methoxy functional groups CH3O- attached to carbons R2 and R5 as well as a methyl group attached to carbon R4 of the phenyl ring.
3	3,4-Dichloromethylphenidate	3,4-DCMP; 3,4-CTMP	3,4-Dichloromethylphenidate	Y	Y	N	A potent stimulant drug related to methylphenidate. 3,4-DCMP, the threo-diastereomer, is approximately seven times more potent than methylphenidate in animal studies, but has weaker reinforcing effects due to its slower onset of action.
4	4 CTMP	dichloropane	Methyl (2S,3S)-3-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate	N	N	Y	Dichloropane (also known as RTI-111 or O-401) is a novel stimulant substance of the tropane class. Stimulant of the Phenyltropane class that acts as a SNDRI. Yet being the Tropane analogue of 3,4-CTMP.
5	4-fluoromethylphenidate	4F-MPH; 4-FMPH; 4FTMP;4F-TMP	Methyl 2-(4-fluorophenyl)-2-(piperidin-2-yl) acetate	Y	Y	N	4-fluoromethylphenidate belongs to the piperidine chemical class and is the 4-fluoro derivative of the internationally controlled substance methylphenidate (Ritalin). It has been advertised online that 4-fluoromethylphenidate was developed as a replacement for ethylphenidate. Dosage indications and duration of effect have also been suggested online.
6	4- Methylmethylphenidate	threo-4-Methylmethylphenidate; 4MeTMP	threo-4-Methylmethylphenidate	Y	Y	N	4-methylmethylphenidate is a ring methylated derivative of the piperidine compound methylphenidate, the active pharmaceutical ingredient in the medicine Ritalin, which is used in the treatment of ADHD. 4-methylmethylphenidate has been researched as a potential cocaine antagonist by blocking the binding of cocaine to the dopamine transporter, when it was reported to be a slightly more potent inhibitor of dopamine uptake, compared to methylphenidate (126 nM vs. 224 nM). [Deutsch 1996] - 4-methylmethylphenidate is compound 1s in this paper, methylphenidate is compound 1a.
7	5-HTP	5-hydroxytryptophan; tryptophan; l-tryptophan; oxitriptan; Oxitriptan; Cincofarm; Levothym; Levotonine; Oxyfan; Telesol; Tript-OH; Triptum	2-amino-3-(5-hydroxy-1H-indol-3-yl) propanoic acid	Y	Y	N	The precursor to serotonin. In some countries it is sold OTC as a supplement for mood stabilisation and insomnia. It is frequently used as a recovery supplement following the use of MDMA or any other drug that depletes serotonin. Do not mix this drug with anything serotonergic, as this can cause serotonin syndrome.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
8	Acetildenafil	Hongdenafil	C25H34N6O3	N	N	Y	An RC analogue of sildenafil (Sildenafil) often missold as a hidden ingredient in many 'natural' sexual potency blends and supplements.
9	Acetyl-L-carnitine	Tripsitter Party Supplement	(3R)-3-acetyloxy-4-(trimethylazaniumyl) butanoate	N	N	Y	
10	**Adderall**	Adderall XR, and Mydayis	N/A	N	N	Y	Adderall is a psychostimulant drug, it is composed of 4 different amphetamine salts containing Dextroamphetamine and Levoamphetamine. Its 4 different salts are: 1/4th Dextroamphetamine Saccharate, 1/4th Dextroamphetamine Sulfate, 1/4 Racemic Amphetamine Aspartate Monohydrate, and 1/4 Racemic Amphetamine Sulfate.
11	**Adrafinil**	Olmifon; CRL40028	(+-)-2-Benzhydrylsulfinylethanehydroxamic acid	Y	Y	N	Adrafinil is very structurally similar to its close chemical cousin and bioactive metabolite, modafinil. The only structural difference is the that terminal amide hydroxyl group of adrafinil ((diphenylmethyl)sulfinyl-2 acetohydroxamic acid) is lacking in modafinil (diphenylmethyl)sulfinyl-2 acetamide). is a eugeroic that was formerly used in France to promote alertness, attention, wakefulness, mood, and other parameters, particularly in the elderly.[3][4] It was also used off-label by individuals who wished to avoid fatigue, such as night workers or others who needed to stay awake and alert for long periods of time. Additionally, "adrafinil is known to a larger nonscientific audience, where it is considered to be a nootropic agent.
12	**Alpha GPC**	choline alfoscerate; L-Alpha glycerylphosphorylcholine;	[(2R)-2,3-Dihydroxypropyl] 2-trimethylazaniumylethyl phosphate	N	N	Y	Alpha-GPC is a naturally-occurring choline compound found endogenously (naturally) in the brain which is also made and used for oral consumption. Structurally, Alpha-GPC is comprised of a choline group bound to a glycerol molecule *via* a phosphate group.
13	Aminotadalafil	385769-84-6 UNII-FY501QO030 FY501QO030 Amino-tadalafil RR-ATDF Tadalafil-Amino Tadalafil, Amino	(2R,8R)-6-amino-2-(1,3-benzodioxol-5-yl)-3,6,17-triazatetracyclo[8.7.0.03,8.011,16] heptadeca-1(10),11,13,15-tetraene-4,7-dione	N	N	N	An analogue of tadafinil, better known as Tadalafil (Sildenafil). Infamous for being missold in the 'Alpha Male' sexual enhancement supplement.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
14	**Aniracetam**	methoxybenzoyl)-2-pyrrolidinon; 1-(p-methoxybenzoyl)-2-pyrrolidinone; P-METHOXYBENZOYL-2-PIRROLIDONE; AKOS005066313; Tox21_110086_1; AB04115; ACN-048215; API0001505; BCP9000303; CCG-204210; CS-1793; DB04599; KS-5313; LP00115; NSC-758223; Ro-135057; 2-Pyrrolidinone,1-(4-methoxybenzoyl)-; IDI1_000403;	1-[(4-Methoxybenzoyl)]-2-pyrrolidinone	N	N	Y	Aniracetam is a pyrrolidinone compound of the racetam family, and has an additional anisoyl ring with a methoxy group at the lone para position. (replacing the amine group of piracetam) with an O-methoxy group on the furthest binding point. Its structure is dissimilar to that of oxiracetam (which is quite similar to piracetam) and pramiracetam (a fairly unique structure) Aniracetam is related structurally to nefiracetam.
15	Areca nut	Betel nut; Paans (the combination of Betel leaves, lime, & Areca catechu)	N/A	N	N	Y	The fruit of the Areca catechu palm tree, also known as the "Betel Nut", contain the stimulant arecoline. Native to SE Asia, the nuts are ground and often combined with mineral lime and wrapped in the leaf of a Betel pepper plant, although they are sometimes consumed buccally ('chewed') alone. Notably, frequent use can stain teeth black and its daily use is associated with increased risk of mouth cancers. Variants of the betel and lime combination are extremely common in many Asian cultures and have a long history of human use.
16	Arecoline (transdermal patch)		Methyl 1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate	Y	Y	N	Arecoline is an alkaloid natural product found in oil form in the areca nut, the fruit of the areca palm (Areca catechu). In some Asian countries, areca nut is chewed along with betel leaf to obtain a stimulating effect.
17	Armodafinil	Nuvigil, Waklert, Artvigil, R-Modawake, Neoresotyl; (R)-Modafinil	2-[(R)-benzhydrylsulfinyl]acetamide	N	N	Y	(R)-Modafinil, or Armodafinil, is a psychoactive molecule of the benzhydryl class. Benzhydryl compounds are comprised of two benzene rings attached to a single carbon molecule. Armodafinil is classified as a sulphinyl benzhydryl molecule, as it also contains a sulphinyl group, a sulfur molecule double-bonded to an oxygen molecule attached to the carbon of the benzhydryl group.
18	Atomoxetine	Strattera	(-)-N-methyl-3-phenyl-3-(o-tolyloxy)-propylamine; (R)-N-methyl-3-phenyl-3-(o-tolyloxy)propan-1-amine	Y	N	N	Atomoxetine is a selective norepinephrine reuptake inhibitor (SNRI) approved as a less stimulating treatment for ADHD in 2002 (U.S.). The precise mechanism by which it produces its therapeutic effects is unknown, but is thought to be related to its SNRI action. It appears to have minimal affinity for noradrenergic receptors or other neurotransmitter transporters or receptors.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
19	B-HO-Hordenine		4-[2-(Dimethylamino)-1-hydroxyethyl] phenol	N	N	Y	Hordenine (N,N-dimethyltyramine) is an alkaloid of the phenethylamine class that occurs naturally in a variety of plants, taking its name from one of the most common, barley (Hordeum species). Chemically, hordenine is the N-methyl derivative of N-methyltyramine, and the N,N-dimethyl derivative of the well-known biogenic amine tyramine, from which it is biosynthetically derived and with which it shares some pharmacological properties
20	Bacopa monnieri	Omnimind; Paneuromix	N/A	N	N	Y	It stimulates your grey matter and kicks it up a notch, leaving you more time to enjoy the good things in life.
21	Benzyl cyanide	2-Phenylacetonitrile; α-Tolunitrile; Benzylnitrile	2-Phenylacetonitrile	N	N	Y	Benzyl cyanide is a useful precursor to numerous pharmaceuticals. Examples include: Anorectics (e.g. sibutramine)
22	Beta-asarone	Cis-Isoasarone; (Z)-Asarone; Cis-Asarone; cis-2,4,5-Trimethoxyphenylprop-1-ene	1,2,4-Trimethoxy-5-[(1Z)-prop-1-en-1-yl] benzene	N	N	Y	It is one of the two isomers of Asarone, a chemical compound of the phenylpropanoid class found in certain plants such as Acorus and Asarum. It is no clear if can be metabolized to trimethoxyamphetamine.
23	Caffeine	Caffeine, Vivarin, Cafcit, Alert; Caffeine; Vivarin; Cafcit; Alert;1,3,7-trimethylxanthine, methyltheobromine	1,3,7-trimethylpurine-2,6-dione	N	N	Y	Caffeine is an alkaloid with a substituted xanthine core. Xanthine is a substituted purine comprised of two fused rings: a pyrimidine and an imidazole. Pryimidine is a six-membered ring with nitrogen constituents at R1 and R3; imidazole is a 5 membered ring with nitrogen substituents at R1 and R3. Xanthine contains oxygen groups double-bonded to R2 and R6.
24	Catechins	Green tea extract	(2S,3R)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	N	N	Y	Green tea (Camellia sinensis) plays an important role in the traditional Chinese herbal medicine. Immediately after harvesting the green tea leaves are steamed and dried instead of fermented, so the bioactive ingredients remains preserved optimally.
25	Celastrus paniculatus	Black oil plant seeds	N/A	N	N	Y	Celastrus paniculatus, also known as Black oil plant, climbing staff tree and intellect tree is a woody, fruit-bearing vine from India. Black oil plant seeds are used in Ayurvedic medicine due to their varied medicinal properties. Celastrus paniculatus' ability to protect the brain and to improve memory functions makes it an effective nootropic.
26	**Centrophenoxine**	Meclofenoxate; Amipolen; Analux; Brenal; Cellative; Centrophenoxin; Cerebron; Cerutil; Closete; Helfergin; lucidril; Lucidryl; Lutiaron; Marucotol; Proserout; Proseryl; Ropoxyl	2-Dimethylaminoethyl (4-chlorophenoxy) acetate	N	N	Y	Meclofenoxate is broken down by the liver into DMAE and PCPA (parachlorphenoxyacetic acid). It has been shown to cause mild memory improvement in people with dementia and has been marketed as an anti-aging supplement.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
27	**Choline Bitartrate**	CHOLINE BITARTRATE; 87-67-2; CHOLINI BITARTRAS; 2-Hydroxy-N,N,N-trimethylethanaminium 3-carboxy-2,3-dihydroxypropanoate; 2-(Hydroxyethyl) trimethylammonium bitartrate; Choline bitartrate, 97%; Choline tartrate (1:1); and many others.	2-Hydroxy-N,N,N-trimethylethan-1-aminium	N	N	Y	Choline is comprised of a quaternary ammonium group and an alcohol functional group, which are connected through an ethyl chain. Its charged cation can bind to a negative group or atom to form various salts, which can produce varying effects. Choline chloride can form a low-melting deep eutectic solvent mixture with urea with unusual properties.
28	Cinnamon extract		2-methoxy-4-prop-2-enylphenol;[(E)-prop-1-enyl]benzene	N	N	Y	
29	**Citicoline**	Neurocoline; cytidine diphosphate-choline; CDP-Choline; cytidine 5'-diphosphocholine	(2R,3S,4R,5R)-5-(4-amino-2-oxopyrimidin-1-yl)-3,4-dihydroxyoxolan-2-ylmethoxy-hydroxyphosphoryl 2-(trimethylazaniumyl)ethyl phosphate	N	N	Y	Citicoline, or cytidine diphosphate-choline, is a naturally occurring substance found in human cell tissue and synthesized as a sodium salt as a supplement. Its chemical structure is comprised of a cytidine nucleoside attached to a choline group through a diphosphate bridge. Citicoline is a chemical intermediary in the biosynthesis of phosphatidylcholine, a major phospholipid in cell membranes.
30	Coluracetam	acetoamide; AJ-08232; DS-14004; HY-17553; AX8209310; KB-271979; ST2407347; TC-072260; 4CH-017490; FT-0697594; Y1294; 463C819; J-690145; I14-13061; High-affinity choline uptake facilitator (CNS disorders), Mitsubishi; High-affinity choline uptake facilitator (depression/anxiety), BrainCells; Neurons growth promoting compound (major depressive disorder/anxiety), BrainCells; 1-Pyrrolidineacetamide, 2-oxo-N-(5,6,7,8-tetrahydro-2,3-dimethylfuro(2,3-b)quinolin-4-yl)-; N-(2,3-dimethyl-5,6,7,8-tetrahydrofuro[2,3-b]quinolin-4-yl)-2-(2-oxo-1-pyrrolidinyl) acetamide and many others.	N-(2,3-Dimethyl-5,6,7,8-tetrahydrofuro [2,3-b]quinolin-4-yl)-2-(2-oxo-1-pyrrolidinyl)acetamide	N	N	Y	Coluracetam, or N-(2,3-Dimethyl-5,6,7,8-tetrahydrofuro [2,3-b]quinolin-4-yl)-2-(2-oxo-1-pyrrolidinyl)acetamide, is a synthetic compound of the racetam family. Racetams share a pyrrolidine nucleus, a five-member nitrogenous ring with a ketone bonded oxygen at R2.[2] This 2-pyrrolidone ring is bound to the terminal carbon of an acetamide group, an ethyl amide chain with a ketone bond (C=O) at the alpha carbon.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
31	Coumarins	Leonotis Leonurus flowers; Monnier's snow parsley seeds; Leonotis Leeonorus 20X extract; wild lettuce	chromen-2-one	N	N	Y	Ingredient of wild lettuce. Biennial, growing up to 2-4 feet, maximum height of 6 feet (cultivated plants usually smaller). The erect stem, springing from a brown tap-root, is smooth and pale green, sometimes spotted with purple. Leaves are from 6 to 18 inches long, flowers are pale yellow, with large open clusters.
32	**Creatine**	N-Carbamimidoyl-N-methylglycine, Methylguanidoacetic acid; Creatine; N-Carbamimidoyl-N-methylglycine; Methylguanidoacetic acid	2-[Carbamimidoyl(methyl)amino]acetic acid	N	N	Y	Creatine is a nitrogenous amino acid produced endogenously and synthesized for consumption. Synthetic creatine is usually made from sarcosine (or its salts) and cyanamide which are combined in a reactor with catalyst compounds. The reactor is heated and pressurized, causing creatine crystals to form. The crystalline creatine is then purified by centrifuge and vacuum dried. The dried creatine compound is milled into a fine powder for improved bioavailability. Milling techniques differ, resulting in final products of varying solubility and bioavailability. For instance, creatine compounds milled to 200 mesh are referred to as micronized
33	Curcumin	Turmeric tea golden ginger; Turmeric drink golden cocoa	(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione	N	N	Y	Turmeric and ginger do not only look like one another; they also fit together very well! That's proven with this excellent, beneficial tea by TAKA Turmeric with Golden Ginger. The delicious organic blend of turmeric and ginger provides a warming and invigorating effect. The black pepper and coconut increase the effect of the active ingredient in turmeric: Curcumin. Do not wait any longer for the perfect turmeric tea: order Golden Ginger.
34	Dehydroepiandrosterone	DHEA; androstenolone; Prasterone	3S,8R,9S,10R,13S,14S)-3-hydroxy-10,13-dimethyl-1,2,3,4,7,8,9,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-17-one	N	N	Y	DHEA supplements are said to increase energy, enhance memory and cognitive function, improve immunity, and reduce the effects of stress. Dehydroepiandrosterone (DHEA), also known as androstenolone, is an endogenous steroid hormone. DHEA also has a variety of potential biological effects in its own right, binding to an array of nuclear and cell surface receptors, and acting as a neurosteroid and neurotrophin. In addition to its role as a natural hormone, DHEA is used as an over-the-counter supplement and medication; for information on DHEA as a supplement or medication

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
35	Deoxypipradol	2-diphenylmethylpiperidine; 2-DPMP; 2-Diphenylmethylpiperidine 2-benzhydrylpiperidine 519-74-4 Desoxypipradrol 2-(Diphenylmethyl)piperidine Piperidine, 2-(diphenylmethyl)- Piperidine,2-(diphenylmethyl)- 2-DPMP AK-24338 2-(Diphenylmethyl)piperidine; 2-Benzhydrylpiperidine; Desoxypipradol; Ivory Wave	2-diphenylmethylpiperidine	Y	Y	N	Desoxypipradrol, acts as a norepinephrine-dopamine reuptake inhibitor (NDRI) developed by Ciba in the 1950s. Desoxypipradrol is closely related on a structural level to the compounds methylphenidate and pipradrol, all three of which share a similar pharmacological action.2-DPMP is a powerful stimulant that has been found in the product 'Ivory Wave'. It was taken as a 'legal high' and has amphetamine-like stimulant effects similar to speed. 2-DPMP effects can be both powerful and long-lasting, with effects that can last as long as 5-7 days - some users have had to go to hospital for help.
36	Dexanabinol	ETS2101; Dexanabinol; (6aS,10aS)-9-(Hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran-1-ol	(6aS,10aS)-9-(Hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d] pyran-1-ol	N	N	Y	Cannabinoid
37	Dexmethylphenidate	D-threo-Methylphenidate; Methyl D-phenidate; Focalin; UNII-M32RH9MFGP; D-Methylphenidate; 40431-64-9; D-TMP; M32RH9MFGP; CHEMBL827; CHEBI:51860; Focalin; methyl (R)-phenyl[(R)-piperidin-2-yl]acetate; D-MPH; Attenade; dexmetilfenidato; AC1L4BP3; SCHEMBL34326; GTPL7554; DUGOZIWVEXMGBE-CHWSQXEVSA-N; ZINC896711; 2-Piperidineacetic acid, alpha-phenyl-, methyl ester, (alphaR,2R)	Methyl (2R)-phenyl[(2R)-2-piperidinyl] acetate	N	N	Y	Dexmethylphenidate, sold under the trade names Focalin among others, is a central nervous system (CNS) stimulant used in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy.It is in the phenethylamine and piperidine classes of medications. It is the active dextrorotatory enantiomer of methylphenidate.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
38	**Dextroamphetamine**	Dexedrine; Metamina; Attentin; Zenzedi; Procentra; Amfexa; D-Amphetamine; Dextroamphetamine sulphate; Dexamfetamine; Dexamphetamine	(2S)-1-Phenylpropan-2-amine	N	N	Y	Dextroamphetamine is a potent central nervous system (CNS) stimulant and amphetamine enantiomer that is prescribed for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. It is also used as an athletic performance and cognitive enhancer, and recreationally as an aphrodisiac and euphoriant. Dextroamphetamine was also used by military air, tank and special forces as a 'go-pill' during fatigue-inducing missions such as night-time bombing missions or extended combat operations. The amphetamine molecule exists as two enantiomers (in other words, two different molecules that are mirror images of one another), levoamphetamine and dextroamphetamine. Dextroamphetamine is the more active, dextrorotatory, or 'right-handed', enantiomer of the amphetamine molecule. Pharmaceutical dextroamphetamine sulfate is available as both a a brand name and generic drug in a variety of dosage forms.
39	Dimethylaminoethanol	DMAE; deanol; di-methyl-amino-ethanol; DMEA	2-(Dimethylamino)ethanol	N	N	Y	DMAE is a precursor of choline and an anti-oxidant that is found naturally in the brain. It is said to improve memory and learning as well as increasing ability to concentrate.
40	DL-Phenylalanine	DLPA; 2-amino-3-phenylpropanoic acid	2-amino-3-phenylpropanoic acid	N	N	Y	DL-Phenylalanine is a racemic mixture of phenylalanine, an aromatic amino acid with antidepressant, analgesic and appetite suppressant properties. The antidepressant effect of DL-phenylalanine may be accounted for by its precursor role in the synthesis of the neurotransmitters norepinephrine and dopamine. Elevated brain norepinephrine and dopamine levels are thought to be associated with antidepressant effects. This agent also plays a role in alleviating mood swings of premenstrual syndrome (PMS), increasing energy and mental alertness and heighten the ability to focus in individuals with attention deficit hyperactivity disorder (ADHD).
41	Drinabant	AVE-1625	N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl) methanesulfonamide	N	N	Y	AVE-1625 is a highly potent, selective antagonist for the CB1 receptor with Ki values of 0.16-0.44 nM. Drinabant reached phase IIb clinical trials as obesity treatment in the treatment of obesity but was shortly thereafter discontinued, likely due to the observation of severe psychiatric side effects including anxiety, depression, and thoughts of suicide in patients treated with the now-withdrawn rimonabant, another CB1 antagonist that was also under development by Sanofi-Aventis.

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TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
42	Dronabinol	ultrapure THC; Namisol; dronabinol; Marinol; syndros; cesamet; δ9-thc; δ9–tetrahydrocannabino; delta9-tetrahydrocannabino; delta9-thc	(–)-trans-Δ^9-tetrahydrocannabinol	N	N	Y	Dronabinol – trade names Marinol and Syndros – is a synthetic form of tetrahydrocannabinol (THC) approved by the FDA as an appetite stimulant for people with AIDS and antiemetic for people receiving chemotherapy. Synthetically created D9-THC, the main psychoactive ingredient in Cannabis.
43	Ephedrine	Ephedrine Erythro Isomer; Ephedrine Hydrochloride; Ephedrine Renaudin; Ephedrine Sulfate; Erythro Isomer of Ephedrine; Hydrochloride, Ephedrine; Renaudin, Ephedrine; Sal Phedrine; Sal-Phedrine; SalPhedrine; Sulfate, Ephedrine; Mini Thins; Sudafed; Trucker's Speed; (-)-alpha-(1-methylaminoethyl)benzyl alcohol	(1R,2S)-2-(methylamino)-1-phenylpropan-1-ol	N	N	Y	Ephedrine is the active ingredient in Ephedra sinica. One isomer (pseudoephedrine) is widely sold as a decongestant while the other (ephedrine) is a commonly used stimulant. Ephedrine is a medication and stimulant. It is often used to prevent low blood pressure during spinal anesthesia. It has also been used for asthma, narcolepsy, and obesity but is not the preferred treatment. It is of unclear benefit in nasal congestion. As a phenethylamine, ephedrine has a similar chemical structure to amphetamines and is a methamphetamine analogue having the methamphetamine structure with a hydroxyl group at the β position.
44	Ethylphenidate	EPH	Ethyl 2-phenyl-2-(piperidin-2-yl)acetate	Y	Y	N	Ethylphenidate is a synthetic molecule of the substituted phenethylamine class. It contains a phenethylamine core featuring a phenyl ring bound to an amino -NH2 group through an ethyl chain. It is structurally similar to amphetamine, featuring a substitution at Ra which is incorporated into a piperdine ring ending at the terminal amine of the phenethylamine chain. Additionally, it contains an ethyl acetate bound to R2 or its structure. Ethylphenidate is structurally differed to methylphenidate by elongation of the carbon chain. Ethyl- regards the side chain of two carbon atoms, phen- indicates the phenyl ring, id- is contracted from a piperidine ring, and -ate indicates the acetate group containing the oxygens. Ethylphenidate is a chiral compound, presumably produced as a racemic mixture.
45	**F-Phenibut**	Fluorophenibut; Fluorobut; b-(4-flourophenyl)-GABA	5-amino-4-(4-fluorophenyl)-1-hydroxypentan-2-one	N	N	Y	As with phenibut, F-Phenibut is a derivative of GABA, except with a fluorine-substituted phenyl group in the b-position of the molecule. It is a chiral molecule and thus has two potential configurations as (R)- and (S)-enantiomers.[4] It has an almost identical chemical structure to baclofen (only replacing a chlorine with a fluorine atom in the para-position of the phenyl group).[5] Additionally, the widely prescribed gabapentinoid pregabalin also possesses a similar structure as phenibut, except that the phenyl group is instead replaced with an isobutyl group.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
46	**Fasoracetam**	NS-105; LAM-105; (5R)-5-oxo-D-prolinepiperidinamide monohydrate; NS-105; AEVI-001; LAM 105; MDGN-001; NFC 1	(5R)-5-(piperidine-1-carbonyl) pyrrolidin-2-one	N	N	Y	A substance in the racetam family. Appears to be a GABA(B) agonist, and has shown to block memory disruptions caused by Baclofen, another GABA(B) Agonist. Similar to another compound in the racetam family Coluracetam, it enhances High affinity choline reuptake (HACU). It is a nootropic, and has been in clinical trials for vascular dementia and attention deficit hyperactivity disorder
47	**Fipexide**	Attentil; Vigilor; BP 662	1-(1,3-benzodioxol-5-ylmethyl)-4-[(4-chlorophenoxy)acetyl]piperazine	N	N	Y	Fipexide is a mild stimulant that is thought to indirectly affect dopamine levels in the brain. It is said to improve short term memory, attention, learning, and cognition. There is a risk of serious liver damage and high fever with use. Fipexide (Attentil, Vigilor) is a psychoactive drug of the piperazine chemical class which was developed in Italy in 1983. It was used as a nootropic drug in Italy and France, mainly for the treatment of senile dementia, but is no longer in common use due to the occurrence of rare adverse drug reactions including fever and hepatitis
48	Fladrafinil	CRL 40941; Fluorafinil; fluoromodafinil	4;4-difluorobenzhydrylsulfinylacetohydroxamic acid	Y	Y	N	Fladrafinil was described in a patent by Louis Lafon Laboratories in the 1980's, the same company that developed the atypical psychostimulant adrafinil (CRL 40028) in the 1970's. Fladrafinil is the 4,4'-difluoro derivative of adrafinil. A substance closely related to Adrafinil and Modafinil. It is the bis(p-fluoro) ring derivative of Adrafinil.
49	Flavonoids		2-phenylchromen-4-one	N	N	Y	Ingredients of wild Lettuce. Biennial, growing up to 2-4 feet, maximum height of 6 feet (cultivated plants usually smaller). The erect stem, springing from a brown tap-root, is smooth and pale green, sometimes spotted with purple. Leaves are from 6 to 18 inches long, flowers are pale yellow, with large open clusters.
50	Flmodafinil	lauflumide; bisfluoromodafinil; RL-40-940	C15H13F2NO2S	Y	N	N	Bisfluoro analogue Modafinil. Has been sold online as a research chemical. Was patented in 2013. Is slightly more potent than Armodafinil. CRL-40,940 (also known as flmodafinil, bisfluoromodafinil and lauflumide) is a selective dopaminergic reuptake inhibitor, and is the bisfluoro analog of the eugeroic modafinil and has been sold online as a designer drug.
51	GABA	γ-aminobutyric acid; gamma aminobutyric acid	4-Aminobutanoic acid	N	N	Y	Gaba is an inhibitory neurotransmitter found naturally in the brain. Research suggests that increased levels of gaba might help reduce the mental decline associated with aging.GABA is sold as a dietary supplement.

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TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
52	Galantamine	Razadyne; Reminyl; Nivalin; Razadyne ER; Reminyl; Lycoremine	(4aS,6R,8aS)-5,6,9,10,11,12-Hexahydro-3-methoxy-11-methyl-4aH-[1]benzofuro [3a,3,2-ef][2]benzazepin-6-ol	N	N	Y	Galantamine is a complex alkaloid that is found endogenously in certain plants and synthesized for medical use. It is comprised of a fusion between a methoxy substituted benzene ring to a hydrogenated and methylated azepine ring along with a hydroxylated benzofuran group.
53	Geranamine	DMAA; methylhexanamine; methylhexamine; geranamine; geranium extract; geranium oil; 2-amino-4-methylhexane; dimethylamylamine; DMAA; 1,3-dimethylamylamine; 1,3-DMAA; 1,3-dimethylpentylamine; 4-methyl-2-hexanamine; 4-methyl-2-hexylamine; orthan; Forthane; Floradrene;	4-methylhexan-2-amine	Y	N	N	Also known as methylhexanamine, this sympathetomimetic drug was developed as a nasal decongestant by Eli Lilly in the 1940s. It has been used as a weight loss aid and missold as a dietary supplement and component of some energy drinks. Carries a risk of heart attack, stroke and other life-threatening cardiovascular issues. It may occur naturally as a component of the oil extracted from the geranium plant.
54	Ginger root extracts		(E)-1-(4-hydroxy-3-methoxyphenyl)dec-4-en-3-one;1-(4-hydroxy-3-methoxyphenyl)-5-methyldecan-3-one	N	N	Y	Ginger is an herbaceous tropical perennial grows 2-4 feet tall from an aromatic, tuberous root. Leaves are grass-like and 6-12 inches long. Flowers are dense, red and yellow cone-like spikes 3 inches long at the end of a 6-12 inch stalk.
55	Gingko biloba	Gingko biloba powder	N/A	N	N	Y	Ginkgo biloba contains ginkgolides that have a positive effect on blood circulation and oxygen levels, which are associated with brain performance and help maintain cognitive function. Ginkgo contributes to a clear mind and mental focus. The brain boosting effects of ginkgo can help improve memory and memory recall, whether you're preparing for an exam or simply want to keep your mind sharp. Effect Ginkgo has stimulating properties. It has a positive effect on cognitive function and mental alertness. Ginkgo helps maintain healthy blood vessels.
56	Ginseng	Tartar Root; Five-fingers	bis[3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] 2,3-dihydroxy-6b-(hydroxymethyl)-4,6a,11,11,14b-pentamethyl-1,2,3,4a,5,6,7,8,9,10,12,12a,14,14a-tetradecahydropicene-4,8a-dicarboxylate	N	N	Y	Ginseng's thin, single stem grows from a bud at the top of the root that rises and separates into a whorl of compound leaves. Small green flowers radiate, umbrella-like from the end of a stalk and are eventually replaced by red berries.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
57	Harmaline		7-methoxy-1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indole	N	Y	N	Harmaline is a fluorescent psychoactive indole alkaloid from the group of harmala alkaloids and beta-carbolines. It is the partially hydrogenated form of harmine. Various plants contain harmaline including Peganum harmala (Syrian rue) as well as the hallucinogenic beverage ayahuasca, which is traditionally brewed using Banisteriopsis caapi. Present at 3% by dry weight, the harmala alkaloids may be extracted from the Syrian rue seeds.
58	Harmalol		1-Methyl-4,9-dihydro-3H-pyrido[3,4-b] indol-7-ol	N	N	Y	Harmalol is a bioactive beta-carboline and a member of the harmala alkaloids.
59	Homosildenafil	methyl-sildenafil	C23H32N6O4S	N	N	Y	An analogue of sildenafil (Sildenafil) with similar effects. Has been missold in certain 'herbal' blends and dietary supplements for sexual potency. Little is known about the pharmacology or safety profile of this drug in humans, potentially less potent than sildenafil.
60	Hordenine	4-Hydroxy-N,N-dimethylphenethylamin	4-(2-Dimethylaminoethyl)phenol	N	N	Y	Hordenine (N,N-dimethyltyramine) is an alkaloid of the phenethylamine class that occurs naturally in a variety of plants, taking its name from one of the most common, barley (Hordeum species). Chemically, hordenine is the N-methyl derivative of N-methyltyramine, and the N,N-dimethyl derivative of the well-known biogenic amine tyramine, from which it is biosynthetically derived and with which it shares some pharmacological properties.
61	Huperzine A	Amino-13-ethylidene-11-methyl-6-aza-tricyclo [7.3.1.0*2,7*]trideca-2(7),3,10-trien-5-one(Huperzine A); (-)1-Amino-13-ethylidene-11-methyl-6-aza-tricyclo [7.3.1.0*2,7*]trideca-2(7),3,10-trien-5-one((-)-Huperzine A);	(1R,9R,13E)-1-Amino-13-ethylidene-11-methyl-6-azatricyclo[7.3.1.$0^{2,7}$]trideca-2 (7),3,10-trien-5-one	N	N	Y	A compound that is extracted from the herbs of Huperziceae family. Is known as an acetylcholinesterase inhibitor, which stops an enzyme from breaking down acetylcholine which results in increases in acetylcholine. Is currently in preliminary trials for Alzheimer's.
62	Hydergine	Gerimal; Niloric; co-dergocrine mesilate; dihydroergotoxine mesylate; Ergoloid mesylates	(6aR,9R,10aR)-N-[(1S,2S,4R,7S)-2-hydroxy-5,8-dioxo-4,7-di(propan-2-yl)-3-oxa-6,9-diazatricyclo[7.3.0.02,6]dodecan-4-yl]-7-methyl-6,6a,8,9,10,10a-hexahydro-4H-indolo[4,3-fg]quinoline-9-carboxamide;methanesulfonic acid	N	N	Y	Ergoloid mesylates are ergot alkaloids which act as neuroprotective anti-oxidants. They are also said to increase blood flow to the brain and generally increase cognitive abilities though the evidence is contradictory on these points. It was approved by the FDA in 1951.
63	Icariin	Horny goat weed extract 10% Icariin	5-hydroxy-2-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-3-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxychromen-4-one	N	N	Y	Horny goat weed extract 10% Icariin | 3 g - Epimedium

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
64	Isopropylphenidate	IPH, IPPH; IPPD	Propan-2-yl 2-phenyl-2-(piperidin-2-yl) acetate	Y	Y	N	Isopropylphenidate is a synthetic molecule of the substituted phenethylamine and piperidine classes. It contains a phenethylamine core featuring a phenyl ring bound to an amino (NH2) group *via* an ethyl chain. It is structurally similar to amphetamine, featuring a substitution at Ra which is then incorporated into a piperidine ring ending at the terminal amine of the phenethylamine chain. Additionally, it contains an isopropyl acetate bound to R2 of its molecular structure, a noticeable departure from methylphenidate, which contains a methyl group in this position.
65	JZL-184		4-Nitrophenyl 4-[bis(2H-1,3-benzodioxol-5-yl)(hydroxy)methyl]piperidine-1-carboxylate	N	N	Y	Cannabinoid
66	Kaempferol	Blue Lotus 20X Extract; Blue Lotus tincture 15X Extract; Kratom X Blue Lilly Liquid; Trichocereus Bridgesii Cutting; Trichocereus Bridgesii Monstruosus Cutting	3,5,7-trihydroxy-2-(4-hydroxyphenyl) chromen-4-one	N	N	Y	Blue Lotus flowers have also yielded a variety of alkaloids, including kaempferol, which has mild MAOI properties. Traditionally used as a narcotic, Nymphaea caerulea helps strengthen the male erection. Blue Lily also contains powerful antioxidants. This versatile plant has a lot to offer. Effect Blue Lotus has calming effects. The main effect of the Blue Lotus 20X extract is sedative, calming and relaxing. Blue Lotus offers a very mild, mind opening (hallucinogenic) experience. This potent extract combines very well with red wine, bringing you into a euphoric and ecstatic state. Last but not least, Blue Lotus has aphrodisiac qualities.
67	Kava Kava	Kava; Piper methysticum; Kawa; Awa; Waka; Lawena; Sakau; Yaqona; Kaffa kaffa;	6-[(E)-2-(cyclohexa-1,5-dien-1-yl)ethenyl]-4-methoxy-5,6-dihydro-2H-pyran-2-one	N	N	Y	Kava is a tropical evergreen shrub with large heart-shaped leaves and woody stems. Its thick roots are mashed or ground and made into a cold beverage used similarly to alcohol. It has a long history of ritual and recreational use in Pacific Polynesia and is now a common herbal product.
68	Kratom	Mitragyna speciosa; krath`m (Thai); ketum; kratum;	Methyl (E)-2-[(2S,3S,7aS,12bS)-3-ethyl-7a-hydroxy-8-methoxy-2,3,4,6,7,12b-hexahydro-1H-indolo[2,3-a]quinolizin-2-yl]-3-methoxyprop-2-enoate	Y	N	N	Kratom is the common name for the plant Mitragyna speciosa Korthals. It is a tree indigenous to Southeast Asia (Thailand, northern Malay Peninsula to Borneo); it is mostly grown in the central and southern regions of Thailand, and only rarely in the northern part. There are more than 40 compounds in the leaves of M. multi-solvent, including many indole alkaloids such as mitragynine (once thought to be the primary active constituent), mitraphylline, and 7-hydroxymitragynine (which is currently the most likely candidate for the primary active chemical in the plant). Other active chemicals in M. specials include raubasine, rhynchophylline, and corynantheidine, among many others.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
69	**L-655,708**	9H-Imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylic acid, 11,12,13,13a-tetrahydro-7-methoxy-9-oxo-, ethyl ester, (13aS)-; Ethyl (13aS)-7-methoxy-9-oxo-11,12,13,13a-tetrahydro-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate; 130477-52-0; CHEMBL52030;	Ethyl 7-methoxy-9-oxo-11,12,13,13a-tetrahydro-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate	N	N	Y	It is a nootropic drug invented in 1996 by a team working for Merck, Sharp and Dohme, that was the first compound developed which acts as a subtype-selective inverse agonist at the α5 subtype of the benzodiazepine binding site on the GABAA receptor. It acts as an inverse agonist at the α1, α2, α3 and α5 subtypes, but with much higher affinity for α5, and unlike newer α5 inverse agonists such as α5IA, L-655,708 exerts its subtype selectivity purely *via* higher binding affinity for this receptor subtype, with its efficacy as an inverse agonist being around the same at all the subtypes it binds to.A radiolabelled form of L-655,708 was used to map the distribution of the GABAA α5 subtype in the brain, and it was found to be expressed predominantly in the hippocampus, an area of the brain involved with learning and memory. Activation of this subtype is thought to be largely responsible for producing the cognitive side effects displayed by many benzodiazepine and nonbenzodiazepine drugs, such as amnesia and difficulties with learning and memory, and so this led researchers to conclude that a drug acting as an inverse agonist at this subtype should have the opposite effect and enhance learning and memory.
70	L-Tryptophan	L-TRP	(2S)-2-amino-3-(1H-indol-3-yl)propanoic acid	N	N	Y	Tryptophan (symbol Trp or W) is an α-amino acid that is used in the biosynthesis of proteins. Tryptophan contains an α-amino group, an α-carboxylic acid group, and a side chain indole, making it a non-polar aromatic amino acid. It is essential in humans, meaning the body cannot synthesize it: it must be obtained from the diet. Tryptophan is also a precursor to the neurotransmitter serotonin, the hormone melatonin and vitamin B3. It is encoded by the codon UGG.
71	**Lemon Balm**		N/A	N	N	Y	Lemon Balm is a perennial (its root survives the winter) herb usually growing 1-2 feet (50 cm) tall. The leaves are ovate to heart-shaped and mint-like. Its flowers are white to yellowish in loose, small bunches and have a lemony-minty smell and flavor. Lemon Balm is used in foods and teas, as an insect repellant, and there is evidence that it has anxiolytic, sedative, mood improving, and nootropic effects. Some people report distinct psychoactive effects taking it as a tea, snorting, or smoking it, sometimes in combination with other plants or drugs, though reports are inconsistent.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
72	Lisdexamfetamine	lisdextroamfetamine; lisdexamphetamine; Tyvense; Elvanse; Aduvanz; Venvanse; Vyvanse	(2S)-2,6-diamino-N-[(2S)-1-phenylpropan-2-yl]hexanamide	N	N	Y	This drug is a CNS stimulant often prescribed for ADHD, narcolepsy and obesity. It is also a pro-drug for dextroamphetamine, and functions as a method for providing extended-release stimulation. It is sometimes prescribed alongside an SSRI for depression. Lisdexamfetamine (contracted from L-lysine-dextroamphetamine) is a prodrug of the central nervous system (CNS) stimulant dextroamphetamine, a phenethylamine of the amphetamine class that is used in the treatment of attention deficit hyperactivity disorder (ADHD) and binge eating disorder. Its chemical structure consists of dextroamphetamine coupled with the essential amino acid L-lysine. Lisdexamfetamine itself is inactive prior to its absorption and the subsequent rate-limited enzymatic cleavage of the molecule's L-lysine portion, which produces the active metabolite (dextroamphetamine).
73	Lobeline	derived from lobelia inflata	2-[(2R,6S)-6-[(2S)-2-hydroxy-2-phenylethyl]-1-methylpiperidin-2-yl]-1-phenylethanone	N	N	Y	Native Americans used lobelia to treat respiratory and muscle disorders, and as a purgative. The species used most commonly in modern herbalism is Lobelia inflata (Indian tobacco). However, there are adverse effects that limit the use of lobelia. Lobelia has been used as "asthmador" in Appalachian folk medicine. Two species, L. siphilitica and L. cardinalis, were once considered a cure for syphilis. Herbalist Samuel Thomson popularized medicinal use of lobelia in the United States in the early 19th century, as well as other medicinal plants like goldenseal. One species, Lobelia chinensis is used as one of the fifty fundamental herbs in traditional Chinese medicine. Several studies show that lobelia is ineffective in helping people to quit smoking.
74	Lovegra		N/A	N	N	Y	Lovegra 100 mg, the pink female equivalent to the blue Viagra pill. Specificly developed for women, The Lovegra pill improves blood flow in the genital area. For more intense sexual satisfaction for women, will increase your pleasure and the vaginal moisture is ensured during the entire sex. Did you already discovered Lovegra? If not … you have to try this!!!
75	Maca	Peruvian ginseng; Lepidium meyenii; maca-maca; maino; ayak chichira; ayak willku. Macaridine.	N/A	N	N	Y	Maca is an edible herbaceous biennial plant of the family Brassicaceae that is native to South America in the high Andes mountains of Peru. It is mostly used for sexual and fertility problems.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
76	Marijuana	Indian hemp; marijuana; Cannabis, Marijuana, Weed, Pot, Mary Jane, Grass, Herb, Devil's Lettuce, Jazz Tobacco; Cannabis; Marijuana; Weed; Pot; Mary Jane; Grass; Herb; Devil's Lettuce; Jazz Tobacco	N/A	N	N	Y	Cannabis is an annual herbaceous flowering plant indigenous to eastern Asia but now of cosmopolitan distribution due to widespread cultivation. It has been cultivated throughout recorded history, used as a source of industrial fibre, seed oil, food, recreation, religious and spiritual moods and medicine. Each part of the plant is harvested differently, depending on the purpose of its use. The species was first classified by Carl Linnaeus in 1753
77	Melatonin	N-Acetyl-5-methoxytryptamine	N-[2-(5-Methoxy-1H-indol-3-yl)ethyl] acetamide	N	N	Y	Melatonin is comprised of a monoamine chain attached to an indole ring at the third carbon. A monoamine chain is made up of an amine group attached to an ethane chain. This monoamine chain can be found in many neurotransmitters, including histamine, dopamine, adrenaline, and noradrenaline. It is also found in many psychoactive substances such as members of the tryptamine and phenethylamine chemical classes.
78	Memantine	Axura, Ebixa, Namenda, Memary	3,5-Dimethyladamantan-1-amine	Y	Y	N	Memantine or 3,5-dimethyladamantan-1-amine is a synthetic molecule classified as a substituted adamantane derivative. Its core structure is adamantane, a diamondoid of four interlocked cyclohexane rings in a stable 3-dimensional lattice conformation. Memantine is substituted with a methyl carbon at both R3 and R5; it contains an amine substitution at R1. Its name is derived from its structure, 3,5-dimethyladamantan-1-amine. Memantine is an arycyclohexylamine, belonging to the same category as ketamine and is a derivative of amantadine (adamantan-1-amine). It was originally synthesized in the late 1960s and like amantadine it is an adamantan-amine based uncompetitive NMDAR antagonists, used in the treatment of Alzheimer's disease and other dementias and is considered to be 'well-tolerated'.
79	Memantine extended release	memantine ER; Namenda XR	3,5-Dimethyladamantan-1-amine	Y	Y	N	See above
80	Menthol	Knaster Fresh	5-methyl-2-propan-2-ylcyclohexan-1-ol	N	N	Y	The menthol classic. Knaster Fresh is a minty blend of hemp aroma and Mentha Spicata. Arctic fresh.
81	Methylmorphenate		N/A	Y	Y	N	Methylmorphenate is a benzylmorpholine and is a derivative of the internationally controlled substance methylphenidate (methyl alpha-phenyl-2-piperidineacetate), where the piperidine ring has been replaced by a morpholine ring. Methylphenidate is used to treat attention-deficit hyperactivity disorder (ADHD).Methylmorphenate possesses two chiral carbons (stereocenters).

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
82	Methylnaphthidate	CHEMBL1183494; hdmp-28; DL-Threo-methylnaphthidate; Methyl 2-(naphthalen-2-yl)-2-(piperidin-2-yl)acetate; 2-Piperidineacetic acid, alpha-2-naphthalenyl-, methyl ester; BDBM50327107; ZINC29484313; and many others.	Methyl (naphthalen-2-yl)(piperidin-2-yl) acetate	Y	Y	N	HDMP-28 (methylnaphthidate) is structurally related to methylphenidate (controlled under the 1971 UN Convention) having a naphthalene ring instead of a benzene ring.HDMP-28 has been found to have reinforcing effects in a study that examined the reinforcing efficacy of psychostimulants in primate brain tissue.
83	Methylphenidate	Methylphenidan; Phenidylate; Concerta; Calocain; Daytrana; Plimasine; Meridil; Ritalin; Methyl phenidylacetate; Methylfenidan; Metilfenidato; Methylin; 113-45-1; Centedrin; Methylofenidan; Centedein; Tsentedrin; 4311/B Ciba; Metadate; Methylphen; Riphenidate; Centredin; Methyl alpha-phenyl-alpha-(2-piperidyl) acetate; alpha-Phenyl-2-piperidineacetic acid methyl ester; NCI-C56280; 2-Piperidineacetic acid, alpha-phenyl-, methyl ester; HSDB 3126; EINECS 204-028-6; C 4311; CHEMBL7	Methyl phenyl(piperidin-2-yl)acetate	N	N	Y	Methylphenidate, sold under various trade names, Ritalin being one of the most commonly known, is a central nervous system (CNS) stimulant of the phenethylamine [3] and piperidine classes that is used in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. The original patent was owned by CIBA, now Novartis Corporation. It was first licensed by the US Food and Drug Administration (FDA) in 1955 for treating what was then known as hyperactivity. Methylphenidate's mechanism of action involves the inhibition of catecholamine reuptake, primarily as a dopamine reuptake inhibitor. Methylphenidate acts by blocking the dopamine transporter and norepinephrine transporter, leading to increased concentrations of dopamine and norepinephrine within the synaptic cleft. This effect in turn leads to increased neurotransmission of dopamine and norepinephrine.[10] Methylphenidate is also a weak 5HT1A receptor agonist.
84	Mexamine	meksamin; 5-Methoxytryptamine; 5-MT; 2-(5-Methoxy-1H-indol-3-yl) ethanamine; meksamin; 5-Methoxytryptamine; 5-MT; 2-(5-Methoxy-1H-indol-3-yl) ethanamine;	2-(5-Methoxy-1H-indol-3-yl)ethanamine	N	Y	N	5-Methoxytryptamine, a tryptamine derivative that naturally occurs in the body at low levels. Apparently enhances dreams. 5-Methoxytryptamine (5-MT), also known as mexamine, is a tryptamine derivative closely related to the neurotransmitters serotonin and melatonin.
85	Modafinil	2-benzhydrylsulfinylethanamide; Modiodial; Provigil; Alertec; CRL-40476; Diphenylmethylsulfinylacetamide	2-[(Diphenylmethyl)sulfinyl]acetamide	Y	N	N	Modafinil is a synthetic stimulant which is also known under the trade names Modiodial in Europe and Provigil in the United Kingdom. It is approved for use in the treatment of daytime sleepiness associated with narcolepsy. Research has also suggested that modafinil may be effective in the treatment of sleepiness disorders other than narcolepsy i.e. idiopathic hypersomnia, night-shift sleep disorder, obstructive sleep disorder, obstructive sleep apnoea, multiple sclerosis, Parkinson's disease, myotonic dystrophy, depression, schizophrenia, attention-deficit disorder and cocaine dependence and withdrawal.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
86	Modafinil Sulphone	CRL 41056 and USP Modafinil Related Compound B	2-[(diphenylmethyl)sulfonyl]acetamide	Y	Y	N	Modafinil sulphone is considered to be one of two metabolites of modafinil, it being the minor metabolite. Modafinil sulphone is structurally related to the previously notified modafiendz which is the bis-fluoro-N-methyl analogue of modafinil.The properties of modafinil sulphone have not been described extensively in the literature. It has been reported that this substance has anticonvulsant activity and therefore may find use in the "treatment of preclinical subconvulsive manifestations", further studies are required in this area. In other research, it has been stated that modafinil sulphone is pharmacologically active with a half-life of approximately 12 hours but it has been reported that it may also not exert any significant activity in the brain or periphery.
87	Mucuna pruriens	Velvet beans; Cow Itch; Itching Bean; Nescafe; Bengal velvet bean; Florida velvet bean; Mauritius velvet bean; Yokohama velvet bean; cowage; lacuna bean; Lyon bean	N/A	N	N	Y	Mucuna pruriens is a tropical vine growing from 3-18 meters with white to dark purple hanging flowers. It's bean-like pods are covered with long stinging hairs and contain black, white, or tan seeds. The leaves, seeds, stems and roots contain L-Dopa, Serotonin, 5-HTP, and Nicotine, as well as N,N-DMT, Bufotenin, and 5-MeO-DMT. It has a tradition of use as a Ayurvedic aphrodesiac, treatment for parkinsons, ayahuasca admixture, and coffee substitute.
88	**N-methyl-4,4'-difluoro-modafinil**	N-Methylbisfluoromodafinil; Dehydroxyfluorafinil; Modafiendz N-meethyl-4,4-difluoro-modafinil	2-{[bis(4-fluorophenyl)methyl]sulfinyl}-N-methylacetamide	Y	Y	N	2-{[bis(4-fluorophenyl)methyl]sulfinyl}-N-methylacetamide is the bis-fluoro-N-methyl analogue of the substance modafinil and is currently marketed by online sellers as a nootropic substance called 'modafiendz'. Modafinil is used to treat excessive sleepiness caused by narcolepsy, shift work sleep disorder and obstructive sleep apnea/hypopnea and is marketed as a prescription medication under a number of names in the EU including; Modasomil, Modiodal, Modiwake, Provigil and Vigil.
89	**N-methyl-cyclazodone**	N-methyl-cyclazodone;2-(cyclopropyl(methyl)amino)-5-phenyloxazol-4(5H)-one	N-methyl-cyclazodone;2-(cyclopropyl (methyl)amino)-5-phenyloxazol-4(5H)-one	Y	Y	N	N-methyl-cyclazodone is an approximately 3x - 5x more potent derivative of the nootropic and psychostimulant compound Pemoline.
90	Naringin	Kanna 50X Tincture	(2S)-7-[(2S,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)-3-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl] oxyoxan-2-yl]oxy-5-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one	N	N	Y	A tincture is one of the most convenient ways to get your dose of Kanna. Kanna extract induces a general feeling of euphoria and sociability, relaxation and increased focus, coupled with an energetic feeling. All natural: No chemicals or sugars have been added. Ingredients: Sceletium tortuosum extract, distilled water, naringin, glycerin, alcohol (14%). Content: 10ml (2 doses)

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
91	**Nefiracetam**	DM-9384	N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide	N	N	Y	Nootropic compound of the racetam family. Seems to enhance both GABAergic and cholinergic signalling. Long term use appears to be neuroprotective. Fat soluble.
92	Nicotine	Nicotine; tabak; tabacco; cigarettes; tobacco; Mapacho	(S)-3-[1-Methylpyrrolidin-2-yl]pyridine	N	N	Y	Nicotine (3-[(2S)-1-methylpyrrolidin-2-yl]pyridine) is a naturally occurring bicyclic compound comprised of a pyridine ring attached to the second carbon of a pyrrolidine ring that has a methyl substituent on the nitrogen. Pyridine is an unsaturated six-membered ring structurally related to benzene but with a nitrogen member. Nicotine additionally contains a substituted pyrrolidine ring, which is a saturated five-membered ring with one nitrogen member. These rings are bridged from the R3 position of the pyridine ring to the R2 position of the pyrrolidine ring. Tobacco is an annual or bi-annual growing 1-3 meters tall with large sticky leaves that contain nicotine. Native to the Americas, tobacco has a long history of use as a shamanic inebriant and stimulant. It is extremely popular and well-known for its addictive potential.
93	**Noopept**	GVS-111; Noopept; Noopept; GVS-111; Omberacetam	N-Phenylacetyl-L-prolylglycine ethyl este	Y	N	N	Noopept, or N-phenylacetyl-L-prolylglycine ethyl ester, is a synthetic peptide. A peptide is a chain of simple amino acids linked by peptide bonds. Noopept contains a phenylacetyl subunit bound to a small peptide chain of proline and glycine. The proline amino acid is composed of a carboxylic acid group bound to a pyrrolidine ring at C2. The glycine amino acid is bound to proline with a peptide bond and contains an amino group bound to the free carbon of ethanoic acid. Noopept is structurally similar to the endogenous neuropeptide cycloprolylglycine, for which it is a prodrug. Noopept is a dipeptide conjugate of piracetam although it is not a racetam as it lacks a pyrrolidone cycle.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
94	NSI-189		(4-Benzylpiperazin-1-yl)-[2-(3-methylbutylamino)pyridin-3-yl]methanone	Y	Y	N	NSI-189 is considered an experimental drug that is currently being investigated by Neuralstem Inc., for the treatment of major depressive disorders (MDD). The research into this drug has been funded by the Defense Advanced Research Projects Agency (DARPA) and the National Institutes of Health (NIH) in the United States. Neuralstem states that NSI-189 "enables the creation of neural stem cell lines from many areas of the CNS, including the hippocampus" and "boost the generation of new neurons". This would be achieved by the stimulation of neurogenesis of human hippocampus-derived neural stem cells in-vitro and in-vivo. This drug by Neuralstem is the first to undergo clinical trials and the company plans to develop NS1-189 into an orally administrable drug for the treatment of MDD, and other cognitive disorders such as Alzheimer's disease and PTSD.
95	Octopamine	b-HO-HPEA	4-(2-amino-1-hydroxyethyl)phenol	N	N	Y	Octopamine is an organic chemical closely related to norepinephrine. In many types of invertebrates it functions as an important neurotransmitter and hormone, but in the human body it normally exists only at trace levels and has no known function. Because it shares some of the actions of norepinephrine, octopamine has been sold under trade names such as Epirenor, Norden, and Norfen for use as a sympathomimetic drug, available by prescription. In mammals, octopamine may mobilize the release of fat from adipocytes (fat cells), which has led to its promotion on the internet as a slimming aid. However, the released fat is likely to be promptly taken up into other cells, and there is no evidence that octopamine facilitates weight loss. It is also used to treat hypotension and as a cardiotonic.

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TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
96	**Oxiracetam**	BCP06209; HY-B1715; Tox21_110218; Tox21_500933; AC-670; AN-929; CGP 21690; CO0043; CT 848; MFCD00242951; RW2749; s4270; AB05478; ACN-001375; CCG-205014; CS-8012; LP00933; MCULE-8223030209; RP17379; TRA0048419; KS-00000O50; 4- Hydroxy-2-oxopyrrolidine-N-acetamide; 4-hydroxypyrrolidin-2-on-1-yl acetamide and many others.	(RS)-2-(4-hydroxy-2-oxopyrrolidin-1-yl) acetamide	N	N	Y	Oxiracetam, or (RS)-2-(4-hydroxy-2-oxopyrrolidin-1-yl) acetamide, is a synthetic compound of the racetam family. Racetams share a pyrrolidine nucleus, a five member nitrogenous ring with a ketone bonded oxygen at R2. This 2-pyrrolidone ring is bound to the terminal carbon of an acetamide group, an ethyl amide chain with a ketone bond (C=O) at the alpha carbon. Oxiracetam is substituted with an additional hydroxy group at R4, which is a chiral center for the molecule. Oxiracetam is presumably produced as a racemate of its enantiomers. Oxiracetam is structurally analogous to piracetam, which lacks the R4 hydroxy substitution of oxiracetam.
97	Peganum harmala	Syrian Rue	N/A	N	Y	N	Syrian rue (Peganum harmala) is a desert plant that grows from the Eastern Mediterranean, throughout the Middle East and up to India, Mongolia and Manchuria. The seeds have a long history of ritual and medicinal use, mainly as an incense. The smoke is widely believed to ward off the evil eye. The brown, triangular seeds contain a high amount of harmala alkaloids that have a MAO inhibiting effect. For this reason Syrian rue became popular among western psychonauts as an ayahuasca analogue.
98	Pemoline	SCHEMBL41636; Pemoline (JAN/USAN/INN); MLS000759491; MLS001424026; Pemoline, >=98% (HPLC); DTXSID3023427; NRNCYVBFPDDJNE-UHFFFAOYSA-; HMS2051C08; HMS3393C08; AOB87716; NSC25159; 5-Phenyl-2-imino-4-oxo-oxazolidin; and many others.	(RS)-2-amino-5-phenyl-1,3-oxazol-4(5H)-one	N	N	Y	A stimulant of the 4-oxazolidinone class. Was used as a medication for ADHD and Narcolepsy, yet was pulled from most markets due to liver failures among children.
99	Periwinkle	Madagascar Periwinkle; Rosy Periwinkle	N/A	N	N	Y	Periwinkle is a very common creeping perennial with dark green leaves and white, pink, to purple flowers. It has a long history of use, although it is not commonly used as an herbal remedy in modern treatments. The plant contains alkaloids and tannins, with a major alkaloid being vincamine, related to the semisynthetic vinpocetine.

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TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
100	**Phenibut**	Fenibut, Phenybut, PhGABA; b-Phenyl-g-aminobutyric acid	4-Amino-3-phenylbutanoic acid	N	Y	N	Phenibut is a derivative of GABA with a phenyl group in the b-position. It is a chiral molecule and thus has two potential configurations, as (R)- and (S)-enantiomers. It has almost the same structure of baclofen (lacking only a chlorine atom in the para-position of the phenyl group) and contains phenethylamine in its structure.Pregabalin has the same structure as phenibut, except that the phenyl group is instead an isobutyl group.
101	Phenylalanine		(S)-2-Amino-3-phenylpropanoic acid	N	N	Y	Phenylalanine is found naturally in the breast milk of mammals. It is used in the manufacture of food and drink products and sold as a nutritional supplement for its reputed analgesic and antidepressant effects. It is a direct precursor to the neuromodulator phenethylamine, a commonly used dietary supplement. As an essential amino acid, phenylalanine is not synthesized *de novo* in humans and other animals, who must ingest phenylalanine or phenylalanine-containing proteins.
102	Phenylpiracetam	phenyl-; BRN 5030440; (2-Oxo-4-phenylpyrrolidin-1-yl) acetamide; 2-(2-Oxo-4-phenyl-pyrrolidin-1-yl)-acetamide; AK-81769; J-500892; Carphedone; Fonturacetam [INN]; phenypiracetam; Carphedo; ACMC-1BLAK; AC1Q4ZOM; AC1L30ZV; Oprea1_208829; Oprea1_429090; MLS000113218; and many others.	(R,S)-2-(2-oxo-4-phenylpyrrolidin-1-yl) acetamide	N	N	Y	Phenylpiracetam is based on the piracetam molecular skeleton with an additional phenyl group attached to the pyrrolidone nucleus, albeit at a different steric location than the substituted phenyl groups observed on aniracetam or nefiracetam. Due to the chiral center at the fourth position of the pyrrolidinone ring, it can exist in an S or R-isomer; the clinically used form is the racemic mixture.[6]
103	**Picamilon**	GABA-NG; N-(3-Carboxypropyl)nicotinamide; UNII-0S5N9SEK4N; 0S5N9SEK4N; 4-[(pyridin-3-ylcarbonyl)amino]butanoic acid; Butanoic acid, 4-[(3-pyridinylcarbonyl)amino]-; N-nicotinoyl-gamma-aminobutyric acid; 4-(pyridin-3-ylformamido) butanoic acid; 4-(pyridine-3-carbonylamino)butanoic acid; 4-[(Pyridine-3-carbonyl)amino] butyric acid; Butanoic acid, 4-((3-pyridinylcarbonyl)amino)-; and many others.	4-(Pyridine-3-carbonylamino)butanoic acid	N	N	Y	An analogue of GABA that does pass the brain blood barrier, which is then hydrolyzed into GABA and Niacin. In which the GABA could produce an anxiolytic effect. The Niacin as a vasodilator. And is usually used as part of a nootropic stac

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TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
104	**Piracetam**	MolPort-000-839-314; NINDS_000259; HMS1569L15; HMS1921L12; HMS2092D18; HMS2096L15; HMS2230B24; HMS3262N20; HMS3371G01; HMS3657A05; HMS3713L15; and many others.	2-(2-Oxopyrrolidin-1-yl)acetamide	N	N	Y	Piracetam, or 2-oxo-1-pyrrolidine-acetamide, is a synthetic compound of the racetam family. Racetams share a pyrrolidine nucleus, a five member nitrogenous ring with a ketone bonded oxygen at R2.[3] This 2-pyrrolidone ring is bound to the terminal carbon of an acetamide group, an ethyl amide chain with a ketone bond (C=O) at the alpha carbon.
105	**Pramiracetam**	68497-62-1; amacetam; Pramiracetam [INN]; Pramiracetamum [INN-Latin]; UNII-4449F8I3LE; 1-Pyrrolidineacetamide, N-(2-(bis (1-methylethyl)amino)ethyl)-2-oxo-; 4449F8I3LE; C14H27N3O2; Neupramir; Pramiracetam (INN); N-(2-(diisopropylamino)ethyl)-2-(2-oxopyrrolidin-1-yl)acetamide; Pramiracetam hydrate; N-[2-[di (propan-2-yl)amino]ethyl]-2-(2-oxopyrrolidin-1-yl)acetamide; and many others	N-[2-(Diisopropylamino)ethyl]-2-(2-oxopyrrolidin-1-yl)acetamide	N	N	Y	Pramiracetam, or N-[2-(Diisopropylamino)ethyl]-2-(2-oxopyrrolidin-1-yl)acetamide, is a synthetic compound of the racetam family. Racetams share a pyrrolidine nucleus, a five member nitrogenous ring with a ketone bonded oxygen at R2. This 2-pyrrolidone ring is bound to the terminal carbon of an acetamide group, an ethyl amide chain with a ketone bond (C=O) at the alpha carbon. Pramiracetam features an additional substituion bonded to RN of the acetamide group of a ethyl amide chain with two isopropyl carbon chains attached to the terminal nitrogen. Pramiracetam is structurally analogous to piracetam with an added diisopropyl ethylamino chain.Pramiracetam is prepared from piracetam by substituting the amide group with a dipropan-2-ylaminoethyl group.
106	PRE-084	PRE-084 Hydrochloride; Pre-084; PRE-084 (hydrochloride); 138847-85-5; Pre 084; 75136-54-8; 2-(4-Morpholinethyl) 1-phenylcyclohexanecarboxylate hydrochloride; SR-01000076063; PRE-084, solid; MLS000860067; SCHEMBL7381926; CHEMBL1449159; CTK8E9795; MolPort-003-959-092; BCP16863; Tox21_500927; HY-18100A; and many others	2-morpholin-4-ylethyl 1-phenylcyclohexane-1-carboxylate	Y	N	N	A sigma-1 receptor agonist derived structurally from PCP. It has cognitive enhancing effects as well as antidepressant effects, and shows promise in treating many nervous system diseases such as ALS and parkinsons.
107	**PRL-8-53**	Prl-8-53; 51352-88-6; methyl 3-[2-[benzyl(methyl)amino]ethyl] benzoate; methyl 3-{2-[benzyl (methyl)amino]ethyl}benzoate; AC1L22UU; AC1Q5Z4V; 9043AF; ZINC31982738; AJ-32456; 3-[2-[Benzyl(methyl) amino]ethyl]benzoic acid methyl ester	Methyl 3-[2-[benzyl(methyl)amino]ethyl] benzoate	N	N	Y	A nootropic research chemical first synthesized in the 70s. One study shows a drastic improvement in mid-term memory among users, but otherwise it is severely lacking in information surrounding it. It has no recreational potential.

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TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
108	**Prolintane**	Prolintane; Prolintane; Phenylpyrrolidinopentane; Catovit; Katovit; Promotil; Villescon	1-Phenyl-2-pyrrolidinylpentane	N	N	Y	1-Phenyl-2-pyrrolidinylpentane (also known as Prolintane or Pyrrolidinopentiophenone, and by the trade names Catovit, Promotil, and Villescon) is a synthetic central nervous system (CNS) stimulant that is structurally similar to the substituted pyrrolidine class of compounds such as MDPV and A-PVP albeit with notably attenuated effects. Prolintane was first synthesized in the 1950s, where it was found primarily to act as as a norepinephrine-dopamine reuptake inhibitor (NDRI)[1] which is thought to confer it stimulant and potential nootropic qualities.
109	Propylphenidate	PPH	N/A	Y	Y	N	Propylphenidate is structurally related to isopropylphenidate from the piperidine and pyrrolidine category of new psychoactive substances. Propylphenidate and isopropylphenidate are also structurally related to methyl- and ethylphenidate, where the isopropyl or propyl is replaced with a methyl or ethyl group. Propylphenidate can be synthesised from methylphenidate.
110	**PWZ-029**	CHEMBL45346; 6H-Imidazo [1,5-a][1,4]benzodiazepin-6-one, 8-chloro-4,5-dihydro-3-(methoxymethyl)-5-methyl-; SCHEMBL6847260; BDBM50034820; 3-Methoxymethyl-5-methyl-8-chloro-4,5-dihydro-6H-imidazo [1,5-a][1,4]benzodiazepin-6-one	8-Chloro-3-(methoxymethyl)-5-methyl-4,5-dihydro-6H-imidazo[1,5-a][1,4] benzodiazepin-6-one	N	N	Y	PWZ-029 is a benzodiazepine derivative drug with nootropic effects developed by WiSys,[1] It acts as a subtype-selective, mixed agonist-inverse agonist at the benzodiazepine binding site on the GABAA receptor, acting as a partial inverse agonist at the α5 subtype and a weak partial agonist at the α3 subtype. This gives it a mixed pharmacological profile, producing at low doses memory-enhancing effects but with no convulsant or anxiogenic effects or muscle weakness, although at higher doses it produces some sedative effects.
111	Quercetin	Trichocereus Bridgesii Cutting; Trichocereus Bridgesii Monstruosus Cutting	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	N	N	Y	Description Endemic to the high Andean region of La Paz, the Bolivian torch is a lesser known psychedelic cactus containing several alkaloids including the psychoactive alkaloid mescaline. Bioassay reports indicate that Trichocereus bridgesii is much more potent than the measured mescaline content suggests. Capable of producing a mind-expanding kaleidoscopic psychedelic experience, the effects of the Bolivian torch have been described as more clear-headed than the Peruvian torch. In Bolivia, the cactus is used as a hedge plant, serving a practical and decorative function.

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TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
112	Quetiapine	Xeroquel; 2-{2-[4-(Dibenzo[b;f][1;4]thiazepin-11-yl)-1-piperazinyl]ethoxy}ethanol; 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b;f][1;4]thiazepine; ICI 204;636 Ketipinor; quetiapine; quetiapinum; ZM 204;636; Seroquel	2-[2-(4-benzo[b][1,4]benzothiazepin-6-ylpiperazin-1-yl)ethoxy]ethanol	Y	N	N	Quetiapine is a dibenzothiazepine derivative. It is an atypical antipsychotic agent and medicinal products containing quetapine as the active pharmaceutical ingredient (as quetiapine fumarate or quetiapine hemifumarate) have been authorised in a number of Member States for the treatment of schizophrenia and for the prevention and treatment of bipolar disorder.
113	R-alpha-lipoic acid	Core Memory Nootropics	5-[(3R)-dithiolan-3-yl]pentanoic acid	N	N	Y	BrainBullets Core are capsules specially designed for anyone who appreciates the importance of a healthy brain. Core optimises your memory and protects your brain. In this way you will give your upper deck the essential vitamins it needs every day to keep your focus and concentration at peak level. BrainBullets Core can be ordered in packs of 15 or 30. Take one capsule each day to maintain your cognitive performance in peak condition.
114	**Razobazam**	UNII-LZ84VWN0U4; Hoe 175; 78466-98-5; LZ84VWN0U4; 4,8-Dihydro-3,8-dimethyl-4-phenylpyrazolo(3,4-b)(1,4) diazepine-5,7(1H,6H)-dione; Pyrazolo(3,4-b)(1,4)diazepine-5,7(1H,6H)-dione, 4,8-dihydro-3,8-dimethyl-4-phenyl-; 5662; and many others.	C14H14N4O2 3,8-Dimethyl-4-phenyl-2,8-dihydropyrazolo[3,4-b][1,4]diazepine-5,7 (4H,6H)-dione	N	N	Y	It is a drug which is a benzodiazepine derivative. Its mechanism of action appears to be quite different from that of most benzodiazepine drugs, and it produces nootropic effects in animal studies.
115	Rimonabant	SR-141716A; Acomplia; SR141,716; Zimulti	5-(4-Chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide	Y	Y	N	Rimonabant is the active pharmaceutical ingredient in the medicinal product Acomplia, which was suspended from the market in the European Union in November 2008 over concerns of serious psychiatric disorders (including depression, sleep disturbances, anxiety, and aggression) associated with its use. Acomplia was withdrawn from the market in January 2009.
116	RO-4491533	2H-1,5-Benzodiazepin-2-one, 4-[3-(2,6-dimethyl-4-pyridinyl) phenyl]-1,3-dihydro-7-methyl-8-(trifluoromethyl)-; RO4491533; CHEMBL1629855; D09YEQ; GTPL6226; SCHEMBL5562484; BDBM50332963; LYTVXCQQTLUEQR-UHFFFAOYSA-N	4-[3-(2,6-Dimethylpyridin-4-yl)phenyl]-7-methyl-8-(trifluoromethyl)-1,3-dihydro-2H-1,5-benzodiazepin-2-one	N	N	Y	It is a drug developed by Hoffmann-La Roche which acts as a potent and selective negative allosteric modulator for group II of the metabotropic glutamate receptors (mGluR2/3), being equipotent at mGluR2 and mGluR3 but without activity at other mGluR subtypes. In animal studies, RO-4491533 produced antidepressant effects and reversed the effects of the mGluR2/3 agonist LY-379,268 with similar efficacy but slightly lower potency than the mGluR2/3 antagonist LY-341,495.

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TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
117	**RO4938581**	9H-Imidazo[1,5-a][1,2,4]triazolo [1,5-d][1,4]benzodiazepine, 3-bromo-10-(difluoromethyl)-; CHEMBL1080588; 883093-10-5; RO 4938581; D0E7PY; 4-tert.Butylcalix[8]arene; GTPL4299; SCHEMBL2426998; EX-A856; AFJRYPJIKHMNGL-UHFFFAOYSA-N; BDBM50311045; and many others.	3-Bromo-10-(difluoromethyl)-9H-imidazo [1,5-a][1,2,4]triazolo[1,5-d][1,4] benzodiazepine	N	N	Y	Ro4938581 is a nootropic drug invented in 2009 by a team working for Hoffmann-La Roche, which acts as a subtype-selective inverse agonist at the α5 subtype of the benzodiazepine binding site on the GABAA receptor. It has good selectivity for the α5 subtype and did not produce convulsant or anxiogenic effects in animal studies, making it a promising potential nootropic.[1][2] [3] Ro4938581 and a related derivative basmisanil (RG-1662, RO5186582) have subsequently been investigated for the alleviation of cognitive dysfunction in Down syndrome
118	**S-Adenosyl methionine**	SAM-e, Methylguanidoacetic acid; S-Adenosyl methionine; SAM-e; Methylguanidoacetic acid	(2S)-2-Amino-4-(((2S,3S,4R,5R)-5-(6-aminopurin-9-yl)-3,4-dihydroxyoxolan-2-yl) methyl-methylsulfonio)butanoate	N	N	Y	S-adenosyl methionine is a molecule, found endogenously as a substrate synthesized by the sub-groups adenosine and methionine through an the enzyme methionine adenosyltransferase. The adenosine subcomponent is comprised of an adedine nucleobase bonded to a ribose chain. This ribose chain is attached to the terminal carbon of the methionine group. Methionine is a butyl carboxylic acid substituted at R2 with an amino group and at R4 with a methylthio (carbon-sulphur) group. S-adenosyl methionine is an essential methyl donator in metabolic reactions.
119	Sakae naa	Combretum quadrangulare	3-benzyl-1-hydroxy-2H-pyridine-4-carbaldehyde	N	N	Y	Sakae Naa (Combretum quadrangulare) is a small tree native to Southeast Asia, the leaves of which are reportedly used as a substitute for kratom in areas where kratom is banned. There is dispute about whether its effects are similar to the effects of kratom.
120	Selegiline	Deprenyl; Eldepryl; Emsam; L-deprenyl	(R)-N,a-dimethyl-N-2-propynylbenzeneethanamine	N	N	Y	Selegiline increases the actions of dopamine in the brain by inhibiting the enzymes that break it down. After being sold for years as an anti-aging supplement and a treatment for Parkinson's disease, the FDA approved use of a Selegiline transdermal patch (Emsam) for treatment of depression in 2006.
121	**SH-053-R-CH3-2′F**	4H-Imidazo[1,5-a][1,4] benzodiazepine-3-carboxylic acid, 8-ethynyl-6-(2-fluorophenyl)-4-methyl-, ethyl ester, (4R)-; 872874-14-1; SCHEMBL7718347; NGYKELBMVXBFSM-CQSZACIVSA-N; ZINC35847341; KB-275294	Ethyl 8-ethynyl-6-(2-fluorophenyl)-4-methyl-4H-imidazo[1,5-a][1,4] benzodiazepine-3-carboxylate	N	N	Y	SH-053-R-CH3-2′F is a drug used in scientific research which is a benzodiazepine derivative. It produces some of the same effects as other benzodiazepines, but is much more subtype-selective than most other drugs of this class, having high selectivity, binding affinity and efficacy at the α5 subtype of the GABAA receptor. This gives much tighter control of the effects produced, and so while SH-053-R-CH3-2′F retains sedative and anxiolytic effects, it does not cause ataxia at moderate doses.[1] SH-053-R-CH3-2′F also blocks the nootropic effects of the α5-selective inverse agonist PWZ-029, so amnesia is also a likely side effect.

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TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
122	Sildenafil	Viagra; Aphrodil	1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d]pyrimidin- 5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate	N	N	Y	Sildenafil citrate is prescribed in the treatment of Erectile Dysfunction. It is commonly referred to as a "lifestyle drug". Lifestyle drugs are prescribed for quality-of-life conditions such as baldness, impotence, obesity and smoking cessation. Sildenafil is a synthetic piperazine derivative.
123	St John's wort	St John's Wort; Sint Janskruid	N/A	N	N	Y	St. John's wort, also known as "perforate" or "common" St. John's wort, is a plant with yellow flowers, that some people, at first glance, may mistake for a common, roadside weed. It has been used for centuries as an herbal mood enhancer. Enjoy the rich flavour and effects of one of Mother Nature's miracle plants.
124	Stablon	Tianeptine, Stablon, Coaxil, Tatinol; Tianeptine; Stablon; Coaxil; Tatinol;Tianeptine	(RS)-7-(3-chloro-6-methyl-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-ylamino)heptanoic acid S,S-dioxide	Y	N	N	In terms of molecular structure and chemistry, tianeptine is a tricyclic antidepressant as its molecular structure is composed of three cyclic compounds. Despite tianeptine's chemical similarity to other TCAs, its effects and mechanisms are fairly unique.
125	**Sulbutiamine**	sulbut; arcalion; enerion; bisibuthiamine; youvitan	4-[(4-amino-2-methyl-pyrimidin-5-yl) methyl-formyl-amino]-3-[2-[(4-amino-2-methyl-pyrimidin-5-yl)methyl-formyl-amino]-5-(2-methylpropanoyloxy)pent-2-en-3-yl]disulfanyl-pent-3-enyl] 2-methylpropanoate	N	N	Y	A thiamine derivative nootropic and stimulant drug. Caution should be used as Sulbutiamine reduces dopamine output over time with consistant usage.
126	Tadalafil	Cialis; Adcirca; Tadacip	(6R,12aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino [1',2':1,6] pyrido[3,4-b]indole-1,4-dione	N	N	Y	Tadalafil, a PDE5 inhibitor used to combat erectile disfunction. Dangerous in combination with other drugs which lower blood pressure.
127	Tannic acid	Guarana Powder [Paulinnia Cupana]	[2,3-dihydroxy-5-[[(2R,3R,4S,5R,6S)-3,4,5,6-tetrakis[[3,4-dihydroxy-5-(3,4,5-trihydroxybenzoyl)oxybenzoyl]oxy]oxan-2-yl]methoxycarbonyl]phenyl] 3,4,5-trihydroxybenzoate	N	N	Y	Use Guarana to get more energy. People who like a boost can use this! It is now available in powder form. Dissolve it in hot water, tea, hot milk, coffee or in any another type of drink. Best is to first take one drink. Then you can experience the effect on your body. If the effect is pleasant, you can always try another drink.
128	**Theanine**	Theanine, L-Theanine, L-g-glutamylethylamide and N5-ethyl-L-glutamine; Theanine; L-Theanine; L-g-glutamylethylamide and N5-ethyl-L-glutamine	N-ethyl-L-glutamine; (2S)-2-ammonio-5-(ethylamino)-5-oxopentanoate	N	N	Y	Theanine, or N-ethyl-L-glutamine, is an amino acid analogue of L-glutamine. Its structure is comprised of a five carbon straight chain carboxylic acid called pentanoic acid, which is bonded to an amino group at R2, and an additional ketone group at R5. Also substituted at R5 of the pentanoic group is an ethylamino chain connected at its amino constituent. Theanine is understood to refer to the levorotary enantiomer, which is well documented, rather than the relatively unresearched dextrorotary enantiomer.

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TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
129	**Tolibut**	28311-38-8; 4-amino-3-(4-methylphenyl)butanoic acid; 4-amino-3-(p-tolyl)butanoic acid; AC1L2LNB; Oprea1_567181; SCHEMBL18386267; 28311-37-7 (hydrochloride); and many others	4-Amino-3-(4-methylphenyl)butanoic acid	N	N	Y	Analogue of GABA, and the 4-methyl analogue of Phenibut. Has similar effects, acts on GABA(B).
130	Tropicamide	N-Ethyl-alpha-(hydroxymethyl)-N-(4-pyridinylmethyl) benzeneacetamide; Visumidriatic; Mydriaticum; Mydriafair; Tropicacyl; Mydriacyl; Paremyd; Minims tropicamide; Mydrum; Bistropamide	(RS)-N-ethyl-3-hydroxy-2-phenyl-N-(pyridin-4-ylmethyl)propenamide	Y	N	N	Medicinal products containing tropicamide are authorised in the European Union. It is an antimuscarinic used in medicinal products to dilate the pupils, specifically as a topical mydriatic and cycloplegic.
131	Tryptophan	2-Amino-3-(1H-indol-3-yl) propanoic acid; Trp; W; TRP	(2S)-2-amino-3-(1H-indol-3-yl)propanoic acid	N	N	Y	Tryptophan (symbol Trp or W)[2] is an α-amino acid that is used in the biosynthesis of proteins. Tryptophan contains an α-amino group, an α-carboxylic acid group, and a side chain indole, making it a non-polar aromatic amino acid. It is essential in humans, meaning the body cannot synthesize it: it must be obtained from the diet. Tryptophan is also a precursor to the neurotransmitter serotonin, the hormone melatonin and vitamin B3.[3] It is encoded by the codon UGG.
132	**Tyrosine**	L-Tyrosine or 4-hydroxyphenylalanine; Tyrosine; L-Tyrosine or 4-hydroxyphenylalanine	L-Tyrosine	N	N	Y	Tyrosine is a non-essential phenylalanine-derived amino acid. Tyrosine's structure is made a para-hydroxylated phenyl ring connected to a pentanoic acid group, which is a five member carbon chain with a carboxyl (C(=O) OH) group on the terminal carbon. This pentanoic acid chain is substituted at R2 with an amino group in levorotary orientation.
133	**URB-597**	KDS-4103; Cyclohexylcarbamic acid 3'-carbamoyl-biphenyl-3-yl ester	[3-(3-Carbamoylphenyl)phenyl] N-cyclohexylcarbamate	Y	N	N	URB-597 belongs to the carbamate chemical class. It is known to be an inhibitor of the enzyme FAAH (fatty-acid amide hydrolase) and this includes the metabolic hydrolysis of the endocannabinoid/anandamide/(a fatty-acid amide). It has been used extensively in neuropharmacological research into endocannabinoid system. It's also known as KDS-4103. KDS-4103 is being developed by Kadmus Pharmaceuticals, Inc. for clinical trials in humans.

(Continued)

TABLE A1 | Continued

N	NPSfinder® name	Other names	IUPAC (isomerdesign)	EDND (April 2019)	UNODC EWA NPS (July 2019)	Unique to NPSfinder® database	NPSfinder® Brief description
134	Vardenafil	Valif 20	2-[2-ethoxy-5-(4-ethylpiperazin-1-yl) sulfonylphenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one	N	N	Y	Besides Cialis (Tadalafil) we now offer Valif 20 (Vardenafil). Valif 20 improves erection and results in successful intercourse. Valif 20 is also known as Vardenafil. The effects of Valif 20 are noticeable 15 to 25 minutes after ingestion. In the absence of sexual arousal Valif 20 will not work optimally. So make sure you are in a horny environment
135	Vasopressin	ADH; Pressyn; Diapid	(2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide	N	N	Y	Vasopressin is a hormone produced in the hypothalamus which increases water retention. asopressin is used to manage anti-diuretic hormone deficiency. It has off-label uses and is used in the treatment of gastrointestinal bleeding, ventricular tachycardia and ventricular defibrillation.
136	Vinpocetine	Cavinton; ethyl apovincaminate	ethyl (15S,19S)-15-ethyl-1,11-diazapentacyclo[9.6.2.02,7.08,18.015,19] nonadeca-2,4,6,8(18),16-pentaene-17-carboxylate	N	N	Y	Vinpocetine is a derivative of vincamine from the periwinkle plant. It increases cerebral blood flow and is said to improve memory.
137	Vitamin A		(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraen-1-ol	N	N	Y	Vitamins are organic (carbon-containing) molecules that are necessary for the functioning of the human body. They have a wide range of effects and functions.
138	Vitamin B12		alpha-(5,6-Dimethylbenzimidazolyl) cobamidcyanide	N	N	Y	See above
139	Vitamin D		(1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol	N	N	Y	See above
140	Withania somnifera	Ashwagandha, an Indian ginseng	(2R,6S,7R,9R,11S,15R,16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-2,3-dihydropyran-2-yl]ethyl]-2,16-dimethyl-8-oxapentacyclo [9.7.0.02,7.07,9.012,16]octadec-4-en-3-one	N	N	Y	Is an Adaptogen. It is commonly used for its ability to prevent anxiety. It also is helpful in relieving insomnia. It's name means "Smell of Horse" due to its smell and the traditional belief that ingesting the this herb will give you the strength and virility of a horse.
141	Yerba mate	South American holly; Beverage: yerba mate; Paraguay tea; Braziliain tea; jesuit tea; ka'a (Guarani)	N/A	N	N	Y	Ilex paraguariensis is a small S. American tree that's leaves contain caffeine and other xanthines. The toasted leaves have a long history of use as a stimulant tea. Falsely rumored to contain a unique chemical mateine.
142	Yohimbine HCL	Yohimbe	methyl (1S,15R,18S,19R,20S)-18-hydroxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate; hydrochloride	N	N	Y	Pausinystalia yohimbe is a West African tree thats bark contains yohimbine. It has a long history of human use as a stimulant and aphrodisiac. It is commonly sold as an herbal supplement to improve erectile function.

The 35 CEs described as nootropic in NPSfinder® are in bold.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 04 November 2020
doi: 10.3389/fpsyt.2020.542301

Chemsex and Mental Health of Men Who Have Sex With Men in Germany

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Background: Chemsex is defined as using certain substances immediately before or during sexual activities to facilitate, prolong and/or intensify sexual experience, mainly by some communities of men who have sex with men (MSM). Four substances are typically associated with chemsex: methamphetamine, mephedrone, GHB/GBL, and ketamine. While there is a lot of evidence for increased prevalence of HIV, sexually transmitted infections and other sexual health measures among MSM, who engage in chemsex, there has been little research on mental health aspects. This study aims to describe aspects of mental health among a sample of German men who have sex with men (MSM) who engage in chemsex and to describe potentially adverse consequences of chemsex behavior.

Method: This paper refers to a subset of participants from the *German Chemsex Survey*, an MSM-community recruited, self-completed online survey with a self-selected convenience sample. The survey comprised 420 different items considering recreational substance use, substance use in sexual settings, mental health, sexual transmitted infections, adverse consequences of chemsex behavior, and experiences of non-consensual sex acts. A group of participants who used methamphetamine, mephedrone, GHB/GBL, and/or ketamine in a sexual setting in the last 12 months ($n = 280$, chemsex group) was analyzed regarding symptoms of depression (PHQ-9), general anxiety disorder (GAD-7), somatization (PHQ-15), and PTSD (Primary Care PTSD Screen). Group comparisons were conducted between the chemsex group and men who did not use substances in a sexual context ($n = 177$, non-chemsex group). Mean scores of mental health measures were compared, as well as scores above a cut-off that indicates clinically relevant symptoms. Logistical regression was utilized to determine whether mental health measures can predict adverse consequences of engagement in chemsex behaviors.

Results: A total of 1,583 men started the survey; 1,050 participants provided information on substance use. Twenty-seven percent of participants ($n = 280$) reported that they used methamphetamine, mephedrone, GHB/GBL and/or ketamine in a sexual setting in the last 12 months. The chemsex group showed significantly higher mean scores for depression, anxiety, and somatization than the non-chemsex group, but effect sizes were

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Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *12 March 2020*
Accepted: *22 September 2020*
Published: *04 November 2020*

Citation:
Bohn A, Sander D, Köhler T, Hees N, Oswald F, Scherbaum N, Deimel D and Schecke H (2020) Chemsex and Mental Health of Men Who Have Sex With Men in Germany. Front. Psychiatry 11:542301. doi: 10.3389/fpsyt.2020.542301

low. Even though mean scores were heightened, they were still far below the cut-off for clinically relevant symptoms. The chemsex group reported significantly higher incidences of non-consensual sex acts compared with the non-chemsex group. Some men in the chemsex-group experienced potentially adverse consequences, such as loss of control regarding time and money spent for chemsex activities or amount of substances used at one occasion (49.6%), negative impacts on social functioning (33.6%), psychotic symptoms (13.2%), and physically aggressive behavior toward others (2.9%). Clinically relevant symptoms did not predict a higher likelihood for adverse consequences.

Discussion: Mean scores for depression, anxiety, and somatization were significantly higher in the chemsex-group, but effect sizes were low. Both groups reported poorer mental health compared to men in the German general population. Mental health measures did not contribute to predict potentially adverse consequences of chemsex behavior.

Keywords: chemsex, mental health, men who have sex with men, party and play (PNP), sexualised drug use, HIV

BACKGROUND

Chemsex is defined as using certain substances immediately before or during sexual activity to facilitate, prolong, and/or intensify sexual experience mainly by some communities of men who have sex with men (MSM) (1). There are four substances typically associated with chemsex: methamphetamine ("crystal meth," "T," "Tina"), mephedrone, GHB/GBL ("liquid ecstasy"), and ketamine (2, 3).

Previous studies have shown that MSM who engage in chemsex show a variety of distinctive features regarding their sexual behavior and their sexual health, including a higher likelihood to be HIV positive than MSM who do not engage in chemsex (4–6), as well as higher rates of sexually transmitted infections (STIs) (6, 7) and higher rates of hepatitis C infections (5, 7). Chemsex is also associated with engagement in group sex, having multiple sexual partners (8, 9) and more high-risk sexual behavior like condomless anal intercourse by HIV-negative men with partners that are HIV-positive or whose serostatus is unknown (10, 11).

In contrast, there has been considerably less research concerning the mental health status of MSM who engage in chemsex. Identifying as gay, bisexual or another non-heterosexual identity generally carries a higher risk for poor mental health compared to the general population, resulting in higher rates of depression and anxiety, suicide, and substance use disorders (12). This connection is often explained by the minority stress model (13). The model states that the connection between a non-heterosexual identity and higher incidences of mental health issues is mediated by ongoing stress and perceived and enacted stigma as a result of being part of a minority. Correlates of depression in a study of 1,340 HIV negative MSM in the UK, who were recruited from sexual health clinics, were a younger age, bisexual or other plurisexual orientation and a greater number of recreational drugs used (14). MSM with depressive symptoms may also be more likely to report high–risk sexual practices (15) and STI diagnoses (14).

Engagement with the LGBT community, found to be a contributing factor to overall well-being of LGBT people (16, 17), also seems to heighten the probability of drug use in general and especially in a sexual context for MSM. There is possibly a different social norm regarding substance use in some MSM communities (18). It has been reported by MSM engaged in chemsex that substance use is common in their friendship- or social group (19, 20).

A recent study of 3,017 gay or bisexual MSM in Australia found no significant relationship between drug use in sexual settings and clinically relevant symptoms of depression or anxiety (indicated by scores of 10 or above on the PHQ-9 and GAD-7, respectively) (21). However, a risk factor for poor mental health in this study was perceiving one's own substance use as problematic, or it being viewed as problematic by others. The authors concluded that there does not seem to be a direct or straightforward connection between substance use and mental health among MSM. In the same sample, no significant differences were found in rates of clinically relevant depression and anxiety symptoms between MSM who had recently injected drugs and those who had not (22).

In a survey of 1,649 MSM from the UK those who used drugs in sexual settings had lower overall life satisfaction than other participants, but no significant differences in body image satisfaction and psychological distress (10).

Since a high rate of HIV infections is often found among MSM who engage in chemsex, the implications of an HIV-infection also have to be considered when determining their mental health status. HIV positive people experience a higher risk of poor mental health outcomes, particularly depression (23, 24). It has been shown that HIV positive MSM who engage in chemsex face higher risks for self-reported anxiety or depression, sexual risk behavior and STI-diagnoses than HIV positive MSM who do not practice chemsex (7). This finding supports the suggestion of complex interconnections between HIV status, chemsex behaviors, and mental health.

To describe these complex interdependencies, Singer has proposed the model of syndemics (25, 26). This model allows an explanation for the observation of harmful impacts that somatic diseases, mental health and social conditions may have on each other, exceeding their singular effects. Syndemics "are most likely to emerge under conditions of health inequality caused by poverty, stigmatization stress or structural violence" [(25), p. 941]. There are consistent findings that a higher number of syndemic factors is associated with a higher risk for high risk sexual behavior and HIV transmission.

The aim of this study was to examine the mental health of German MSM practicing chemsex. Up to now, no other European sample of men who practice chemsex has been studied in this regard. In addition, the evaluation of mental health is more comprehensive than in previous studies, including for the first time somatization symptoms and trauma measures. Eventually, experiences of non-consensual sex as well as adverse outcomes of chemsex practice were investigated, which have not been widely covered before.

METHODS

Design and Sampling

The "German Chemsex Survey" was a self-completed online survey (September until December 2018). It was targeted at MSM who use substances, particularly in a sexual setting, and was advertised accordingly. Participants were recruited via free-of-charge advertising on "PlanetRomeo" (the most popular German MSM-dating website/smartphone application), postings on LGBT-related websites and social media channels, as well as HIV/sexual health clinics. The sample was a self-selected convenience sample. To be included, participants had to be at least 18 years of age, identify as male, be attracted to and/or have had sex with men and have sufficient knowledge of German to be able to complete the survey. There was no financial compensation for participating. For this study, a subset of the collected data was analyzed. The aim was to describe and examine a group that practices chemsex, defined by the four substances most closely associated with chemsex. To determine whether certain characteristics are tied to engagement in chemsex, a non-chemsex group was identified for comparison.

Ethical Considerations

All data in the study was collected anonymously. Participants could withdraw from the study at any time. They were supplied with a list of drug counseling and sexual health support services at the end of the survey should their participation have raised questions or concerns. The Ethics Committee of the Medical Department of the University of Duisburg-Essen granted its approval for the study (number UDE-18-8209-B0).

Measures

The survey consisted of 420 items covering demographic characteristics, recreational substance use, substance use in sexual settings, mental health, sexual behavior, sexually transmitted infections, social support, experiences of discrimination and stigmatization, internalized homonegativity, the "big five" personality factors, harm reduction strategies, quality of life, and health care service utilization. Mental health was assessed using the German version of the Patient Health Questionnaire (PHQ-D) (27) with its three subscales for depressive symptoms (PHQ-9) (28), generalized anxiety symptoms (GAD-7) (29), and somatization symptoms (PHQ-15) (30). In addition, participants were asked to complete the four-item Primary Care PTSD Screener (31, 32), the Life Events Checklist for DSM-5 (33, 34) that covers potentially traumatizing life events, and the first question of the Suicide Behaviors Questionnaire-Revised (35, 36) which records lifetime suicidal thoughts and attempts. Based on a previous study (37), questions were added assessing non-consensual acts during sexual encounters, experiences of violence in connection with sex and non-consensual drug use when using substances in sexual settings. There was also a list of possible negative consequences of chemsex use, that those who reported chemsex could choose from.

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics 25.0. *P*-values of < 0.05 were taken to indicate statistical significance. The analyses presented here compare two groups: (i) men who used at least one "chemsex substance" (methamphetamine, GHB/GBL, ketamine, or mephedrone) in a sexual setting in the previous 12 months ($n = 280$); and (ii) men who did not report any substance use in sexual settings (apart from alcohol and/or nicotine) in the previous 12 months ($n = 177$).

For group comparisons regarding numerical variables Mann-Whitney-*U* tests were used, since all tested attributes were not normally distributed. For significant results, effect size was calculated by Cohen's d. Chi-square tests were used to compare the distribution of categorical variables. For significant results, effect size was calculated by the Phi coefficient. To assess associations between psychopathology and adverse consequences after practicing chemsex, logistic regression models were conducted.

Sample Characteristics

In total 1,583 people commenced the survey, 712 of whom completed all questions (45.0%). Data of non-completers were included on a pairwise basis, resulting in a different number of responses per analysis. Two hundred and eighty participants met the criterion of having used at least one of the four chemsex substances in a sexual context within the previous 12 months. One-hundred and five of the 280 men who reported chemsex (37.5%) dropped out at various points. Forty-four people from the 177 men who did not use any substances apart from alcohol and/or nicotine in a sexual setting also did not completely finish the survey (24.9%). See **Figure 1** for a flowchart of development of participants' numbers in the course of the survey.

For details on the sample demographics for the chemsex and the non-chemsex group, see **Table 1**. Group comparisons were conducted to determine whether both groups are comparable regarding their demographics. A *t*-test showed that people in the non-chemsex group were significantly younger. Chi-square tests showed significant differences between the groups regarding country of birth, employment status and monthly net income. For employment status, a *post-hoc* test showed significantly more

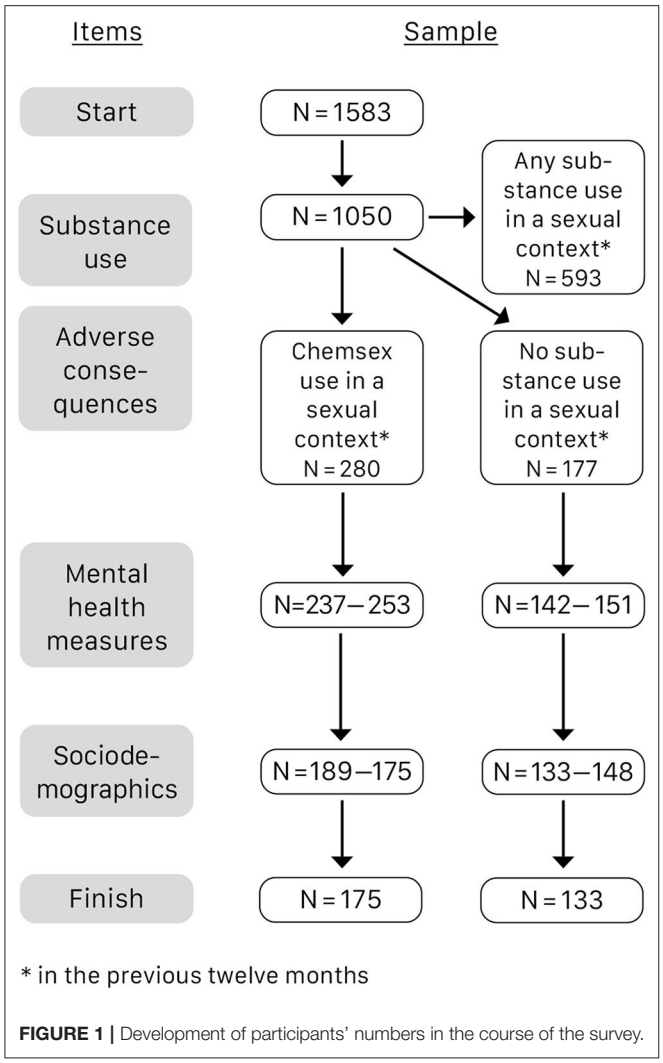

FIGURE 1 | Development of participants' numbers in the course of the survey.

university students in the non-chemsex group. A *post-hoc* test for monthly net income showed that in the non-chemsex group there were significantly more people that earned < 1.000 Euros per month. All other attributes were evenly distributed.

Eighty four participants from the chemsex group (30.0%) reported having injected at least one of the substances. For substance used in a sexual setting by the whole chemsex sample and by IV substance users see **Table 1**.

RESULTS

For an overview of all group comparisons, see **Table 2**.

Depressive Symptoms

The PHQ-9 scale has a maximum score of 27, with higher scores indicating higher levels of depressive symptoms. The chemsex sample's (n = 253) mean score on the PHQ-9 scale was 5.02 (SD = 4.14). 11.9% of the participants had a score of 10 or above and thus can be considered having clinically relevant depressive symptoms. PHQ-9 mean scores differed significantly in comparison to the non-chemsex group, with higher scores for the chemsex group. The groups did not differ regarding the distribution of clinically relevant symptoms.

General Anxiety Symptoms

The GAD-7 scale has a maximum score of 21, with higher scores indicating higher levels of anxiety symptoms. The chemsex group participants' (n = 242) mean score on the GAD-7 scale was 3.81 (SD = 3.79), and 8.3 % of the sample had a score of 10 or above, suggesting clinically relevant anxiety symptoms. GAD-7 mean scores were significantly higher in the chemsex group, the distribution of clinically relevant symptoms did not differ between the groups.

Somatization Symptoms

The PHQ-15 scale has a maximum score of 30, with higher scores indicating higher levels of somatization symptoms. The chemsex sample's (n = 252) PHQ-15 mean score was 5.14 (SD = 3.79), and 13.5% of the sample showed clinically relevant symptoms as indicated by a score of 10 or higher. There were significantly higher PHQ-15 mean scores in the chemsex group than in the non-chemsex group. The groups did not differ regarding the distribution of clinically relevant symptoms.

Trauma

76.8% of all the chemsex group (n = 237) reported experiencing at least one potentially traumatizing event from a list of twelve. Most commonly, these were a serious accident (36.9%), a life-threatening illness (36.4%), physical violence from an unknown person (36.9%) or physical violence from a known person (34.3%). The mean number of events experienced by the chemsex group was 1.87 (SD = 1.70), and 11.6% show clinically relevant symptoms of PTSD, as indicated by a score of 3 or above in the PTSD primary care screener. Participants from the chemsex group reported having experienced a traumatic event significantly more often than those from the non-chemsex group. The groups did not differ regarding the distribution of clinically relevant symptoms of PTSD.

Suicidality

12.7% of participants from the chemsex group (n = 251) reported having planned for suicide at least once in their lifetime, 9.6% had actively attempted suicide at least once. The groups did not differ regarding suicide plans or attempts.

Non-consensual Acts During Sex

In the chemsex group (n = 233), 47.2% reported having experienced their sexual partners not respecting their boundaries, which differs significantly from the non-chemsex group (n = 133; 26.8%). 15.5% of men engaging in chemsex (n = 233) reported the experience of violence in a sexual setting, which is not significantly different from the non-chemsex group (n = 138; 9.4%). 17.7% of the chemsex group (n = 234) reported that sexual partners had administered drugs to them without their consent.

Infectious Diseases

41.2% of the chemsex group (n = 199) reported being HIV positive, 2.0% reported being infected with hepatitis C.

TABLE 1 | Sample demographics.

Variable	Chemsex group		Non-chemsex group		*p*-value
	N	M (SD)	*N*	M (SD)	*t*-test
Age	189	40.22 (10.66)	146	37.60 (12.62)	0.045*
	N	%	*N*	%	χ^2
Gender identity	280		173		0.153
Male	277	98.9	168	97.1	
Transgender man	3	1.1	5	2.9	
Sexual identity	277		168		0.325
Gay/Homosexual	256	92.4	151	89.9	
Bisexual	15	5.4	15	8.9	
Queer	6	2.2	2	1.2	
Relationship status	263		161		
Single	112	42.6	77	47.8	0.292
In a relationship	151	57.4	84	52.2	
Country of birth	188		145		0.024*
Germany	155	82.4	132	91.0	
Other[a]	33	17.6	13	9.0	
Employment status	189		147		0.022*
Full-time employed	127	67.2	92	62.2	
Part-time employed	20	10.6	12	8.3	
Retired	11	5.8	5	3.5	
Student[b]	10	5.3	25	17.0	
Unemployed	9	4.8	6	4.2	
Other	12	6.3	7	4.8	
Monthly net income	188		144		0.022*
< 1.000 Euros[b]	24	12.8	36	25.0	
1.000–2.000 Euros	63	33.5	49	34.0	
2.000–3.000 Euros	50	26.6	33	22.9	
More than 3.000 Euros	51	27.1	26	18.1	
Highest school leaving certificate	175		133		0.431
University or university of applied sciences entrance diploma	136	77.7	102	76.7	
General certificate of secondary education	27	15.4	19	14.3	
Certificate of secondary education	12	6.9	10	7.5	
Other/none	0	0.0	2	1.5	
Substance use 12 months in a sexual context	280				
Amyl nitrite (Poppers)	246	87.9			
Medication for erectile dysfunction	213	76.1			
GHB/GBL	206	73.6			
Alcohol	202	72.1			
Ecstasy	167	59.6			
Amphetamines	161	57.5			
Ketamine	156	55.7			
Methamphetamine	130	46.4			
THC	149	53.2			
Cocaine	122	43.6			
Mephedrone	98	35.0			
Opioid analgesics	15	5.4			
Heroin	3	1.1			

(Continued)

TABLE 1 | Continued

Variable	Chemsex group		Non-chemsex group		*p*-value
	N	M (SD)	*N*	M (SD)	*t*-test
Substances injected in a sexual context 12 months	84				
Methamphetamine	72	85.7			
Mephedrone	34	40.5			
Ketamine	30	35.7			
Substance use 12 months not in a sexual context	280		173		
Alcohol	266	95.0	135	78.3	
Amyl nitrite (Poppers)	250	89.3	0	0.0	
Medication for erectile dysfunction	216	77.1	0	0.0	
GHB/GBL	209	74.6	0	0.0	
Ecstasy	193	68.9	2	1.2	
THC	186	66.4	20	11.8	
Amphetamines	186	66.4	0	0.0	
Ketamine	175	62.5	1	0.6	
Cocaine	141	50.3	0	0.0	
Methamphetamine	134	47.9	0	0.0	
Mephedrone	107	38.2	0	0.0	
Opioid analgesics	32	11.4	7	4.1	
Heroin	5	17.9	0	0.0	

*$p < 0.05$.
[a]*There were no clusters of non-German countries of birth.*
[b]*Attribute that differed significantly according to post-hoc test.*

TABLE 2 | Group comparisons between chemsex group and non-chemsex group, Mann-Whitney-*U* test for metric variable, Chi-square test for categorical variables.

Variable	Chemsex group		Non-chemsex group		Test statistic	Significance	Effect size
	N	Mdn (IQR)	*N*	Mdn (IQR)	Mann-Whitney-U	*p*-value	*r*
PHQ-9 score	253	4.00 (4.00)	150	3.00 (4.25)	14725.5	0.000*	0.18
GAD-7 score	242	3.00 (4.00)	149	2.00 (3.00)	15648.0	0.029*	0.11
PHQ-15 score	252	5.00 (5.00)	151	3.00 (4.00)	15807.0	0.004*	0.14
Number of traumatic events	237	2.00 (2.00)	142	1.00 (2.00)	14749.5	0.023*	0.11
	N	%	*N*	%	χ^2	*p*-value	Phi
PHQ-9 score $\geq$ 10	253	11.9	150	12.0	0.002	0.966	
GAD-7 score $\geq$ 10	242	8.3	149	8.7	0.025	0.874	
PHQ-15 score $\geq$ 10	252	13.5	151	10.6	0.729	0.393	
PTSD Screener score $\geq$ 3	234	11.5	139	12.9	0.164	0.686	
Suicide plans lifetime	251	12.7	152	14.5	0.243	0.622	
Suicide attempts lifetime	251	9.6	152	5.3	2.393	0.122	
Non-consensual sex acts	233	47.2	133	26.8	15.075	0.000*	0.194
Violence in a sexual setting	233	15.5	138	9.4	2.749	0.097	
HIV positive	199	41.2	96	13.5	22.700	0.000*	0.277
HIV status unknown	199	3.5	96	9.4	4.331	0.037*	0.121
Hepatitis C positive	198	2.0	70	0.0	a	0.576	
Hepatitis C status unknown	198	8.1	70	11.4	0.711	0.399	

[a]*Fisher's Exact Test was executed.*
*$p < 0.05$.

Significantly more men from the chemsex group were HIV-positive than those from the non-chemsex group. There were no differences for the rates of unknown current HIV-status between the groups, as for the rates of hepatitis C-infections.

Adverse Consequences of Use and Their Associations With Mental Health Measures

49.6% of participants from the chemsex group ($n = 280$) reported a loss control during or after a chemsex session in the last 12 months, meaning that they either spent more time or money on chemsex than they originally intended or that they could not entirely remember the event. 33.6% stated that they have been missing work or other appointments after a chemsex session or that they were still under the influence of drugs when working. 13.2% reported hearing voices or having paranoid experiences after engaging in chemsex. 2.9% have assaulted another person as an after-effect of a chemsex session.

Logistical regression analyses were conducted to determine whether those who show clinically relevant symptoms of depression, anxiety, somatization or PTSD are more likely to show any of the adverse consequences. For each model, the adverse consequence was taken as the outcome variable with the clinically developed symptoms as dichotomous predictors. None of the models showed a good fit, with Nagelkerke's R^2 values of 0.160 (assault of another person), 0.092 (missing work or other appointments), 0.078 (hearing voices or having paranoid experiences), and 0.056 (spending more time or money or loss of memory). In all models, only two predictors turned out to be significant: clinically developed somatization symptoms predicted assaults ($p = 0.033$; $OR = 5.653$, CI:1.152–27.730) and anxiety symptoms predicted missing work or other appointments or going to work while still under the influence of drugs ($p = 0.011$; $OR = 9.070$, CI:1.667–49.334).

DISCUSSION

With regard to mental health measures, a direct comparison of the chemsex and non-chemsex group, found significant differences for the mean scores of depression, somatization, and anxiety, as well as lifetime number of traumatic events experienced, which were all higher for the chemsex group. No differences between the groups for the rates of clinically developed symptoms were found. Those who practice chemsex reported significantly more incidences of violation of their sexual boundaries as well as a higher rate of HIV infections, compared to those who do not practice chemsex.

Mental Health

All mean scores of mental health measures were significantly higher for the chemsex group, but these differences show only small effect sizes, pointing to a weak interrelation. Comparing the distribution of clinically relevant symptoms between the different groups, there were no significant differences.

The prevalence rate of 11.9% for clinically relevant symptoms of depression in the chemsex group is almost twice that of the general male population in Germany (6.1%) (38), but comparable to a recent sample of MSM from the UK, which showed a rate of 12.4% with a PHQ-9 score $\geq$ 10 (14). In contrast to a study of Australian MSM that identified 28.3% with a PHQ-9 score $\geq$ 10 (21), this study's chemsex sample expresses fewer depressive symptoms over all. Compared to clinically relevant symptoms of somatization in the general population concerning 8.1% of people (30), the chemsex sample's rate of 13.5% was slightly higher. In comparison to the German general population's rate of 5.9% with clinically relevant symptoms of Generalized Anxiety Disorder (39), the chemsex sample's rate was only slightly higher, at 8.3%. Compared to 17.9% in the sample of 3,017 Australian MSM (21), the chemsex group seems to show comparably little symptoms of anxiety. The rate of 11.5% in the chemsex sample that screened positive for PTSD is considerably higher compared to the general population in Germany, for which a 12 months prevalence for PTSD in men of 0.9% was measured (40).

The number of lifetime suicide attempts reported by those engaged in chemsex was 9.6%. A recent study from Sweden found a percentage of lifetime suicide attempts for gay men of 10.0%, whereas merely 2.2% heterosexual men attempted suicide in their lifetime (41). In conclusion, the chemsex sample has a history of lifetime suicide attempts that is comparable to other MSM, but higher than in the general population.

We can observe some strain on those who practice chemsex compared to those who do not, as suggested by heightened mean scores for depression, somatization and trauma events. However, these differences are not reflected in the rates of clinically relevant symptoms. Overall, it seems that the chemsex group does not differ much from other MSM groups that aren't solely comprised of men who engage in chemsex. Previous research has suggested a complex interplay between substance use, sexual behavior and mental health measures, with various factors impacting on and influencing each other. There is no information about the sample's rate on substance dependency, which has a negative impact on mental health (21). The rate of 41.2% HIV positive chemsex participants also allows us to conclude that mental health may be negatively impacted (23, 24). These are all potential negative influences on mental health statuses.

It has also been shown that those who practice chemsex have closer ties to the LGBT community than other MSM (6, 19, 42), which has a positive effect on well-being (16, 17).

Adverse Outcomes

About half of the participants that practice chemsex have experienced a loss of control during or after a chemsex session in the last 12 months, meaning that they either spent more time or money on chemsex than they originally intended or that they could not entirely remember the event. This adverse outcome could not be predicted by clinically developed symptoms of depression, anxiety, somatization, or PTSD. About a third stated that they have been missing work or other appointments after a chemsex session or that they were still under the influence of drugs when working. Clinically developed symptoms of anxiety showed to be a significant predictor for this outcome. About one in ten men reported hearing voices or having paranoid experiences after engaging in chemsex. This outcome could not be predicted by any clinically developed symptoms. Three

percent of participants have assaulted another person as an after-effect of a chemsex session. This outcome could be predicted by clinically developed symptoms of somatization.

Overall, all models predicting negative outcomes showed low models-of-fit. Even though two significant predictors could be identified, the results have to be interpreted cautiously, since the rates of clinically relevant symptoms for all measures were lowly pronounced in this particular group, so the distribution is uneven. The rates of the adverse outcomes of assaulting someone and having paranoid experiences or hearing voices were also quite unevenly distributed, which further limits the models' explanatory power.

Non-consensual Sex Acts

46.6% of chemsex users report non-consensual acts during sex, and violence during sex was experienced by 16.8%. Significantly more experiences of non-consensual acts were reported in the chemsex group compared to the non-chemsex group, of which 28.0% reported such incidents. A small effect size shows for this result. There were no significant differences regarding the experience of violence during sex for the different groups. A recent study from the UK that chose a similar sampling approach as this study, recruited MSM participants via Grindr, a dating app that is often used by MSM to find sex partners (43). Of these men, 37.7% reported having at least experienced one form of intimate partner violence. Being a victim of sexual intimate partner violence was significantly correlated with an increase of substance use in the last month, showing yet another interconnection relevant to the complex behavior of chemsex practice. There is more evidence that not only exposure to intimate partner violence as a victim, but also as a perpetrator, is associated with increased chance of substance use (44). Intimate partner violence is known as a syndemic risk factor (45).

According to a recent study the experience of non-consensual sex is far more common for MSM, with a rate of 22.8%, compared to 4.3% of men that have sex exclusively with women (46).

The study by Bourne et al. from 2014 regarding chemsex in the UK found anecdotal evidence of non-consensual sex associated with substance use, particularly in cases that men had accidentally overdosed. Interviewees in this study reported that there "was a particularly blurry line regarding consent in the context of chemsex" [(1), p. 59]. 17.7% of those practicing chemsex in this study also reported that sexual partners administered drugs to them without their consent. So far, there has been no systematic research regarding chemsex and consent, but these findings suggest the necessity of addressing the topic.

HIV and Hepatitis C Infections

The rate of 41.2% HIV positive in the chemsex group is higher than the rate of HIV-positive German MSM in 2010, which was 8.0% (47). The HIV rate in the general population in Germany in 2015 was 0.1% (48). The distribution of HIV positive people in the chemsex group in this study differed significantly from the non-chemsex group with a medium effect size.

Those who injected chemsex substances showed a significantly higher incidence of HIV-infection, which is consistent with other studies' findings (22). Frequency of use was also relevant in this sample, with more frequent users showing higher rates of HIV. Practicing chemsex more often and injecting the drugs appear to be risk factors for HIV infection, and although this cannot be determined by this study's correlational data, there are findings pointing in this direction (5). Based on this, the use of pre exposure prophylaxis (PrEP) could be a useful strategy for those engaged in chemsex.

The overall rate of hepatitis C infections in the chemsex group was 2.0 %, which does not differ significantly from the non-chemsex group. The hepatitis C rate among the German general population is 0.3% (49).

Limitations and Future Research

The limitations of this study include the cross-sectional design, which does not allow causal explanations, as well as the self-selected sample with high levels of income and education overall. It is possible that chemsex users do tend to have a certain socio-economic status but determining this would require a representative survey. The questionnaire was only available in German, excluding participants with insufficient German language skills. It was also promoted by Aidshilfe (the largest HIV/AIDS peer-support organization in Germany), so the high HIV rate in the sample might be a sampling effect. The study was targeted at substance users and advertised, respectively, so drug use was high overall throughout the sample and the findings should not be used to estimate a prevalence of substance use in the German MSM population.

Even though not all users reported consuming in a sexual setting, the identified non-chemsex group that did not practice sexualized drug use may still not be comparable to other non-chemsex MSM samples. There have also been found some demographic differences between the groups, which could put some restrictions on the comparison between the chemsex group and the non-chemsex group. The non-chemsex group was found to be younger with a higher rate of university students and people with low income. There were also more people not born in Germany in the chemsex sample. Since there was a dropout rate of 37.5% in the chemsex group and 22.2% in the non-chemsex group and all demographic data was retrieved at the very end of the study, there might be a bias concerning the demographic data.

For future research, it would be useful to study a more diverse group in terms of socio-economic status. Additionally, more research would be necessary to determine complex interrelations between the different factors, in order to assess which are risk factors for poor mental health, and in which situations. Another topic that would be useful to explore and study further is the relation between chemsex and non-consensual sex.

Outlook

Support and treatment options for MSM who practice chemsex and want to reduce or quit their substance use are sparse so far. In previous studies, men have reported a hesitancy to attend regular drug counseling services or programs out of fear not be understood (50). There is a distinct need for counseling tailored to chemsex users and their needs which is not generally focused on abstinence, and which also incorporates harm reduction

strategies (2). There are promising findings for German MSM, who use methamphetamine that some harm reduction strategies are already applied and well-accepted (51). In programs aimed at abstinence, the established connection between sex and substance use makes sexual situations potential triggers for relapse, and thus needs to be specifically addressed (37). There are treatment approaches integrating professional support as well as MSM peer-support approaches (50), which seem especially important, given the evidence that substance use is considered a social norm in some parts of the community (18, 22). There is also a need for well-trained and informed staff in sexual health and outreach clinics (52).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Department of the University of Duisburg-Essen, approval nr. UDE-18-8209-B0. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB article writing, data analysis, and literature search. HS study conceptualization, data analysis, and article writing. FO survey programming and data analysis. DS study conceptualization. TK consulting data analysis. NH and NS editing article. DD study conceptualization and editing article. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: NS received honoraria for several activities (advisory boards, lectures, manuscripts) by AbbVie, Hexal, Janssen-Cilag, MSD, Medice, Mundipharma, Reckitt-Benckiser/Indivior, and Sanofi-Aventis. During the last 3 years, he participated in clinical trials financed by the pharmaceutical industry.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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