

Title: High lifetime, but low current, prevalence of new psychotropic substances (NPS) use in German drug detoxification treatment young inpatients

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Summary

Background: Over the last 15 years, a large number of new psychoactive substances (NPS) has been identified, with their use being associated with a range of acute medical and psychopathological complications. Conversely, NPS addictive liability levels have not been systematically assessed in clinical populations. **Aims of the study:** Investigating the lifetime and current prevalence of NPS use in a sample of substance use disorder (SUD) patients admitted to an inpatient detoxification treatment centre. **Methods:** Assessment of previous/current NPS intake carried out with the means of standardised questionnaire based on the European version of Addiction Severity Index. **Results:** Some 206 patients (males 77.1%; average age: 30.7 years-old; most typical diagnosis: opioid/polydrug dependence) participated to the survey. Roughly half (e.g. 111/206; 53.9%) of them reported a lifetime use of NPS, most typically synthetic cannabinoids. Conversely, the current prevalence of NPS use was 2.9%; no NPS dependence condition was diagnosed. Among NPS users, 56.3% reported severe side-effects such as heavy anxiety or psychotic experience, and 64% reported an aversion of ever using the respective NPS again, whilst 84.3% of those reporting a single NPS intake reported an aversion. **Discussion:** The sharp contrast between lifetime prevalence of NPS use and prevalence of current use might be explained by the high frequency of severe side effects reported by NPS users.

Key Words:

New psychoactive substances – NPS - detoxification – side effects – clinical sample – addictive disorders

Introduction

Over the last 15 years or so, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has reported an increasing number of new psychotropic substances (NPS). In addition to several hundreds of NPS, typically including synthetic cannabinoids, psychedelic phenethylamines, and cathinone derivatives already detected in previous years, with the 2019 annual report 55 further NPS were detected during the previous 12 months (EMCDDA, 2019). NPS were initially advertised as legal substitutes for long-established and regulated drugs, such as cannabis or ecstasy, and were associated with their acquisition availability from the web, with slang terms such as "bath salts", "Spice", etc. (see review: Scherbaum et al., 2017).

Although clinical reports have described the range of NPS-related acute intoxication risks (Hermanns-Clausen et al., 2012; Rasimas, 2012), these drugs' overall clinical impact on addiction medicine is unclear. In particular, the prevalence of regular/long-term use, which is ultimately leading to addiction, as opposed to sporadic consumption, is unclear. Within the addiction medicine treatment services scenario, an NPS molecule could in fact either totally replace the drug traditionally consumed (e.g. cannabis) hence leading to a substance-related disorder; or its use, for various reasons, e.g. occurrence of significant related side effects, may remain sporadic and/or exploratory.

Within this framework, we aimed at addressing the following research questions: a) how widespread is lifetime vs current NPS use among patients admitted to an inpatient detoxification treatment; b) within this group of patients, which is the rate of those admitted for detoxification from an NPS; c) in case NPS had been used by these patients only sporadically/over short periods of time, which are the reasons behind the development of an aversion towards a further use of these new molecules?

Methods

Substance use disorder (SUD) patients included in this prospective survey were identified from two qualified detoxification wards; e.g. one focussing on detoxification from either opiates/opioids, and the other one from alcohol, cannabis, and stimulants. The study took place in the LWL-Klinik Marsberg, the only psychiatric hospital in a rural district in the Western part of Germany. At admission, a detailed survey regarding the history of misusing drugs' intake was carried out. Data analysis related to all patients consecutively admitted over a 15-month period. As NPS use was mostly expected in the younger age group, the comprehensive survey focussed on those with less than 40 years of age only.

The survey focussed on: traditional misusing substances (e.g. alcohol, benzodiazepines, heroin, cannabis, amphetamine, ecstasy, and cocaine); 'niche' compounds, e.g. molecules which are well known to addiction medicine but are less frequently identified in the health care system, e.g. herbal highs (*Datura stramonium*/^o"jimson weed"), LSD and absinth; and NPS, as taken from the following: EMCDDA 2019; Schifano et al, 2015; Schifano et al 2019. A particular focus here was on both, synthetic cannabinoids and synthetic cathinones, which have frequently been identified in Germany (Angerer et al., 2017; Scherbaum et al., 2017).

The survey was carried out with the means of a standardised questionnaire, based on the European version of Addiction Severity Index (McLellan et al., 1980; Gsellhofer et al., 1993). For each substance, it was ascertained if the use was either current (reference period: last 30 days before admission), or lifetime. Questions were raised relating to the frequency of intake, the approximate duration of use, etc. Finally, special focus was on the occurrence of side effects associated with drug misuse, and if these effects had led to the eventual aversion towards the use of any specific molecule.

Ethics

Participation of patients in this study was voluntary. All patients gave their written consent in participating to the survey. Ethical approval was granted by the ethics committee of the University Hospital Essen.

Results

During the 15-month observation period (e.g. from 11.8.2016 to 18.11.2017), a total of 1,160 consecutive inpatient admissions were organized. However, since patients were included only once in the data analysis, 687 unique patients were here considered. Out of these, 316 were over 40 years old and were therefore excluded from the survey. Fifty-four out of the 371 remaining patients were clinically judged to be too sick/intoxicated during their entire stay in hospital to be able to respond to a systematic survey; 75 did not give their consent to participate; and 36 presented with a further range of difficulties, including: lack of fluency in German language; acute mental illness; and severe deficits in intellectual functioning.

Hence, some 206 patients were included in the survey. Most (77.1%) were males; their average age was 30.7 years old, with a standard deviation of 5.7 years and a median value of 31 years. Main substance-related disorders leading to inpatient detoxification treatment were as follows: opiate (F 11.2 according to ICD-10; 108 patients-52.4%); alcohol (F10.2; 29 patients-14%); cannabis (F12.2; 7 patients-3.4%); sedative/hypnotics (F13.2; 2 patients-1%); amphetamine (2 patients-1%); and poly-drug (F19.2; 58 patients-28.2%) dependence. None of the patients were diagnosed with a NPS dependence.

Patients reported a lifetime use of a wide range of substances (see figure 1), most typically including: cannabis (95.6%, n=197); amphetamines (88.3%, n=182); and cocaine (84.0%, n=173). Conversely, lifetime levels of hallucinogenic fungi ("magic mushroom") and NPS intake were respectively reported by n=127 (61.7%) and n=111 (53.9%) patients.

Within the NPS group, synthetic cannabinoids ("spice", "herbal mixture") were those (n=106) most frequently mentioned.

Please insert here figure 1

Regarding current use (last 30 days before admission, see figure 1), those psychoactive substances most typically mentioned included: alcohol (n=127; 61.7%), cannabis (n=119; 57.8%), and heroin (n=90; 43.7%). Only 6 (2.9% of 206) patients reported a current NPS (e.g. synthetic cannabinoids in all cases) use; their intake had occurred with an average of 15.7 out of last 30 days prior to admission; see figure 2.

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Only 18 out of 111 NPS patients mentioned a regular daily intake having occurred over a period of several weeks in the past. Out of these, most (15 patients; 83.3%) reported a synthetic cannabinoids' use. Conversely, 46 patients reported only a single NPS use, which was in 44 (95.6%) cases a synthetic cannabinoid; in 1 case *Mitragyna speciosa*/kratom; and in another case a "research chemical" (allegedly a synthetic cathinone). The remaining 47 patients reported an NPS sporadic use over a long period of time; most of these molecules included synthetic cannabinoids (40 cases; 85.1%), but *Mitragyna speciosa*/kratom; synthetic cathinones; and 1pLSD were sporadically reported as well.

Serious side effects were reported by 56.3% of those reporting lifetime NPS use. Regarding NPS, the following side effects were most typically mentioned: anxiety, including fear of dying (n=35; 49.3%); psychotic experiences (n=25; 35.2%); nausea/vomiting (n=4; 5.6%); and unconsciousness (n=4; 5.6%). Although most ill-health effects were

associated with synthetic cannabinoids' intake, significant anxiety and psychotic experience levels were also mentioned following the use of synthetic cathinones' and 1pLSD. An aversion to use a specific drug again in the future were reported by up to 64% of the total group of patients. In particular, at least 20% of the consumers had reported an aversion following the use of: heroin (24%), "crystal meth" (34%), solvents (31%), Salvia divinorum (38%), khat (50%), muscarine (35%), Datura stramonium ("jimson apple"; 38%) and NPS (64%). Out of those 46 patients who had reported a single NPS use, 39 (84.8%) reported a proper aversion towards further use of these molecules. By comparison, only 11% out of 191 patients with a lifetime history of cannabis use had developed an aversion towards cannabis use (see figure 3).

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Discussion

To the very best of our understanding, this is the largest survey assessing NPS use in a consecutive cohort of young SUD patients admitted for inpatient detoxification. Overall, patients were most typically dependent on heroin, alcohol and cannabis. Although roughly 1 out of 2 patients had reported a lifetime NPS use, current (e.g. 30-day prior admission) levels were very low (e.g. less than 3%). Among NPS, synthetic cannabinoids were the most represented, probably reflecting previous observations from Germany (Angerer et al., 2017; Scherbaum et al., 2017). **Although 70.6% of patients in this study presented with either an opioid or a polydrug dependence, the use of new synthetic opioids (NSO) was here not reported. This is in sharp contrast to the situation in the USA, where**

NSO use is a widespread phenomenon associated with a high number of drug deaths (Vohra et al., 2020). The low levels of NSO use in Germany was also observed in a recent multi-centre study of patients admitted to detoxification wards (Specka et al., 2020). In addition, according to the last report of the Drug Commissioner of the Federal Government of Germany (2019) NSO had only a minimal relevance in the statistics of drug deaths in Germany (0,5%; 6 out of 1276 drug deaths in 2018). According to current data of the Federal Criminal Police Office, NSO were only rarely (<1%) detected in the chemical analysis of drugs seized by customs authorities or the police in Germany (Dahlenburg, 2020; personal communication to one of the Authors-NS).

In comparison with previous findings from a German addiction survey (Piontek et al., 2016) which included a same-age group sample from the general population, current clinical data showed a much higher lifetime prevalence of NPS use (4.2% in Piontek et al., 2016; vs. 53.9%). Somehow consistent with current results, a US-study investigating patients with various drug-related disorders entering residential treatment found that the lifetime prevalence of synthetic cannabinoids' use was 38% (Bonar et al., 2014). Furthermore, although the prevalence of current NPS use was here much lower, this was still a much higher prevalence than in the German general population of this age range (0.1% in Piontek et al., 2016; vs 2.9%). Hence, one could argue that subjects with a previous experience and/or a regular use of long-term known illegal substances, including cannabis, may be at risk to use NPS as well (Winstock & Barratt, 2013).

In other words, NPS use was reported to be typically either a single or a sporadic intake, with even 'current use' not being here an everyday use and no patients having been diagnosed from an NPS dependence. There

may be a range of reasons for this sporadic pattern of consumption, including intermittent NPS availability levels and negative peer pressure over NPS use. However, current findings may emphasize the occurrence of ill-health related aversion towards NPS intake as a further relevant issue.

There is an overall paucity of data on both the prevalence of NPS use, and overtime occurrence of aversion towards their use, in patients with substance-related disorders (Orsolini et al., 2019). In a sample of psychiatric inpatients with mainly depressive episodes and schizophrenia, the reported use of natural cannabis was much higher than synthetic cannabinoids' use (Welter et al., 2017). Conversely, a recent study investigating patterns of drug use in 877 youngsters from the Berlin party scene (Betzler et al., 2019) a significant difference between lifetime and current prevalence of NPS use was identified; e.g. synthetic cathinones were respectively reported in 15.9% vs 1.3%; and synthetic cannabinoids in 10.3% vs 0.8%. Similarly, Martinotti et al (2015), in surveying 3,011 young (e.g. <24 years) Italian subjects, found that NPS lifetime use was reported by 4.7% of the sample, e.g. mephedrone: 3.3%; synthetic cannabinoids 1.2%; and *Salvia divinorum* 0.3%.

The use of NPS observed here was mainly sporadic and relating to synthetic cannabinoids. Although SUD patients may be attracted to NPS for a range of reasons (Bonar et al., 2014), their sporadic use is possibly being associated with risk taking and novelty seeking personality traits. A well described group of NPS enthusiasts, the so-called e-psychonauts, is reportedly attracted by a range of novel chemicals' intake experiences, with this NPS intake being, per definition both experimental and sporadic (Orsolini et al., 2017). Further sporadic use intake occasions are described in the context of regular drug checks, e.g. during imprisonment, where the user gives preference to NPS because they are not being typically detected in conventional drug screens.

Conversely, NPS use was arguably sporadic, as here suggested, because of the large range of NPS-related ill-health effects, including anxiety,

psychotic experiences, epileptic seizures and cardiovascular system failure (Hermanns-Clausen et al., 2012). These untoward effects were reported by more than 50% of those who reported an NPS use and this may have led to aversion to use the respective drugs again. This is consistent with previous data, which described the occurrence of these effects as more frequently associated with synthetic cannabinoids, as opposed to natural cannabis, in a series of dual diagnosis inpatients (Nia et al., 2016). In contrast with the stereotype of the SUD client ingesting any recreational drug, it is here suggested that there are basic health awareness issues even in those vulnerable subjects who typically and consistently incur in health damaging practices through their dependent use of substances. This 'basic health awareness knowledge' is indeed the precondition for the implementation of advanced harm reduction measures such as syringe exchange programmes or drug consumption facilities (Scherbaum et al., 2010).

Limitations

This study was carried out in a psychiatric clinic located in a rural county, and the clinical sample focussed on young adults (less than 40 years of age) only. Hence, the results might not necessarily be representative of the whole population of NPS-using SUD German patients. Indeed, the lifetime prevalence of NPS use in metropolitan cities characterized by a lively party scene (e.g. Berlin) may presumably be even higher than what here described. **However, in a multicentre study carried out in metropolitan areas of Western Germany (especially Cologne and the Ruhr zone) a comparable current prevalence of NPS use was observed as in the Marsberg study (in both studies between 2-3%) and even a lower lifetime prevalence (32.6% vs. 53.9%; Specka et al., 2020).** Conversely, the main finding of the current study is not relating to the identification of a reliable prevalence level of drug use, including NPS intake, but to the sharp contrast between lifetime and current prevalence of NPS use. This contrast is better interpreted within the context of a high frequency of aversive reactions when taking NPS (Arillotta et al, 2020; Corkery et al, 2020; Orsolini et al, 2019; Schifano et al, 2015; 2019; 2020). **Other possibilities to explain the contrast between lifetime and current prevalence of NPS use might be a lack of subjectively 'attractive' psychotropic effects and the impact of information campaigns on NPS.**

Another limitation is relating to the self-reporting nature of drug use levels here described, levels which were not verified by laboratory tests. Conversely, testing for such a broad range of substances would have been both very problematic and expensive (Schifano et al., 2020). Self-reports may be subject to distortion issues such as both memory falsification and response tendency towards assumed social desirability. However, drug use history was collected at admission, where it may have been in the best interest of patients to provide optimal levels of clinical information for a successful inpatient detoxification treatment to occur. Furthermore, it has been suggested that drug use history data provided by SUD patients is overall considered to be reliable, provided that the fear of any sanctions is eliminated (Darke, 1998; Swiss Federal Office of Public Health/ Schweizer Bundesamt für Gesundheit, 2013).

The examination was here carried out in a clinical sample from a well-structured and specialized centre. Hence, although the results of lifetime NPS prevalence use were here reportedly higher than those identified in the general population, one could argue that the granularity of the information here elicited was more satisfactory than what could be achieved with surveys administered in busy club parties' scenarios. Finally, since those subjects with a continuous and consistent NPS use do not typically see themselves as 'drug addicts' (Schifano et al., 2015), one could argue that they may find it difficult to self-refer to the standard existing addiction assistance system; hence, NPS users could have been here under represented.

Conclusions

Main take home message of the current study relates to the observation that there may have been here a 'trade-off' between NPS desired vs unwanted side effects. If the ratio was identified as being unfavourable, NPS consumption (or at least its consistent intake) was not here reported as attractive for the consumer. In addition, the dissemination of

information about the range of unpleasant NPS side effects within the consumer community, including the website fora, may have led here to a negative image of NPS, and especially of synthetic cannabinoids, and this may have limited the continuous intake of these drugs overtime. More research needs to be carried out in this area, so that clinicians will be properly and consistently updated about changes in drug, including NPS, scenarios.

Declaration of Interest

Norbert Scherbaum received honoraria for the participation in Advisory Boards and for holding lectures by the companies AbbVie, Sanofi-Aventis, Mundipharma, Indivior (formerly Reckitt-Benckiser), Medice and Lundbeck in the past five years. Friedrich Seiffert, Fabrizio Schifano, Michael Specka, Udo Bonnet and Stefan Bender have no known competing interests to declare.

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Figure 1: Lifetime and current prevalence of drug use

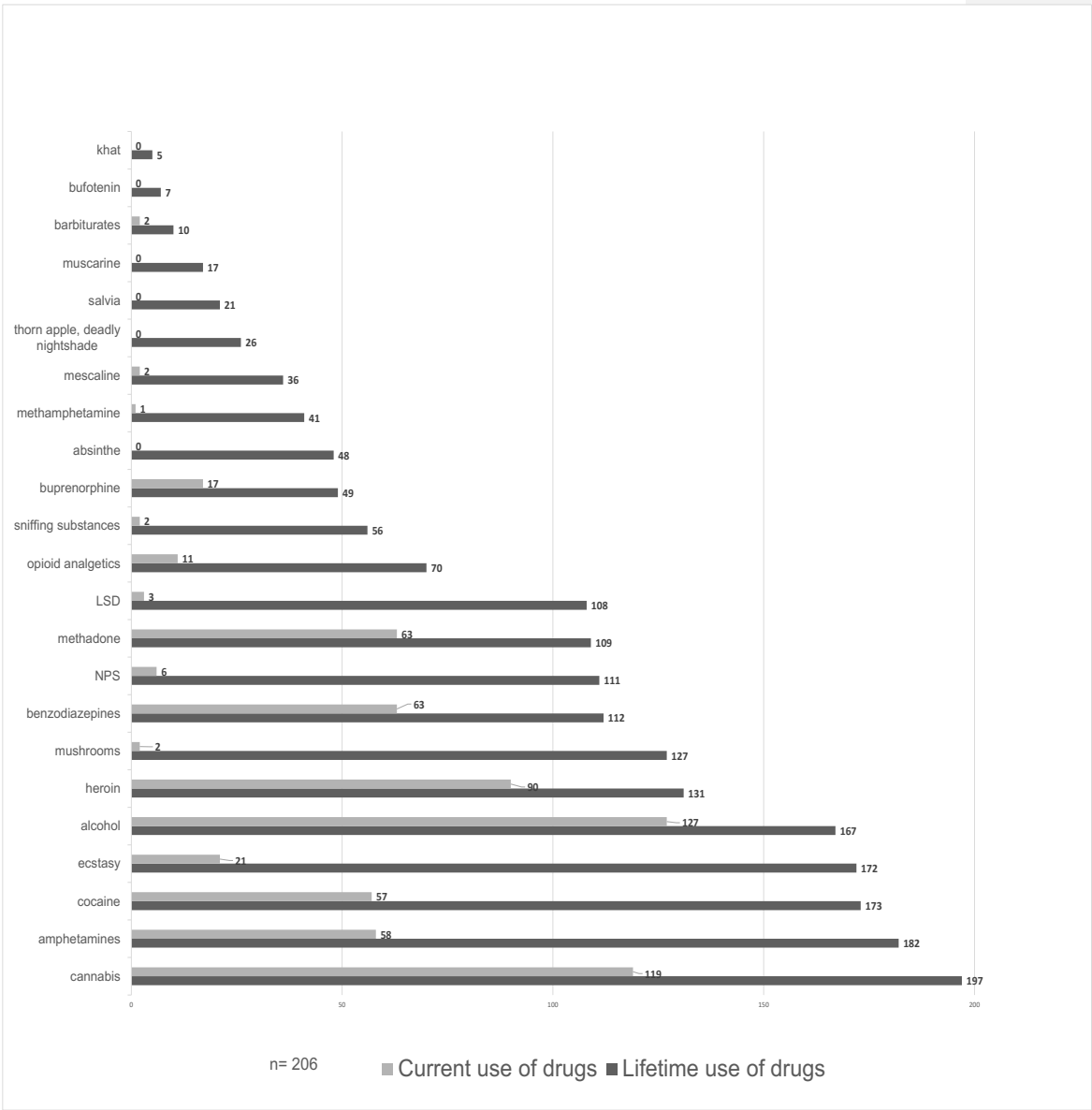


Figure 2: Prevalence of use of different NPS (among a total of 111 patients reporting NPS use)

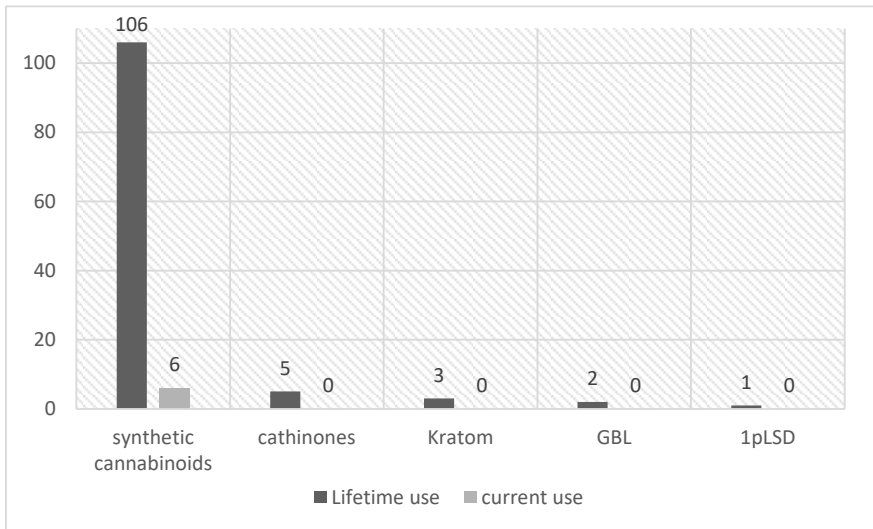


Figure 3: number of patients reporting lifetime and sporadic use of different drugs, and the respective percentage of patients reporting on an aversion to use the drug in the future

