Received: 1 December 2016 | Revised: 7 March 2017 | Accepted: 13 March 2017

DOI: 10.1002/hup.2591

WILEY

SPECIAL ISSUE ON NOVEL PSYCHOACTIVE SUBSTANCES

Novel psychoactive substances (NPS) use in severe mental illness (SMI) patients: Potential changes in the phenomenology of psychiatric diseases

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Abstract

Objective: Literature is quite poor about the clinical effects of novel psychoactive substances (NPS) and the long-term consequences of NPS use in psychiatric patients. Consequently, it is of the greatest interest to examine which effects NPS can exert in patients with previous severe mental illness (SMI), such as psychotic patients. The aim of this work was a comprehensive review about NPS use in patients with SMI.

Methods: We searched Medline or PubMed for relevant English-language citations and reviews describing relationships between NPS use and mental disorders, as well as for the main groups of substances and associated psychiatric manifestations. All studies reporting single case or case series of patients were selected.

Results: The NPS use in patients with SMI is probably underestimated. The one existing systematic review considers only 14 studies, 12 of which are case reports. Most clinical results report acute symptom exacerbation of preexisting psychosis. Paranoid, mood, and aggression symptoms occur more frequently.

Conclusions: NPS use could modify clinical features of SMI, but these conclusions cannot be generalizable. More evidence is needed to establish the causal and effective connection between NPS use and course of illness, type of psychiatric symptoms, and outcome of treatment in terms of adherence or response.

KEYWORDS

limits in research, long-term outcome, novel psychoactive substances, severe mental illness, symptom changes

1 | INTRODUCTION

The European Union defined a "novel psychoactive substance" as a new narcotic or psychotropic drug, either in pure form or in a preparation, that is not scheduled under the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971, but which may pose a public health threat comparable to substances listed in the aforementioned conventions (Martinotti et al., 2014). Novel psychoactive substances (NPS) are a wide and heterogeneous group of substances, often pharmacological analogs of prohibited compounds. They are also known as "legal high," "bath salts," "research chemicals," or, in a broader sense, "designer drugs." Actually, there has been growing clinical, public, and media awareness and concern about their availability and potential harmfulness (Baumeister, Tojo, & Derek, 2015).

The ability of NPS to induce a very wide range of mental state modifications is well known, as well as to cause transitory psychotic states or even long-lasting psychiatric disorders, so to become a factor of growing importance for public health. NPS show variable and specific mechanisms of action, potentially interfering with neurobiology of several psychiatric disorders. According to a recent extensive review by Schifano, Orsolini, Duccio Papanti, and Corkery (2015), mechanism of action and main mental consequences of NPS consumption in healthy subjects are presented in Table 1. Mechanisms of action are very wide and heterogeneous, ranging among different 5-HT

TABLE 1 Novel psychoactive substances classification (modified from Schifano et al., 2015)

Class	Molecules	Action
Novel derivatives of "classical" psychedelic phenethylamines or MDMA-like drugs	"Nexus", 2C-I, 2C-E, 25C-NBOMe, 3C-bromo-dragonfly	Affinity for 5-HT2A receptors, inhibition of the dopamine or noradrenaline or serotonin reuptake
Synthetic cannabimimetics (Sc)	Functionally similar to Δ9-tetrahydrocannabin	CB1 receptor agonism, *N*-methyl-D-aspartate receptor antagonism, monoamine oxidase inhibition, 5-HT2A receptor dysfunction
Synthetic cathinones	Methcathinone, mephedrone, methylone, and so forth	Increase levels on serotonin, dopamine, and noradrenaline pathways, sympathomimetic or amphetamine-like effects
Novel tryptamine derivatives	DALT; AMT; 5-MeO-AMT; 4-HO-DALT; 5-MeO-DIPT; 5-MeO-DMT; DET; 4-OH-DMT	Agonist at 5-HT2A receptors and serotonin transporter inhibition
Piperazines	m-chlorophenyl-piperazine and benzylpiperazine	HT2A receptor agonist
Other categories	Amphetamine: type stimulants DMAR, MPA, "blow"; synthetic cocaine substitutes: RTI-111, RTI121, RTI-126	Dopamine or noradrenaline or serotonin transmission
	Synthetic opioids: AH-7921, nortilidine	Mu or delta or sigma opioid receptor agonist
	GABA-A receptor agonists: GHB, GBL, 1,4-butanediol; GABA-B receptor agonists: baclofen	GABA receptors
	Dissociative drugs: special K, MXE	Hallucinogen

receptors' agonism and antagonism, dopamine or noradrenaline increase, CB1 receptor agonism, and so forth.

The phenomenon may be of great clinical relevance, considering that many psychiatric patients consume psychotropic drugs, both "traditional" like cannabis and of the NPS family. Very poor epidemiological data are available at regard; Martinotti et al. (2014) presented results obtained in Italian healthy and psychiatric populations (Table 2), showing 14.1% of use of NPS in psychiatric patients, compared to 29.3% of cannabis and 4.6% of cocaine consumers. The NPS use is higher in depressed (15.6%) and bipolar (14.8%) patients. Despite this, little is known about the effects of NPS and the long-term consequences of NPS use on the mental state of psychiatric patients. Literature is quite poor on the topic, only limited to single cases or small patients' sample description. In this contest, the purpose of this survey was to conduct a systematic review about the clinical consequences of the use of NPS in patients with severe mental illness (SMI; psychotic disorders and bipolar disorder patients), aiming at obtaining information about the clinical outcome of their interaction with the previous psychopathology state of the patients and at identifying some possible specific clinical features associated with their consumption.

2 | METHODS

We searched Medline or PubMed for relevant English-language citations and reviews describing relationships between NPS use and mental disorders. We used the terms "new psychoactive substances," "novel psychoactive substances," and "new substances in mental illness or psychiatric disorders." A similar search was carried out for the main groups of substances and associated psychiatric manifestations. The search strategies did not provide any limits to the dates of the considered papers. All the papers regarding clinical cases or surveys on the topic of NPS use consequences in severe psychiatric patients were included in the review. Exclusion criteria considered only a qualitative evaluation of the considered articles. The clinical field of interest was defined as that of patients affected by SMI, because the one previous review used this definition to describe the clinical area considered. All the included papers reported cases of patients affected by psychotic disorders and bipolar disorders, so that these are the diagnostic categories for which the term of SMI was used.

3 | RESULTS

The results of this systematic review provided few results about the clinical consequences of NPS use in patients previously affected by severe psychiatric disorders. The one existing survey of the literature is by Gray, Bressington, Hughes, and Ivanecka (2016), who realized a systematic review about the effects of NPS in patients with SMI. This survey considered clinical cases from 12 case reports, one cross-sectional survey, and one qualitative study, with patients aged

TABLE 2 NPS use (%) in Italian healthy subjects and psychiatric patients (Martinotti et al., 2014)

	Healthy subjects
Cannabis	25.6
Cocaine	8.7
NPS	9.8
Synthetic cannabinoids	1.0
Metamphetamine	1.6
GHB	0.3

Note. No differences for mephedrone, phenethylamines, desomorphine, *Salvia divinorum*.

NPS, novel psychoactive substances.

between 20 and 35 years. Interestingly, the survey reported NPS use in psychiatric patients from different countries (Table 3). providing putative information about regional differences in substances' diffusion.

The main clinical consequences in the mental state of the patients are reported in Tables 4–6. They varied from acute psychotic or paranoid symptoms (six cases) to not better defined agitation or aggression behavior (five cases) and to other not specific acute symptoms (mood swings, altered consciousness, etc.). Poor information is provided whether the acute, drug-induced symptoms are a new exacerbation of the previous patients' condition or represent new clinical features of their illness.

Some clinical considerations can be made regarding the cases presented in the Gray's review.

Boucher, Hernu, and Citterio-Quentin (2015) have shown that NBOMe use in a patient with schizophrenia caused abnormalities in the executive functions. This is an interesting report about the cognitive effect of the substance, even if it is not well specified in the paper the preceding degree of cognitive impairment in the patient.

Celofiga, Koprivsek, and Klavz (2014) have shown that synthetic cannabinoids determine elevated affect, severe agitation, anxiety, new paranoid delusions, hypomania, and possible haptic hallucination in patients with paranoid schizophrenia. Obviously, the symptoms belong to the potential clinical manifestations of the illness, so to be more probably seen as a clinical relapse in a previously improved patient. But information is clearly poor with respect to possible new drug-induced clinical aspects.

Every-Palmer (2011) has described synthetic cannabinoids use in a sample of 15 male psychiatric patients on antipsychotic treatment (10 with schizophrenia, four with schizoaffective disorder, and one with bipolar disorder). A total of 69% of them relapsed soon after the substances use, with prevailing psychotic and anxiety symptoms.

TABLE 3 Nations of the reported patients (Gray et al., 2016)

Nation
UK
France
Slovenia
US
Ireland
US
India
US
UK
UK
US
Ireland

TABLE 4 Single case reports on NPS in severe mental illness patients (Gray et al., 2016)

Patient	NPS
Paranoid schizophrenia	"El blanco"
Severe, persistent schizophrenia	NBOMe
Paranoid schizophrenia	Synthetic cannabinoids

NPS, novel psychoactive substances.

TABLE 5 Cohort study on NPS in severe mental illness patients (New Zealand; Every-Palmer, 2011)

Patient	NPS
Bipolar poliabuser	Bath salts
Bipolar	Amphetamine
Bipolar	"Bath salts"
Paranoid schizophrenia	*Datura stramonium*
Bipolar	*Salvia divinorum*
Schizophrenia	"Bath salts"
Paranoid and mood disorder	Synthetic cathinone
Psychotic	"Bath salts"
Schizophrenia	Benzylpiperazine
Schizoaffective, bipolar schizophrenia	Synthetic cannabinoid (JWH-018)

NPS, novel psychoactive substances.

TABLE 6 Qualitative study on NPS in severe mental illness patients (Ireland; Lally, Higaya, Nisar, Bainbridge, & Hallahan, 2013)

Patients	NPS
Psychotic disorders	Any type

NPS, novel psychoactive substances.

Interestingly, Khanra, Khess, and Srivastava (2015) showed that patients with preexistent paranoid schizophrenia and hallucinogens use disorder help themselves by taking *Datura stramonium* to avoid distress and persecution thoughts. This should obviously be confirmed in real clinical situations but refers to the hypothesis of a search of self-medication in the patients' decision to consume substances.

Marques, Reis, Barrocas, and Gois (2013) described auditory hallucinations and persecutory and religious delusions in a female patient with bipolar disorder who had taken *Salvia divinorum*. The observation is in accordance with what is known about the effect of the drug, but it seems to introduce some clinical features of drug-induced psychopathology potentially different than those usually observed in bipolar patients.

Synthetic cathinones and benzylpiperazine are reported to cause agitation (Smith, Williams, & Shaikh, 2013) and repetitive movements, irritation, inability to concentrate, and incoherent thoughts (Tully, Hallahan, & McDonald, 2011) in patients with schizophrenia. Also, in these cases, it is unclear to what extent the reported induced symptoms repeat or not those of the preexistent clinical features of the patients.

"Bath salts" (more often cathinones) are reported to have different effects in patients with SMI. Their intake caused acute psychosis in female patients with bipolar disorder and substances poliabuse (Falgiani, Desai, & Ryan, 2012), agitation, violent behavior, confusion, disorientation in male patients with bipolar disorder (Imam, Patel, Mahmoud, Prakash, King, & Fremont, 2013), psychotic symptoms, tangential thought process, disorganized speech and behavior, auditory hallucinations, and paranoid delusions in patients with schizophrenia (McClean, Anspikian, & Tsuang, 2012). The effects seem in accordance with the preceding type of disease-related clinical symptoms, even if behavioral and psychotic symptoms are prevailing independently from the original disease.

Some information is provided also on NPS effect with respect to resistance to pharmacological treatment, with reported psychotic

symptoms persisting for 4 weeks despite olanzapine treatment in a patient with schizophrenia after "bath salts" consumption (McClean et al., 2012), associated with bizarre behavior, suicidality, visual, tactile, and auditory hallucinations (Thornton, Gerona, & Tomaszewski, 2012). In Gray's review, NPS use is suggested to cause resistance to previously effective treatments, particularly with respect to NPS-induced aggression, in patients with SMI, with negative influence on doses or types of requested medical treatment.

4 | DISCUSSION

Consumption of traditional substances of abuse (alcohol, cannabis, opioids, and cocaine) (Martinotti et al., 2014) is often in comorbidity with other psychiatric disorders (Merikangas, Herrell, Swendsen, Rössler, Ajdacic-Gross, & Angst, 2008; Toftdahl, Nordentoft, & Hjorthøj, 2016). Beyond "classic" substances of abuse, it is recognized for NPS a growing importance for public health. As seen, NPS are a wide and heterogeneous group of new narcotic or psychotropic drugs (Martinotti et al., 2014), classified into at least six main classes (phenethylamines, synthetic cannabinoids, synthetic cathinones, tryptamines, piperazines, and others; Schifano et al., 2015). Potential NPS consumers are found also among psychiatric patients, especially, in Italian population, in depressed (15.6%) and bipolar (14.8%) patients. Although reports on mental effects of NPS in subjects not previously identified as psychiatric patients are very wide, little is known about their effect in psychiatric patients, like those generally defined as SMI patients.

NPS show variable and respectively specific mechanisms of action, potentially interfering with neurobiology of several psychiatric disorders, as extensively reviewed by Gray et al. (2016). This survey aimed to conduct a review about use of NPS, in patients with SMI, to integrate knowledge about NPS neurobiological action with their clinical effects in these patients. The occurrence of psychotic symptoms is in fact usually related to several neurotransmission abnormalities, like increased central dopamine levels, cannabinoid CB1 receptor activation, HT2A receptor activation, *N*-methyl-D-aspartate receptors' decreased activity, k-opioid receptor activation, and so forth. NPS interfere at these neurobiological levels, and this is why NPS use can induce really severe psychiatric symptoms also in subjects not previously affected by a defined mental disorder. The critical question is represented by the NPS effect in SMI. In the papers reviewed by Gray et al. (2016), the reported clinical effects were altered states of consciousness, enhanced mood, confusion, anxiety, agitation, acute psychotic states, hallucinations (multisensory), paranoid delusions, aggression, dissociative states, and severe mood swings.

But information is poor regarding the question whether the observed acute effects in patients were exacerbations of preceding clinical alterations or new psychopathological states with different clinical features.

NPS use in people with SMI could have stronger and more severe effects than in healthy subjects, mostly because of the NPS interaction with dopamine system, involved in controlling behavior and thought processes (Cools, 2008) and with an established role in psychosis (Howes & Kapur, 2009), or with other neurotransmitter systems, like serotonin and glutamate, all of them already altered in psychotic patients. Dopamine function is disturbed by substances like NPS, triggering their psychoactive effects interacting with the basically altered substrate and thus explaining a worse clinical outcome in terms of symptom control, type of clinical manifestation, adherence to treatment, and rates of violence and aggression (Soyka, 2000).

The limit of all the aforementioned observations is that they focused just on reporting the acute effects of NPS and that they have analyzed just small patients' sample, often single cases (Boucher et al., 2015; Falgiani et al., 2012; Fröhlich, Lambe, & O'Dea, 2011; Khanra et al., 2015; McClean et al., 2012; Thornton et al., 2012), four cases (Celofiga et al., 2014), or five cases (Imam et al., 2013). In addition, the small samples were not sex homogeneous, formed either by males (for example, Fröhlich et al., 2011; Imam et al., 2013) or females (Falgiani et al., 2012).

As a general remark according to the poor and really scarce existing literature, NPS may exert some relatively severe effects on people with SMI. Their use appears in fact related to severe dissociative states and confusion in psychotics, behavior changes (acute anxiety with agitation and aggressive or extremely aggressive behavior), cognitive decline, frequent need of restraint, relapse or worsening of a preexistent psychosis or preexistent bipolar disorder (Schifano et al., 2015), persistent worsening of psychotic or manic-like symptoms course, or onset of new severe symptom (65%; Celofiga et al., 2014; Every-Palmer, 2011; Lally et al., 2013).

What is still unclear and must be better addressed in future studies is whether in SMI, they simply worsen preexistent psychotic states in schizophrenic or bipolar patients or they are able to induce new clinical features, with type of manifestations different than those previously showed by each patient. In this view, consciousness alterations, severe mood swings, aggression behavior, and paranoid-hallucination symptoms seem more likely to play a role of specifically NPS-induced symptoms within the previous clinical conditions.

However, it must be considered that the full extent of NPS use by people with SMI is still widely underrecognized and most of SMI patients who use NPS do not come for this reason to the attention of health professionals. Indeed, the cooccurrence between severe mental disorders and NPS use often leads to more important implications for clinical treatments and course of illness, considering a possible earlier age of onset, the increase of frequency, and length of episodes and diminished treatment compliance. NPS use in patients with SMI is very likely to have long-term consequences of increased sensitization to psychotic episodes, with a number of potential clinical complications certainly still unclear.

5 | LIMITS

The results of the survey have several limits. First, NPS group includes an increasing number of both known and newly emerging substances, with several and multiple mechanisms of action, whose pharmacodynamic properties are not fully well known. These aspects play a crucial role because they make difficult to identify neurobiological effects in long-term users, often consuming different substances associated or over time. This is certainly even more relevant in subjects affected by SMI.

A second limit is linked to the absolute lack of control of NPS consumption. NPS use is illegal, and these kind of substances are occupying an increasingly predominant position on the illicit market of drugs. There are not therefore sufficient methods or specific test to identify all NPS in users. They more frequently access to emergency

departments because of symptoms that are not specific, often similar to those due to different substances intoxication.

Objective data to determine the effective consumption are completely not sufficient, and any retrospective study is impossible to be usefully carried out.

As a third limit, there are few studies about NPS use in patients with SMI and, as seen, limited to case studies. Large samples are very difficult to be collected, due to the number and extreme heterogeneity of the substances potentially implicated, as well as to the fact that they are mostly illicit and information on consumption is just very seldom and incompletely given by consumers. Moreover, the consumers are themselves often unaware about the really taken substances, and their preexistent mental disorder may further reduce their ability of comprehension and of awareness of their own behavior.

Otherwise, ethical reasons make obviously quite impossible any type of regular controlled study. The available information is so limited to single cases or small groups of patients, and no clinical conclusions can be generalizable with the wider populations of people affected by different forms of SMI and using different and mostly unknown types of NPS.

6 | CONCLUSIONS

The NPS use in patients with SMI is a frequent phenomenon, probably still underestimated. NPS potentially have serious effects on people with SMI. The most commonly reported effects of NPS were psychotic symptoms and significant changes in behavior. Otherwise, the scarce observations determine that more evidences are needed to establish the causal and effective connection between NPS use and course of illness, type of psychiatric symptoms, and treatment outcome in terms of adherence or response. Therefore, careful and constant monitoring and accurate clinical evaluation will be necessary to search a real connection between NPS use and course and clinical phenomenology of an SMI.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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How to cite this article: Bersani G, Prevete E. Novel psychoactive substances (NPS) use in severe mental illness (SMI) patients: Potential changes in the phenomenology of psychiatric diseases. *Hum Psychopharmacol Clin Exp*. 2017;32:e2591. https://doi.org/10.1002/hup.2591