NOVEL PSYCHOACTIVE SUBSTANCES CONSUMPTION IS MORE REPRESENTED IN BIPOLAR DISORDER THAN IN PSYCHOTIC DISORDERS: A MULTICENTER - OBSERVATIONAL STUDY

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Abstract

Objective

Comorbidities between psychiatric diseases and use of traditional substances of abuse are common. Nevertheless, there is few data regarding the use of novel psychoactive substances (NPS) among psychiatric patients. Aim of this multicentre survey is to investigate the consumption of a number of psychoactive substances in a young psychiatric sample.

Methods

Between December 2013 and September 2015, a questionnaire has been administered in ten Italian psychiatric care facilities to a sample of 671 patients, aged 18-26 (mean age 22.24; SD 2.87).

Results

8.2% of the sample declared to have used NPS at least once, and 2.2% has consumed NPS in the previous three months. The three psychiatric diagnoses most frequently associated with NPS use were bipolar disorder (23.1%), personality disorders (11.8%), and schizophrenia and related disorders (11.6%). In univariate regression analysis, bipolar disorder was positively associated with NPS consumption.

Conclusions

The use of NPS in a young psychiatric population appears to be frequent, and probably still underestimated. Bipolar disorder shows an association with NPS use. Therefore, careful and constant monitoring and an accurate evaluation of possible clinical effects related to NPS use are necessary.

Introduction

Comorbidities between psychiatric diseases and use of traditional substances of abuse (alcohol, cannabis, opioids, and cocaine) are common. Nevertheless, there are few data regarding the use of novel psychoactive substances (NPS) among psychiatric patients (Martinotti et al., 2014). NPS use in young people is an emerging issue, especially in relation to the dynamic and potentially unlimited nature of their market (Schifano et al., 2005); over the past 5 years, there has been an unprecedented increase in the number, type and availability of these substances (EMCDDA, 2015). The term "Novel Psychoactive Substances" have been legally defined by the European Union as new narcotic or psychotropic drugs, in pure form or in a preparation, not scheduled under the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971, but which may pose a comparable public health threat (Council of the European Union decision 2005/387/JHA) (UNODC, 2014a).

The European Commission (2011), in response to recent developments in the European drug market, has investigated the experiences and attitudes of adolescents and young adults towards NPS. The sample included over 12,000 young people (aged 15–24 years), randomly selected across the 27 EU Member States. Overall, 5% of the participants reported having used NPS: Ireland (16%), Poland (9%), Latvia (8.8%) and United Kingdom (8%) were at the top of the ranking list, while Italy (0.8%), Finland (1%) and Greece (1.6%) were at the bottom (Eurobarometer, 2011). A recent study on a population of 3011 subjects aged 16-24 highlighted a quick increase in NPS use figures in Italy, as in 2015 the rate stands at 4.7% (Martinotti et al., 2015a).

These substances are often synthesized in underground laboratories, simply modifying the molecular structure of controlled drugs, hence raising further concerns in terms of the presence of contaminating agents (UNODC, 2014a). NPS are raising a growing number of sanitary concerns, but so far their clinical effects are still poorly known, and may vary considerably between substances (Anderson et al., 2015). A consistent body of clinical evidence currently demonstrates the potential acute and chronic health harms associated with the use of NPS (Schifano et al., 2015); however, these substances are still often unknown to health professionals, mainly because of the lack of evidence-based sources of information (Simonato et al., 2013).

With regards to the most frequently observed clinical features related to NPS consumption, anxiety, dysphoria, increased aggression, mood fluctuations and perceptual/thought disturbances are to be mentioned (Anderson et al., 2015). Moreover, Papanti et al. (2013) coined the term "Spiceophrenia," to define some peculiar psychopathological characteristics of spice-induced psychosis (e.g. paranoid thoughts/combativeness/irritability); according to their assumptions, it is possible to hypothesize that the use of synthetic cannabinoids may "trigger" the occurrence or the relapse of psychosis in

psychosis vulnerable individuals or in patients with a prodromal psychotic syndrome (Papanti et al., 2013). Other studies showed that synthetic cathinones appear to be peculiarly involved in the development of both self- and other-oriented aggression; users of cathinones tend in fact to manifest violent behaviours, including suicide (Marinetti and Antonides, 2013).

In light of all this, the purpose of this multicentre survey was to investigate the diffusion of NPS consumption in a young Italian psychiatric sample, and to correlate it with the psychiatric diagnoses. Secondary aims were represented by the assessment of different associated behaviours, such as the use of caffeine, tobacco and drinking habits.

Methods

Sample

A questionnaire was administered to a sample of 671 psychiatric patients (48.5% men; 51.5% women), aged 18-26 (mean age 22.24, S.D. 2.87). The sample was composed of patients consecutively admitted in ten recruiting psychiatric inpatient units, located in the north, centre and south of Italy, from December 2013 to September 2015. The centres involved in the study were: the G d'Annunzio University of Chieti, the University of Turin, the University of Bologna, the "Fatebenefratelli" General Hospital of Milan, the University of Perugia, "Tor Vergata" University of Rome, the University of Catanzaro, the University of Messina, the University of Catania and the University of Cagliari. Aim of this wide selection was to obtain a sample which could be representative of the whole Italian scenery, involving some of the most populated areas of the country. The study received the approval of the local ethics committee and of the Institutional Review Board. All subjects with a DSM-5 clinical diagnosis were invited to participate. Exclusion criteria were failure to obtain informed written consent and a diagnosis of substance use disorder.

Data collection was carried out in an anonymous way; all participants received a detailed explanation of the design of the study and a written informed consent was obtained from all respondents, according to the Declaration of Helsinki.

Measure

A questionnaire investigating NPS use and binge drinking, already used for previous studies, was adopted (Martinotti et al., 2014). The test was self-administered and consisted of 31 items, which investigated socio-economic characteristics (age, gender, residence, job status and living status), alcohol use, legal stimulants use (tobacco, caffeine), 'classic' substances use (e.g., cannabis, cocaine, opiates), and use of NPS. The NPS included in the questionnaire were synthetic cannabinoids ("spices", "spice drugs"), synthetic cathinones (e.g., mephedrone), piperazines, tryptamines,

phenethylamines (Nbome–fly–solaris), ayahuasca, salvia divinorum, kratom, γ-hydroxybutyric acid (GHB), methoxetamine (Special M) and desomorphine (krokodil). Popular street names were used along with chemical ones.

Statistical analysis

The SPSS version 22 was used for the analyses. In all statistical analyses, a two-sided significance level of 5% was used. To identify predictors correlated with NPS use and binge drinking, univariate logistic regression analyses were performed for the demographic and clinical features of the sample. For the features with a p value of less than 0.05 in the univariate logistic regression analyses, a multivariate logistic regression analysis was performed. The predictors with a p value of 0.05 or less in the multivariate analysis were identified to be significantly correlated with NPS and bing drinking.

Results

The psychiatric diagnoses were distributed as follows: 21% (N=141) schizophrenia and other psychotic disorders; 16.1% (N=108) depressive disorders; 11.3% (N=76) bipolar disorders; 20.4% (N=137) anxiety disorders; 19.7% (N=132) personality disorders; 4.3% (N=29) obsessive-compulsive disorder (OCD); 5.8% (N=39) eating disorders; 1.3% (N=9) other disorders (*see table 1 for details regarding socio-demographic characteristics of the sample*).

-Insert Table 1. about here-

With regards to alcohol consumption, 70.6% (N=474) of the sample declared alcohol use, and 47.7% (N=320) reported to have drunk alcoholic beverages until losing control at least once (binge drinking: this term defines the consumption of five or more drinks in a row for men and four or more drinks for women) (Wechsler and Nelson, 2001). Among the "classic" illicit drugs, the most used were cannabis, with a prevalence of 31.4% (N=211), and cocaine, with a prevalence of 10.7% (N=72). 8.2% (N=55) of the sample reported to have used NPS at least once, while 2.2% (N=15) has assumed NPS in the last three months. The most commonly consumed novel psychoactive substances were synthetic cannabinoids ("spices") (4.5%, N=30). The three psychiatric diagnoses most frequently associated with NPS consumption were bipolar disorder (23.1% N=15), personality disorders (11.8% N=13), and schizophrenia and related disorders (11.6% N=13) (*see figure 1 for details*).

-Insert Figure 1. about here-

In univariate regression analysis, bipolar disorder emerged as significantly associated with NPS consumption ($p < .001$). However, in the multivariate model, no psychiatric diagnosis was directly associated to NPS consumption, while predictors were: use of other illicit substances (cannabis, cocaine), binge drinking behaviours, coffee consumption, and living status (living with a partner) (*see table 2 for details*).

-Insert Table 2. about here-

In the univariate analysis, bipolar disorder was positively associated with binge drinking, while obsessive-compulsive disorder showed an inverse association. In the multivariate analysis, factors associated with binge drinking were male gender, being unemployed, smoking habit, coffee consumption, use of cocaine and cannabis, and bipolar disorder diagnosis (*see table 3 for details*).

-Insert Table 3. about here-

Discussion

To the best of our knowledge, this study investigates the use of NPS in psychiatric patients within the largest sample ever collected. Our results suggest a prevalence of NPS use among psychiatric patients that appears to be higher than in general population (UNODC, 2014b). This could represent an important finding, because a deleterious effect of NPS on psychopathological domains is often advocated. Several NPS have been associated, based on their mechanism of action, to an increased risk of psychosis: mephedrone and phenethylamines through an increase of dopamine levels (Brisch et al., 2014), synthetic cannabinoids via the activation of CB1 receptor (Hajos et al., 2008), methoxetamine through agonism on 5-HT2A receptors and antagonism on NMDA receptor (Morris and Wallach, 2014), Salvia divinorum via k-opioid receptor activation (Ranganathan et al., 2012). In subjects with psychiatric disturbances, the intake of NPS could have detrimental effects in terms of worsening of the symptomatology and chronicity of the disorder, with comparable, and in some cases even worse outcomes, than traditional drugs of abuse. Moreover, the medical consequences associated with NPS use and their potential interactions with psychotropic medications need to be mentioned (Corkery et al., 2014; Dines et al., 2015).

On the other hand, the use of NPS may be considered as an attempt to relieve the distressful emotional and cognitive experiences due to the psychiatric disorder. Indeed, the self-medication with drugs of abuse among psychiatric patients, as postulated for the first time by Khantzian, had a wide resonance in the last decades (Khantzian, 1997). This hypothesis states that individuals with psychiatric disorders may use substances for relieving their symptoms, thanks to the unique pharmacological properties of the substance, whereby the presence of specific symptoms would lead to the search of a specific substance. Although theorized for the traditional drugs, this hypothesis seems particularly attractive for NPS as well, given the frequent search and the easy supply of these substances on the Internet market (Orsolini et al., 2015) and the presence of online communities of recreational drug users that report detailed experiences with groups of substances (e-psychonauts) (Deluca et al., 2012). Moreover, attempts towards potential therapeutic applications of NPS, moving from their pharmacological properties, have been recently made (Davidson and Schifano, 2016). However, at present these hypotheses are merely speculative and they are not specifically addressed in this paper. In our study, a generic proneness toward the use of recreational substances was the best predictor of use of NPS. Therefore, especially in this subpopulation of patients, questions specifically addressed to NPS consumption may represent a good screening strategy in clinical practice. Interestingly, coffee consumption resulted as an independent risk factor for NPS use, an association never described so far in both clinical and non-clinical settings. Moreover, a more independent living status, without a direct parental control, has been found to be another risk factor for NPS use.

On the contrary, specific psychiatric diagnoses were not directly associated with an increased risk of NPS consumption. This finding could be due to an insufficient sample size or to the heterogeneity of NPS, so an analysis based on single NPS classes (e.g. synthetic cannabinoids or synthetic cathinones) may highlight relationships with specific diagnoses. However, bipolar disorder patients showed a proneness towards both traditional and novel substances of abuse in comparison with other psychiatric disorders. The reason of this higher prevalence of NPS use among bipolar patients is somehow puzzling. It is well known that NPS use can induce transitory psychotic experiences, in both new users and psychiatric patients (Caton et al., 2005). These experiences, described in the past by Bonhoeffer as exogenous psychotic experiences and by Morselli as Lysergic Psychoma, may closely resemble psychotic experiences (Martinotti et al., 2015b). However, our data do not confirm this hypothesis. In our sample, the use of NPS resulted to be uncommon among patients affected by schizophrenia and other psychosis. A possible hypothesis is that NPS may induce transient episodes, but not usually a full-blown psychosis. Differently, a casual relation between bipolar disorder and NPS may be hypothesized. NPS use is probably able to worsen a pre-existing scenery or a sub-

threshold disorder, determining a higher severity of symptoms and a higher frequency of episode relapsing.

The positive association between bipolar disorder and binge drinking confirms the literature data on the association of bipolar disorder with alcohol use and misuse (Balanzá-Martinez et al., 2015; Martinotti et al., 2009).

Among the main limitations of this study it must be underlined the use of self reported data, without the support of laboratory analysis to rule out false negatives and false positives. Another main limitation is the lack of data regarding the temporal relationships between the emerging of psychiatric symptomatology and the use of recreational drugs, as well as regarding the reasons that had lead to substance use. Moreover we considered only the main psychiatric diagnosis, without investigate potential comorbidities. Finally, we studied the group of NPS as a whole, despite the heterogeneity among the single substances. However, given the wide diffusion of polyabuse behaviours, we decided not to differentiate the sample by use of different NPS. Despite these limitations, this study provides significant findings in a field still under-investigated and of great relevance for 21st-century psychiatry.

Conclusion

In conclusion, our research highlighted that the use of NPS in a sample of psychiatric patients is highly represented and needs to be regularly investigated, demonstrating that a deep knowledge of these substances is now compulsory for psychiatrists. Moreover, we demonstrated that bipolar disorder, more than schizophrenia and other psychosis, is the main psychiatric diagnostic framework within which the use of NPS is reported. Further studies and preventive strategies developments are therefore needed to better address this issue.

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Table 1: Sociodemographic characteristics.

VARIABLE	PERCENTAGE (%)
Age	22.24 (S.D. 2.87)
Gender	Male 48,4%

	Female 51,6%
Level of education	Primary degree: 1,2% Middle school: 25,4% High school: 62,4% University: 10,9%
Job status	Student: 34,7% Student/Worker: 8,3% Worker: 24,7% Unemployed: 32,2%
Living status	Parents: 76% Friends: 7,3% Alone: 9,3% Partner: 7,3%
Psychiatric diagnosis (DSM-5)	Psychotic Disorders: 21% Depressive disorders: 16,1% Bipolar disorder: 11,3% Anxiety disorders: 20,4% Personality disorders: 19,7% OCD: 4,3% Eating disorders: 5,8% Other disorders: 1,3%

Table 2: Risk factors for NPS consumption

	Univariate analysis	Regression Logistic analysis

	p value	*p* value < .05	O. R.	C.I. (95%)
Age	.241			
Gender	.549			
Level of education				
Primary degree	.669			
Middle school	.613			
High school	.687			
University	.924			
Job status				
Student	.077	.		
Student/Worker	.511			
Worker	.742			
Unemployed	.215			
Living status				
Parents	.124			
Friends	.491			
Alone	.399			
Partner	.081	.038	4.8	1.1-21.0
Psychiatric diagnosis				
Psychotic Disorders	.777			
Depressive disorders	.733			
Bipolar disorder	<.001			
Anxiety disorders	.086			
Personality disorders	.274			
OCD	.072			
Eating disorders	.142			
Smoking status	<.001			
Coffee consumption	.001	.038	5.9	1.1-31.4
Alcohol Use	<.001			
Binge drinking	<.001	.013	3.7	1.2-11.7
Cannabis Use	<.001	.003	4.0	1.6-10.2
Cocaine Use	<.001	<.001	13.3	5.8-30.5

Table 3: Risk factors for Binge Drinking

	Univariate analysis	Regression Logistic analysis		
	p value	*p* value < .05	O. R.	C.I. (95%)

Age	.291			
Gender (male)	.003	.011	1.7	1.1-2.5
Level of education				
Primary degree	.185			
Middle school	.267			
High school	.651			
University	.074			
Job status				
Student	.119	.		
Student/Worker	.755			
Worker	.746			
Unemployed	.033	.007	1.9	1.2-2.9
Living status				
Parents	.114			
Friends	.037			
Alone	.063			
Partner	.852			
Psychiatric diagnosis				
Psychotic Disorders	.388			
Depressive disorders	.054			
Bipolar disorder	<.001	.025	2.2	1.1-4.2
Anxiety disorders	.165			
Personality disorders	.190			
OCD	.012			
Eating disorders	.140			
Smoking status	<.001	.003	1.8	1.2-2.7
Coffee consumption	<.001	.007	1.9	1.2-3.1
Cannabis Use	<.001	<.001	3.0	1.9-4.8
Cocaine Use	<.001	<.001	8.0	2.7-23.6

Figure 1: Psychoactive substances use in the sample