Substance use and psychiatric consequences: a case series

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Abstract

Illicit substance use is well known as an important contributor to the global burden of diseases. Physical and psychopathological risks and fatalities associated with substance consumption are frequently underestimated. Nevertheless, health issues related with substances often involve first-time or sporadic clients and could not limited to subjects with substance use disorders (SUD). We reported 5 cases of acute psychiatric presentations related to recreational drug use. In contrast with previous study about SUDs, we observed high education levels and good employment rates among patients. Polysubstance abuse appeared to be the norm: cannabis, cocaine and alcohol were the most commonly referred substances. Unknown substances use was often reported. Symptoms presentation at the admission usually involved aggressiveness, hallucinations and other perception disorders, mood lability and spatial and temporal disorientation. This data shows that the psychopathological potential of illicit substance is considerable, even in subjects without previous psychiatric symptoms. We hypothesized that some substance features and subjects' characteristic may be involved in symptoms onset: substances potency, amounts and frequency of use, previous psychiatric history, personality features and traumatic experiences.

KEY WORDS: addiction, substance misuse, psychosis.

Introduction

Illicit substance use is well known as an important contributor to the global burden of diseases; indeed, the extent of drug use problem in specific clinical settings such as psychiatric or emergency units is not limited to subjects with substance use disorders (SUD) or dependence, but it also includes occasional recreational drug users (1). The physical and psychopathological risks of non-habitual substance consumption are frequently underestimated, and substance-related fatalities often involve first-time or sporadic clients. Furthermore, it is known that dual diagnosis, in which co-occurring disorders affect each other and interact, is particularly common; however, among several proposed hypotheses, such as common factor models, secondary substance use disorder models, secondary psychiatric disorder models and bidirectional models, in most cases of dual diagnosis the aetiology remains unclear (2). Recreational drug use is defined as any substance (legal, controlled, or illegal) with pharmacologic effects that is taken voluntarily for personal pleasure or satisfaction rather than for medicinal purposes (3). Moreover, in recent times, in addition to "classic" substances of abuse, Novel Psychoactive Substances (NPS) have emerged, determining a further health issue of grow-

ing importance (4-8). The term NPS has been legally defined by the European Union as a new narcotic or psychotropic drug, 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 that posed by substances listed in those conventions (9). In this context, the term "new" does not necessarily refer to substances recently synthesised, since often NPS are the result of the "recycling" of molecules studied in the past by official pharmacology, but it rather refers to substances that have recently become available in a specific market. There is currently an increasing body of clinical evidence to demonstrate the potential acute and chronic health harms associated with the use of NPS, but often very little is known by both consumers and health care professionals (9-11). Unfortunately, to date, few surveys about the current diffusion of NPS have been conducted. Furthermore, there is the increasing evidence that a large NPS use is unintentional (12). Some clinical evidence showed the potential serious psychiatric and physical related consequences due to NPS consumption (9,12). Originally, the most common NPS belonged to the families of phenethylamines and tryptamines; however, the past few years have witnessed the appearance on the market of substances belonging to a wider range of "chemical families", such as cathinones, synthetic cannabinoids (Spice), phencyclidine, benzofurans (13). NPS-related deaths have been investigated mainly in the UK (14-16), but in this context, polysubstance use and behavioural risk taking seem to be particularly widespread in some peculiar European locations, such as the Balearic Islands nightlife scene. Access to emergency department or psychiatric units is commonly not limited to patients with substance use disorder (SUD) or dependence, but it also includes subjects with patterns of non-habitual recreational drug consumption (17). Risks of occasional substance use are frequently underestimated and often involve first time or sporadic clients. In particular, holiday periods seem to represent a risky time of excess and experimentation, especially for young people (18). Visiting a nightlife-focused holiday resort can submerge individuals in environments where hedonistic partying is the norm, drugs are typically heavily promoted and widely available, thus globally increasing revellers engagement in health-endangering behaviours during their stay (19). Indeed, Majorca, Menorca, Ibiza and Formentera are among the most popular tourist destinations in the whole of Europe: such an international and representative nightlife resort appears as a crucial key setting to address substance-related health problems and fatalities. Preliminary studies conducted in Ibiza highlight that, in both young tourists and foreign casual workers, risky behaviours appear considerably exacerbated, including problematic alcohol use, drug use, complex polydrug abuse, and sexual risk taking (20-22). A survey conducted by Bellis et al. (19) shows that people on holiday in Ibiza present higher rates of drug, polydrug, alcohol and tobacco use than in the UK. Overall, 7.3% of individuals of the sample analysed went to hospital or to see a doctor while in Ibiza (23). Anecdotal reports also warn that traffickers are playing with the lives of holidaymakers, which are being used as "guinea pigs" in the trialling of dangerous NPS. Furthermore, according to literature (24), levels of drug and polydrug use are higher among young people who visit nightclubs, raves and dance parties than among young people in the general population (25). The growth in international travel associated with nightlife, the additional risks posed by clubbing in an unfamiliar country, the threats of new and often unknown psychoactive substances and the changes in substance use and risk-taking amongst people visiting an international resort mean that both interventions, and basic health and safety measures are now required to be planned on an international basis (23, 26).

In this context, we will present the data of a series of cases followed up in Ibiza during the summer, when disco-club season is at its peak. These subjects were recruited and evaluated at the Can Misses Hospital, Psychiatric Ward in 2015 and 2016. Data collection was carried out in an anonymous and confidential way; all participants received a detailed explanation of the design of the study and a written informed consent was systematically obtained from every subject, according to the Declaration of Helsinki. Data regarding the wider sample are reported elsewhere (27-29).

Representative cases of psychoactive substances intoxication

Case 1

This case refers to a 27-year-old woman from Norway, who spent summer holidays in Ibiza with some friends. She claimed to be a student, occasionally hired for temporary jobs.

She was admitted to the psychiatric service of Can Misses Hospital, accompanied by her friends, after a psychotic episode with paranoid characteristics. At admission, she presented psychomotor agitation, verbal and externally directed aggression, and affect lability. Nevertheless, physical restraint was not necessary. She denied previous access to mental service before. The medical history was negative for Psychiatric diagnosis. Olanzapine, Haloperidol and Lorazepam were administered.

She felt threatened, believing she had been the victim of a theft, in which someone stole her documents and identity card to prevent her from going back home to Norway.

A figure of the past seemed to be involved in her delusional ideation, probably an ex boyfriend, but we could not investigate further, due to her evident conceptual disorganization.

Hostility and paranoia characterized the first three days after admission, to the point that we could not conduct the clinical interview anytime sooner.

At the first contact, she refused to answer to any questions, she felt uncomfortable with medical staff, worried about being used as a guinea pig for our experiments. She showed distress and feelings of hopelessness, altering her prosody in speech and the tone of voice. Conceptual disorganization, delusional ideation and affect lability were evident; the facial expression did not correspond to the content of speech, moving from laughter to tears without a meaningful connection, staring at the window and asking the interviewer to give her documents back. She denied any substance consumption.

The day after, lowered mood and effects of delayed insomnia, lack of energy and space-time disorientation, confusion and mannerisms were observed. She talked about a boyfriend, who was in jail at the moment, who frightened her and beat her habitually. Her mood often changed, showing anger and aggression, bursting into tears all of a sudden. A frequent switch between different languages was the main aspect of the clinical interview: she spoke English when she felt comfortable and her native language to discuss emotionally distressful contents.

At the third day of hospitalization, she appeared more focused and less tired. Mannerisms were reduced. She was reading a book written by a famous actor and she commented on this appropriately. She was also more organized in the content of her speech, and she tried to describe the events that led to her hospitalisation: she had taken part in a rave party with her friends. She admitted she consumed lots of drugs simultaneously (cocaine, ecstasy and alcohol) in that occasion, but also in the previous days of her holiday.

She also reported a previous tendency of getting in trouble or risky situations, underlying it with an ironic attitude. This interview was brief, like the previous ones, because of the change of her mood and state of mind. She suddenly became aggressive, refusing to answer any further question, and staying still on the bed with closed eyes.

At the end of the last control a prosecution of hospitalisation was recommended, due to her unstable conditions.

Psychic examination at admission: psychomotor excitement, irritability, verbal aggression, conceptual disorganization. Form and content of thoughts were altered. Delusional symptomatology with paranoid characteristics was observed. Hostility, affect lability and space-time disorientation were highlighted. No insight of illness.

Diagnosis: Substance Induced Psychotic Episode in Borderline Personality Disorder.

Toxicology report: positive for cocaine and amphetamine.

Case 2

Around 5 am, a young Arabic woman was accompanied by the police to the Emergency Department of the Can Missess Hospital, because of her aggressive behaviour against people in the street, in the centre of Eivissa city. At the moment of admission to the service, the woman showed irregular breath, rapid pulse (125 bpm), dilated pupils and high body temperature (38.5°C). No identity document was retrieved. The woman was extremely agitated and screamed words difficult to understand in both Arabic and English. An intravenous dose of Diazepam was administered without evident clinical benefits. Intravenous administrations of Midazolam were repeated for a total of 24 mg, without any apparent benefit: agitation and aggressive behaviours continued to persist.

Poor hygienic conditions were also highlighted: she was dirty and smelling, her feet were covered in dirt and excoriated. She appeared to have no wounds, but the medical examination was really difficult: the patient screamed every time that either the doctor or the nurse tried to get closer to her. She seemed to be very scared, and she tried to escape several times. Psychiatric conditions required restraining and, in order to improve communication, an Arabic interpreter was called. In the presence of the interpreter, the only woman in the ER other than the patient, the woman seems more prone to dialogue. She said her name was Aydan and she then asked in perfect English that all men in the room got out. She was reluctant to answer to any question about the night before. She was poorly oriented in space and time: she knew she was in Europe but she did not recognize the “white bedroom” and she did not remember when she arrived in Ibiza and who travelled with her. During the interview, and despite she was still retrained, she often sat down on the bed and swayed her head screaming the name of God: “I am the daughter of God…He threw me down… I did a mistake… He does not want me anymore”. She confessed that she needed to urinate but that she could not, because it was an unholy act.

Then, she was moved to the Psychiatric Department. She spits on the nurses who try to wash her and change her clothes. Intramuscular haloperidol 2 mg/ml was administered and the patient finally rested.

A few hours later, a man who declared to be her husband showed up to the ward. He insisted he had to take Aydan with him in order to get a plane to Paris. He then came back with an interpreter who explained Aydan’s situation. Aydan and her husband came from Azerbaijan and they were in Ibiza for their honeymoon. They married two weeks before and they decided to travel across Europe. They had already visited Prague, and they wanted to go to Paris before coming back to Azerbaijan.

With the assistance of the interpreter, the husband was convinced to delay the flight, but he refused to give further explanation about the night before the admission of his wife, and why she was found alone wandering in the city.

Aydan did not meet her husband. When she woke up, she was more oriented in both time and space, but she was still easily distracting, she refused to drink and eat. She was verbose and echolalic. Perseveration and formal thought disorders could be highlight-

ed. Mystic delusion and excessive thoughts of guilt and shame were still present. She did not remember she was married. She refused any physical contact with nurses and doctors.
In the afternoon, 12 hours after the admission, her husband came back to visit her. After a few moments, Aydan threw herself in his arms. The woman, calm and quiet, explained in perfect English who he was, and why they were in Ibiza. During the rest of the hospitalization, she became more compliant and she accepted several interviews with psychiatrists and psychologists. Anyway, no memories of the night before admission were recollected.
The patient denied any use of psychoactive substances.
Diagnosis: Substance Induced Manic episode, with mixed and psychotic features
Toxicological Urine Examination: no common substances were highlighted (cocaine, opiates, THC, MDM, BDZ) apart from the presence of barbiturates (metaqualone).

Case 3
In this case is involved a 20-year-old boy. He already knew the island, spending different summer working as a waiter in clubs. During the season he spent most of his time going to discos and parties with friends rather than dedicating to work activities. During the last week-end, he took part to a rave party in Ibiza, taking many drugs simultaneously. A few days later, he was admitted to the emergency room of Can Misses Hospital accompanied by his parents, warning by his friends about his aggressiveness and unusual behaviours.
During the first interview, at the emergency room, he was conscious, oriented and collaborative, but with some elements of suspiciousness. He showed an articulate talking, with a disorganization in the content of thoughts: he did not remember anything about the previous days, trying to give explanations with confuse hypothesis. He recognized alcohol binging, use of cannabis and crystal-meth besides other unknown substances. Perceptive alterations, visual hallucinations and pseudoallucinations (over the last few days he had been hearing a song in his brain) were observed.
Paranoia characterized the first three days after the admission so that it was impossible to run a clinical interview. During the second interview, he started to talk about his life and family: he had adoptive parents, an adoptive sister, and three brothers. He reported previous psychological contacts during primary school, because of some problems with other children at school and because teachers complained with his parents about his restlessness and lack of attention. The medical history seems to be negative for previous psychiatric diagnosis. He reported daily use of cannabis with and without alcohol in the last two weeks, and crystal-meth, LSD and ketamine occasional consumption. He reported a recent use of an unknown liquid psychoactive substance.
He perfectly described allucinatory symptoms and persecution feelings occurred after this liquid substance intake: these feelings and thoughts resulted in an unjustified aggressive behaviour. He reported that the hallucinatory symptoms disappeared after few days, whereas the music in his brain, paranoid symptoms and aggressiveness persisted and were still present during the admission. The hospitalization lasted five days. At the discharge, a complete remission of the symptoms was observed.
Diagnosis: Substance Induced Psychotic Episode.
Toxicology report: positivity for cocaine and amphetamine.

Case 4
The case refers to a 43-year-old woman. Originally from Slovakia, she had been regularly employed as realtor in Ibiza, since 2012. She was accompanied to the psychiatric service of Can Misses Hospital by her boy-friend because of a manic episode, characterized by externally directed aggressiveness and psychomotor excitement. Nevertheless, she did not require physical contention. She denied any previous access to mental service and also denied any drug use before.
The first interview was conducted two days after the admission, due to psychomotor excitement. During the psychological assessment, she asked to do it in a comfort room, where privacy and isolation could lead to a better understanding of her situation.
She seemed less nervous and upset with a moderate somatic anxiety, so that she said that was waiting for some clinical lab results. At the beginning, she claimed to be a translator, able to speak different languages so that she used Italian, English and Spanish simultaneously.
The speech was pressing and unstoppable with the tendency to derailment. Disorganization and unusual content of though were highlighted during the session. She passed from clinical subjects to personal experiences related to her journeys abroad: she started appreciating the Italian culture and continued describing intense emotionally contents without a meaningful connection among these themes. Nevertheless, delusional symptoms and hallucinations were not observed. Over the manic excitement, she says she was able to carry out many tasks without feeling tiredness, although she usually slept only 3/4 hours a night.
Furthermore, she showed poor insight about the reason that led her to admission. At this point, she described a previous discussion with her boss, accusing him to be despotic, taking this event as a potential reason of distress and, ultimately, of her hospital admission. One week before, he humiliated her in front of some customers, complaining her incapacity to managing specific duties. Suddenly, over an emotional activation, she burnt into tears and talked about the relationship with her mother, apparently without a clear link, but probably related to the question of her value, recently frustrated by her boss and by her

mother in the past, as well. She referred to feel a sense of responsibility, in terms of demonstrating her moral integrity and capacity to carry out her projects, specifically after her father's death. At the same time, she desired to have a child, expressing an exasperated sensitivity about this theme and admitting to perceive more interest in sexual activities, over the last weeks. Furthermore, she appeared hostile and suspicious about the clinical scales administered.

The day after, during the second session, she showed more cooperativeness and she was well-groomed. Nevertheless, excitement and grandiosity were emphasized: she continued to speak three languages simultaneously, like the day before, showing euphoria and mannerisms.

She walked around, presenting difficulties in keeping attention, quickly passing from a topic to another one, without a clear linking. Disorganization in the shape of thoughts was observed. In the middle of this assessment, she admitted to have participated to a rave party the day before the admission, assuming cocaine, amphetamines, alcohol and a probably unknown substance that someone else would have put in her drink. Moreover, she highlighted that in the last fifteen days she took more alcohol than usual (1 bottle of wine/a day- 5 drinks per night per day), although she denied previous consumption of drugs. She also mentioned she started a draft of a book, written with the aim of talking about herself and the most important experiences that built her personality. She described herself as determined and headstrong, declaring to hide a man inside her body, so that she could not tolerate abuse and inequity anymore, as happened some days before at work. She flipped through the pages while admitting that, also promising to send me a copy of her book, as soon as possible. Mannerisms and hyper-expression were clear. Before the conclusion of the session, she asked to keep in touch with us.

Psychological assessment at admission: externally directed and verbal aggressiveness along with euphoria and carelessness in the appearance. Shape and contents of thought alterations, with conceptual disorganization but without delusional symptoms. Hostility and suspiciousness were marked along with the prosody of speech with a tendency to derailment. Mannerisms and disorientation were observed. Amnesia and difficulties in keeping attention on the task characterized the cognitive aspect. The intake of any substance was denied.

Toxicology report: positivity for cocaine and amphetamine.

Diagnosis: manic episode induced by substances.

Case 5

The case concerns a 27-years-old male who was brought to the psychiatric unit by the police, after his own report to the police of a supposed theft of identity. His ID document was probably lost and this event represented for the patient the first prove of a clearly and organized project made by an undefined group of persecutors. He had been working as a DJ since the beginning of May, with good performances and success, gaining a discrete level of popularity in the island. His delusional suspects began a week before the admission at the hospital, during a night in the disco where he was used to play his music. He started to have bizarre feelings to be observed by all the organizing components on the stage, perceiving a sense of menace and threaten. Then, he suddenly noticed one of his colleagues going up to the backstage. Here he felt the clear sensation, in the form of certainty, that he was there to kill him. So he interrupted his performance and fled away to his house. Here, he also had the same sensation of being persecuted by the other subjects sharing his apartment. The next morning he woke up with a girl in his bed, hypothesizing that she had been placed there in order to cause a breakdown with his own wife. At this point he decided to escape from his house, hiding inside a cabin around a bus stop. During the following ours he remained hidden in different hotels of the island, until his referral to the police, with his firm idea of a specific plan made up by a group of persecutors to steal his identity.

In the psychiatric unit he was admitted in a forced regimen for the first days, showing high level of aggressiveness and suspiciousness, manic symptoms, with paranoid ideation and delusional about poisoning. At the beginning, he was isolated and reluctant to any contacts. He also refused food, medications and other supplies. After the first two days of treatment, he gradually improved, giving the possibility to build a therapeutic relation. He admitted a previous use of cocaine, also in large quantities, and probably other stimulants. The night of his first psychotic breakdown, he also reported a relevant use of a substance that he supposed to be cocaine, but that he did not recognize in its effects. He also reported to be in treatment for alcohol and cocaine use disorders, with a regular intake of topiramate and disulfiram. During the reconstruction of his story, he showed a transient level of insight, criticizing some events, sensation, and thoughts that he admitted as difficult to be believed, and probably impossible in their nature or at least in some of their elements. He also hypothesized a specific role of the substance he took the night of the psychotic onset, as one of the cause of his breakdown. However, his suspiciousness still continued to emerge, tapering the possibility of a clear critique of his believes. After 72 hours of a symptomatic treatment with haloperidol and loxapine, his symptoms rapidly improved. At discharge the patient was almost not symptomatic in terms of manic and psychotic symptoms. However, for long time, the night of the psychotic onset remained an area of high discomfort for Francis, who was still full of doubts and psychotic certainties.

Toxicology report: positivity for cocaine.

Diagnosis: Substance Induced Psychotic episode.

Discussion

In this case series we describe the acute psychiatric presentations related to recreational drug use in an adult population of subjects on holiday in Ibiza. To the best of our knowledge, this is the first description of clinical cases exploring psychopathological issues related to both "classical" and Novel Psychoactive Substances in a psychiatric inpatient unit located in one of the most popular nightlife resort, as Ibiza is known during summer.

These cases are representative of a wider sample reported in our previous studies (27-29). We observed high education levels and good employment rates among patients, and this seems to be in contrast with previous studies, describing low levels of education and employment as a trait feature of patients with SUD (23). A possible explanation of this phenomenon might be that the characteristics of substance-using clients definitely changed in recent years. In particular, recreational drug users greatly differ from "drug addicts" of the past (9, 22, 30). Moreover, Ibiza is a peculiar scenario, where subjects from low-income classes may not be able to find affordable of facilities, while on the opposite, young tourists choose to spend most of the money earned during the winter period.

Although in every evaluated case a main "preferred" substance could be frequently identified, the presence of polysubstance abuse appeared to be the norm. Cannabis and cocaine (or crack) were the most commonly referred substances, for both past and recent use. These findings are 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 (31). Moreover, in our sample the majority referred polydrug abuse, with alcohol as the most involved substance, followed by cocaine. The combination of psychoactive drugs may have numerous health implications (31). Polydrug use has been linked to increased levels of intoxication. Furthermore, other studies identified negative psychological effects from polydrug use, including drug dependence and psychiatric comorbidity (31).

Some patients also reported the use of unknown substances. This confirms the theory that drug users are often unaware of the purity or even the actual composition of the drugs they are consuming. Palamar et al. found that subjects who report no lifetime use of Novel Psychoactive Substances or unknown pills often test positive for new drugs (32). Adulteration or replacement with other substances to increase economic gain is common in the illegal drug market, with growing health-related risks due to the low safety margins of adulterants (32). In fact, these substances are associated with acute toxicity, neurotoxic harm and deaths in several European countries (33). In this case series, as well as in the general sample, mean scores of psychometric scales showed that psychiatric manifestations linked to psychoactive substances are characterised by a significant 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 (34, 35).

Hallucinations (mainly visual ones) and other perception disorders were frequently reported at the moment of hospital admission, confirming the hypothesis that drug-induced psychotic disorders are frequently associated with visual symptoms (36). This could be probably explained by the powerful interaction exerted on the 5HT receptors by modern hallucinogens, like MDMA and other similar compounds. These data are consistent with other studies about NPS and hallucinogens. NPS markedly compromise human sensory. As a consequence, drastic changes of the perception-movement cycle (37), caused by NPS, may influence both criticism and judgment. Therefore, chemical deliriums are not primary, but secondary to intense changes in the relationship with reality, on the basis of a distortion of the perception. The chemical delirium is characterised by confirmation and interpretation, not by revelation and fantastic contents (38). The delusions shown by NPS patients are similar to paraphrenic delusions, with a feeling of unreality, while the ability to analyse the feeling is preserved. In this regard, the model of the Lysergic Psychoma could be an interesting proposal (39).

Among the psychiatric manifestations observed in our sample, psychotic and mood symptoms predominated. Our findings are 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 (40).

It should be noticed that some patients reported spatial and temporal disorientation. These transient cognitive disorders are quite unusual in psychiatric illnesses, with the exception of dissociative disorders, frequently described in literature as substance-induced symptoms (41). Both quantitative and qualitative conscience alterations should be taken into account when assessing a patient with a probable alcohol/drug use. The presence of these alterations could drive the differential diagnosis between a psychotic state induced by substances and a classical psychotic onset without the involvement of a specific substance use. Moreover, a qualitative conscience disorder, the twilight state, may represent a transitory state between the induced psychotic experience and a full-blown psychosis (38). The twilight or auroral state was intended by crepuscular consciousness (Daemmerzustand-Daemmerung-zustand), a classical condition in which the field of consciousness is restricted, and it is limited around a few, or even a single content (38). In the twilight state, an actual decrease in vigilance is not observed and the subject is able to perform oriented and finalized movements in space. Moreover, the field of crepuscular conscious-

ness can also stretch or widen concomitantly or suddenly. The auroral state is therefore in itself favourable to a visionary nature, made up of illusions and hallucinosis. Fading, the object escapes the fixation, leaving a free background that is populated by another figure: the real hallucination. The experiences of depersonalization, allopsychic or autopsychic, or derealisation, are typical and reversible possibilities of the auroral condition (36, 38). The psychotic form that develops on the crepuscolarity of the toxic drug experience is not connoted and declined into schizophrenic and melancholic or maniac form: it can be defined only as psychosis, with alterations both of the ideational and cognitive aspect, both of the timico-umoral and perceptive aspect, which tends to remain in this undifferentiated condition, without crystallizing into a determinate form, where the affective spectrum crosses the schizophrenic spectrum (38). After this state of conscience, it is possible to enlarge again the frame of experience, coming back to the experience before the intake of substances. However, in some cases, this conscience enlargement can be realised in the direction of a new meaning and interpretation of the experience, in a delusional atmosphere not connected with the previous reality.

Most of our subjects had been psychiatric inpatients or outpatients during their lifetime and referred illicit drug use in the past. These data are consistent with the study of Bellis et al., reporting that most subjects visiting Ibiza were already illicit drugs users in their home country, with nearly the totality of the subjects continuing to consume psychoactive substances in Ibiza. The "holiday" use of most drugs in the island appears to differ from the "home" pattern of consumption due to the binge behaviour, with many individuals using drugs 5 or more nights per week (26). This also suggests that the possibility to develop psychiatric symptoms after a recent drug use is more common in patients with a positive history of psychiatric and substance use disorders. However, it should also be emphasized that in a relevant fraction of the sample no psychiatric antecedent was reported. According with another study by Bellis et al., 7.2% of British tourists tried MDMA for the first time, with similar percentages amongst Spanish (8.6%) but not Germans (1.8%) or those visiting Majorca (0.8, 1.5 and 1.2%, respectively) (25).

This data shows that the psychopathological potential of illicit substance is considerable, even in subjects without previous psychiatric symptoms. We hypothesized some triggers factors, such as high potency substances, amount of consumption, frequency of use.

Therefore, we postulated two possible ways by which substances may induce clinical relevant psychiatric symptoms:

1. previous psychiatric history, personality features and traumatic load may represent a vulnerability point that interacting with substances may lead to a major problem, in both the area of mood and thought
2. short time-frame consumption of large quantities/high potency substances may be able to generate independent psychotic or mood consequences.

The possibility to uncover or develop a major, long lasting psychiatric disorder, such as schizophrenic disorder, mood disorders or other axis I diagnosis is still matter of debate. However, a recent large-sample prospective study showed that almost one out of three subjects with an acute psychotic reaction induced by substances is developing schizophrenia or bipolar disorder within a 5-time period after the episode (42).

Another relevant characteristic that emerged from this case series is the presence of high level of aggressiveness at hospital admission: it needs to be taken into account by clinicians as another peculiar characteristic of patients with substance-induced psychopathology. Regardless the presence of a mood or psychotic episode, the presence of aggressiveness appears to be transnosographic, probably representing an intrinsic element correlated with substance use (43). Consequently, it increases the risks of workplace violence for psychiatry staff, mainly nurses and nursing assistants, as reported by a recent Italian study (44).

Binge drinking and sleep deprivation are issues that also need to be considered: they represented indeed a relevant component in almost all the evaluated subjects. The data on binge drinking are consistent with the current findings of scientific literature, according to which binge drinking has showed to be a very common way of alcohol consumption, specifically among adolescents and young adults (45).

Although the use of NPS is rapidly increasing in Europe (7,46), with report of relevant psychopathological consequences and fatalities (27,28), the use of alcohol, cocaine and "first generation" psychedelics still represent the main substances involved in both direct and indirect deaths (although better methods of their analysis in post-mortem samples should be designed) (28). Indeed, if this trend is not determined by the direct use of the novel and highly toxic drugs, other theories should be proposed:

1. Is there a wider "base" of substance misusers, with the subsequent exposition of more subjects which may be at higher risk for predisposing factors? (2)
2. May the combination of different lifestyles and behaviours, such as polyabuse patterns, binge drinking, drunkorexia, intense physical activities during rave parties, be implicated? (3, 35)
3. Are there chances that the research and exploration of the limits proposed online by psychonauts may be becoming a trend in real life as well?

In conclusions, in this case series of subjects admitted to a psychiatric ward in a night-life resort, the use of psychoactive substances resulted to be notable and characterised by poly-use of both traditional and novel substances, with a relevant number of complex

psychopathological consequences, not always transient in their nature. Positive and manic symptoms were highly represented, as well as state of conscience alterations. Aggressiveness was also significantly high, specifically among those reporting a recent use of cannabinoids as the main substance.
All the above-mentioned considerations should be investigated in further studies, in association with a careful monitoring of critic "hotspots" of substance misuse, in order to design better and targeted prevention strategies.

Acknowledgements

This paper was supported in part by grants of the European Commission (Drug Prevention and Information Programme 2014-16, contract no. JUST/2013/DPIP/AG/4823, EU-MADNESS project).

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