New psychoactive substances (NPS), psychedelic experiences, and dissociation: clinical and clinical pharmacological issues

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Abstract:

Purpose of the review: A significant increase in the number, type, and availability of new psychoactive substances (NPS) with dissociative and psychedelic potential has occurred worldwide over the last few decades. Psychedelic substances have historically been used in order to achieve altered states of consciousness such as dissociative states.

We aimed here at describing both the large number of novel ketamine-like dissociatives and tryptamine/lysergamide/phenethylamine psychedelics available, whilst describing the acute/long term clinical scenarios most commonly associated with their intake.

Recent findings: An updated overview of the clinical and clinical pharmacological issues related to some of the most popular NPS categories has been provided, describing both psychosis and remaining psychopathological issues related to them.

Conclusions: Although the complex link between NPS and psychiatric illnesses is yet to be fully understood, NPS misuse is now a significant clinical issue and an increasing challenge for clinicians working in both mental health and emergency departments.

Introduction

The growing epidemic of addiction to both classic and new psychoactive substances (NPS) has become a reason of significant concern [1]. The latest published statistics from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) show that the number of NPS notified to the agency was over 670 by the end of 2017; 632 of these substances were notified after 2004 [1]. Of this latter total, 179 were synthetic cannabinoids, 127 synthetic cathinones; 77 phenethylamines; 38 synthetic opioids; 35 arylalkylamines; 27 tryptamines; and 23 benzodiazepines. Given the globalised nature of the market, NPS can pose serious cross-border threats to public health as well as an increasing challenge for mental health practitioners [1]. In fact, large levels of availability of NPS with dissociative and psychedelic potential have been identified worldwide [2].

In this context, one might wonder which are the issues explaining attraction towards both psychedelics and dissociatives. According to Jaffe [3], those who self-administer with these molecules try to experiment with: '*...states of altered perception, thought, and feeling that are not experienced otherwise, except in dreams or at times of religious exaltation…'.* Hence, one could argue that for dissociatives and psychedelics enthusiasts the positive reinforcement can revolve around escape from the ego and/or a frustrating environment. Moreover, in this self-medication perspective, the chemical experience may be seen by the users as helpful to overcome depressive or pre-psychotic states of mind [4•]. At times, this drug intake may help the subject to identify new meanings (e.g. relating to the creation of the universe; the mathematical order of the systems of nature; the meaning of life; etc.) of currently perceived bizarre/pathological experiences, however creating more psychological imbalance [5]. This understanding of 'novel meanings' may, in turn, reinforce the mood and the creative dimension of the user [6-7]. According to some Authors, these positive effects of psychedelics have opened up the possibility of the use of some selected substances for therapeutic purposes [8].

Dissociation and the psychedelic/hallucinogenic experience

The contemporary definition of 'dissociation' bears similarities with the concept of 'Splitting' or 'Spaltung', e.g. the lack of associations between thoughts, emotions, attitudes and acting [9-11]. Over the last century or so, the term dissociation has been associated with a range of different meanings, including [12]: a) a peculiar and complex personality organization; b) a defense mechanism, from the psychoanalytical perspective; c) a process which characterizes the initial splitting/division of the personality following a traumatic event; d) a broad set of experiences and symptoms that are characterized by the breakdown of integrated psychological functioning. More

recently, with the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [13], 'dissociation' has been related to the *disruption of and/or discontinuity in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behaviour....',* and includes clinical elements such as amnesia, depersonalisation, derealisation, identity confusion, and identity alteration. DSM-5 dissociative disorders include: the dissociative identity disorder; the dissociative amnesia; and the depersonalization/derealization disorders.

At a Trans-diagnostic level, the experience of dissociative symptoms has been linked to the occurrence of acute stress and/or traumatic events [14••]. On a cognitive/emotional level, dissociation may be a learned automatic response to reduce or avoid aversive emotional states [14••].

Per se, dissociation can be either a pleasant or an unpleasant experience. Historically, human beings have researched a range of methods to reach, typically with plants or herbs, pleasant states of dissociation from reality [15-16]. More recently, with the identification of the semi-synthetic, strongly psychedelic, LSD molecule, the modern era of the psychedelic culture has started [17-18].

The label 'dissociative' was initially related to the peculiar state of consciousness generated by the uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine [19]. Typically, dissociative molecules are those altering perceptions of sound and sight, and also generating feelings of detachment from reality, with these mind-altering effects which not generally being conceived as proper hallucinations [20]. Dissociatives include phencyclidine (PCP), ketamine, and a range of derivatives [21-24•].

Conversely, psychedelic/hallucinogen experiences typically include thought and visual/auditory changes, or altered states of consciousness. Most hallucinogens can be roughly divided into tryptamines, lysergamides and phenethylamines [20; 25-26•].

Aims

In this study, we aimed at: (a) identifying and describing the large number of psychedelic and dissociative NPS available; and (b) describing the acute/long term clinical scenarios most commonly associated with the intake of a range of NPS, including: new/novel psychedelics and ketamine-like dissociatives.

Methods

We searched Medline/PubMed to identify studies using the terms 'new psychoactive substances,' 'NPS,' 'legal highs,' 'designer drugs,' 'research chemicals,' 'emerging drugs of abuse,' 'emerging drugs of misuse,' 'dissociatives,' 'ketamine-like drugs,' 'hallucinogenic drugs,' 'psychedelics', and 'psychopathological consequences'. The search was filtered by 'English and human'. Further references were retrieved from national/international agencies' reports.

The tryptamine and lysergamide psychedelic/hallucinogenic NPS

New/novel psychedelics include a vast range of molecules associated with hallucinogenic effects, but at times also possessing stimulant and/or entactogenic properties. The common issue in the pharmacology of hallucinogenic drugs is agonism or partial agonism of 5-HT2 serotonin receptors, particularly 5-HT2A and/or other 5-HT2 receptors [20; 27], although further neurotransmitters' pathways may be involved as well. For example, the naturally occurring tryptamine ibogaine interacts strongly with the NMDA receptor, σ–receptors, µ-opioid receptors, and muscarinic receptors, apart from causing serotonin and dopamine reuptake inhibition at their transporters

[20]. Hence, the different hallucinogenic drugs may have different levels of potency, effects, duration, and risks.

The tryptamine psychedelics

Tryptamines are a group of monoamine alkaloids, very similar to the endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). Apart from their agonism at 5-HT1A, 5-HT2A and 5-HT2C, the vesicular monoamine transporter 2 (VMAT2), σ-1, serotonin transporter (SERT) and traceamine-associated (TAR) receptors are also involved [28••]. Novel tryptamines, available as capsules, tablets, powder, or liquid formulations, include: 5-MeO-AMT (5-methoxy-α-methyltryptamine), made available as an LSD alternative and presenting with a range of sympathomimetic effects; 5-MeO-DALT (N-diallyl-5-methoxy-tryptamine); 4-HO-DALT (N,N-diallyl-4-hydroxytryptamine); 5-MeO-DIPT (5-methoxy-diisopropyltryptamine-aka 'foxy' or 'foxy methoxy'), which is structurally related to dimethyltryptamine/DMT and bufotenin; DET (N,N-diethyltryptamine), significantly inhibiting monoamine oxidase and producing hallucinogenic effects similar to DMT or mescaline; 5-IT (5-(2-aminopropyl)indole); and 5-MeO-DMT (5-methoxy- N, N-dimethyltryptamine) [28••-29].

The predominant clinical effects of tryptamines consist in visual hallucinations, alterations in sensory perception, distortion of body image, depersonalization, marked mood lability and anxiety/panic. Untoward effects include agitation, tachyarrhythmia and hyperpyrexia. DMT, in particular, produces strong hallucinogenic LSD-like effects, powerful entheogenic experiences/intense visual hallucinations, and euphoria. Since DMT is inactive after oral administration, unless combined with Monoamine Oxidase Inhibitors (MAOis, e.g. like in Ayahuasca), it is usually injected, snorted, or smoked. There are small numbers of confirmed post-mortem toxicology reports on tryptamines. Some hallucinogens like αMT (α-methyltryptamine) and AET (α-ethyltryptamine) have strong stimulant effects.

Tryptamines in nature: Some tryptamines are naturally found, i.e. in Delosperma species plants (dimethyltryptamine, DMT; 5-MeO-DMT/5-methoxy-n,ndimethyltryptamine); and in amphibians (bufotenin), whilst 5-hydroxy-indolethylamines are common constituents of venoms of the genre Hyla, Leptodactylus, Rana, and Bufo alvarius [5; 25]. DMT has also been found in other plant sources, e.g. Phalaris arundinacea and Mimosa hostilis [28••].

Most popular psychedelic fungi include psilocybin mushrooms, which contain psilocybin and psilocin; their hallucinogenic effects occur within the first 2 h after oral intake and last up to 4–8 h. Psilocin is a partial 5-HT2A agonist, with little dopaminergic or noradrenergic activity [28••]. These mushrooms, known as 'teonanacatl', meaning 'God's flesh' [30-31] were used by the Aztec shamans, but also in Australia and in Eastern Tanzania [32], in healing ceremonies and in a variety of religious and divinatory rituals. Turton et al. [33] described the subjective experience of intravenous psilocybin, which included altered somatosensory, visual, auditory, and proprioceptive sensations, perceptual changes, and a variety of effects on cognition, mood, memory, and spiritual or mystical experiences. Psilocybin-induced visual perceptual alterations may include complex visual hallucinations of scenes and pictures, visual elementary hallucinations of regular patterns, colours, light, and light flashes [34]. In another study [35], psilocybin induced profound changes in mood, perception, and thought, with most subjects having described the experience as

pleasurable, enriching, and non-threatening. However, at the highest dosages administered, strong dysphoria and/or anxiety/panic were reported. Psilocybin has frequently been reported to cause transient headache [36]. A case of a severe rhabdomyolysis and acute renal failure after Psilocybe mushroom ingestion has been reported as well, followed by encephalopathy with cortical blindness and eventual recovery over several months [37].

Peyote (Lophophora williamsii) is a small cactus native to the American Southwest and Northern Mexico that has been used for millennia and is consumed as a sacrament during services of the Native American Church [38-39]. It contains the psychedelic compound mescaline, which is also found in the San Pedro and Peruvian Torch cacti. Halpern and colleagues [40] compared 61 Navajo Native American Church members who regularly ingested peyote with 79 individuals reporting minimal use of peyote, alcohol, or other substances. For the peyote-using group, total lifetime peyote exposure was not associated with neuropsychological performance. By contrast, recreational use of peyote has led to adverse events, including one case of a prolonged (2 weeks) peyote-induced psychosis [41].

Ayahuasca, also known as yagé or hoasca, is a decoction prepared from a mixture of two plants: the pounded bark from Banisteriopsis caapi vines and leaves from Psychotria viridis. The latter contains the hallucinogen DMT. Its use has been incorporated as a sacrament into the religious practices of two syncretic Brazilian churches; União do Vegetal (UDV) and the Santo Daime. Ayahuasca has a long history of use by natives in the Amazon valley of South America [31; 42]. Bouso and colleagues [43•] found that ayahuasca users who were members of the UDV Brazilian did not show psychopathology or worse neuropsychological performance in comparison with non-users, and this was consistent with findings reported earlier by Grob and colleagues [44]. De Araujo and colleagues [45] speculated that the robust visions induced by ayahuasca may be initiated in the primary visual cortex.

The lysergamide/LSD-like psychedelics
LSD and other lysergamides share a complex molecular structure with both tryptamine and phenethylamine backbones. However, lysergamide structures are sufficiently elaborated from these skeletons for them to be more usefully considered a distinct class of hallucinogenics [20].

In the recreational drug scenario, LSD appears as a crystalline powder soluble in water which is made available as sugar cubes or small squares of papers/stamps meant to be typically ingested. Its effects are rapid and include headache, raised pulse rate, dilated pupils, nausea, blood pressure alterations, and sometimes increase in body temperature. Its effects may vary according to both the subject expectation/mood and the setting, and typically include: idiosyncratic perceptual disturbances such as stationary objects appearing to move and changing shape, synesthesia, distortions of body image, and perception of time [28••]. Tolerance, dependence, and withdrawal experiences have been described by users. Adverse effects may include 'bad trips,' that is an unpleasant, often terrifying, post-intake drug experience. Spontaneous recurrence of the drug-induced experience (i.e. flashbacks) is fairly common after LSD use [28••].

In a recent study by Schmid et al. [46], 200 micrograms of LSD produced a pronounced alteration in waking consciousness that lasted for 12 hours and included visual hallucinations, audio-visual synesthesia, and derealization/depersonalization experiences. Compared with placebo, LSD increased closeness to others, openness, and trust; all effects subsided completely within 72 hours. In other studies, LSD was found to increase suggestibility [47-50] and enhance music-evoked emotion [51]. Although

the association between lifetime use of psychedelics and mental health is a reason of current debate [52], LSD use has been associated to potentially life-threatening consequences, including rhabdomyolysis [53]; vascular ischaemia related to a single ingestion [54]; and cortical blindness [55].

Some novel LSD derivatives have recently reached the market, such as LSZ (lysergic acid 2,4-dimethylazetidide), 1-P-LSD (1-propionyl-D-lysergic acid diethylamide hemitartrate), ETH-LAD (6-ethyl-6-nor-lysergic acid diethylamide), PRO-LAD (6-propyl-6-nor-lysergic acid diethylamide), and AL-LAD (6-allyl-6-nor-lysergic acid diethylamide). They produce effects resembling those of LSD, having similar pharmacological action at 5-HT2A receptors, but possessing different potencies, kick-off effects and duration [28••].

Lysergamides may be found in nature: e.g. LSA naturally occurs in the seeds of both Argyreia nervosa and Ipomoea violacea (for a thorough review, see [56•].

The phenethylamine psychedelics

Phenethylamines are synthetic compounds available in tablets, capsules, powder/crystal. They act on serotoninergic receptors, leading to psychedelic effects, and some of them inhibiting the monoamine reuptake as well. Because of its stimulant effects, 3,4-methylenedioxy-methamphetamine (MDMA, 'ecstasy') is one of the most popular drugs among young and party people. Recently, a growing use of new powerful molecules, such as the '2C' and 'D' series; the benzodifurans; and others (e.g., 4-methylthioamphetamine/4-MTA; and 6-(2-aminopropyl)benzofuran/6-APB) has been reported [29].

Overall, these new psychedelic phenethylamine derivatives' psychoactive effects have been suggested to be dose-dependent, ranging from mere stimulant effect at lower doses to hallucinogenic and entactogenic effects at higher doses. Being selective noradrenaline/dopamine reuptake inhibitors as well, these stimulants produce euphoria, talkativeness, disinhibition, increased locomotor activity, alertness and sexual arousal. Their intake may be associated with loss of appetite, tachycardia, anxiety, nausea, headache, dizziness, skin irritation, and hangover effects. Intoxications symptoms include: hypertension, vomiting, hyperthermia, convulsions, respiratory deficits, liver, and kidney failure and death in case of overdose [5; 27; 29]. Psychotic symptoms, accompanied by dissociation and hallucinations, and intense psychedelic experiences are associated with high dosages [27].

The 2C family is a synthetic psychedelic group of drugs. 2C-I is possibly the most popular member of the 2C family, created in the 70s from mescaline. Because of its MDMA-like effects, it is commonly used at parties where is known as 'smiles' [28••], 2014). In the USA, 2C-I is currently a Schedule 1 controlled substance [57]. 2C-I's common effects include: muscle spasm, euphoria and raised energy levels, associated with paresthesia, and intensification of the sense of touch and skin sensitivity, especially at high doses. Moreover, it can cause tachycardia, dehydration, polyuria, nausea, and midriasis [28••].

Recently, several highly active derivatives, the so called 'NBOMes', have entered the NPS market; they include: 25B-NBOMe (2-(4-bromo-1,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine); 25C-NBOMe ((2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-ethoxyphenyl)methyl]ethanamine) aka 'N-Bomb'/'Pandora'); and 25I-NBOMe ((4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine) aka 'N-bomb'). NBOMe compounds act as potent full agonists at the 5-HT2A and 5-HT2C receptors (for a comprehensive review, see [28••]). In addition, 25I-NBOMe and 25C-NBOMe are pharmacologically active at very low, submilligram doses. Their higher 5-HT2A

receptor affinity, compared to the 2C-derivatives, explain the frequent associated reports of hallucinations and delusions. NBOMe-containing products are usually available as tablets, capsules, powder, liquid, spray, and blotters. They are usually taken sublingually/orally or via nasal insufflation, with some of them are sold as lysergic acid diethylamide (LSD) replacement [28••]. Suzuki and colleagues [58] provided a comprehensive literature review of toxicities associated with N-(2-methoxybenzyl)-2,5-dimethoxy-4-substituted phenethylamines (NBOMe) ingestion. The most common adverse reactions may be agitation and aggressiveness, tachycardia, hypertension, and seizures.

Bromo-dragonfly (1-(8-bromobenzo[1,2-b; 4,5-b9]difuran-4-yl)- 2-aminopropane; 'B-fly') is a distant derivative from the core phenethylamine structure, with a potency similar to that of LSD but with a far longer duration of effect (1–3 days) and greater toxicity [20]. Andreasen and colleagues [59] reported a fatality involving 'B-fly'.

Regarding the 'D family', Balíková [60] reported both fatalities and near misses after ingestion of the psychedelic phenethylamine 2,5-dimethoxy-4-bromoamphetamine (DOB).

PCP, ketamine and remaining dissociatives

Phencyclidine (PCP) and ketamine ('K') were developed initially as general anaesthetics for human and animal use, but before long they emerged as 'street' drugs. Other related dissociative analogues entered the recreational drug market relatively recently [61], including: the β-keto-arylcyclohexylamines (e.g. methoxetamine, deschloroketamine, and 2-fluoro-2-deschloroketamine) molecules [1; 62•]; 4-MeO-PCP [63]; and the 1,2-diarylethylamines (e.g. diphenidine, ephenidine, methoxydiphenidine and various analogues such as fluorolintane and N-ethyl-lanicemine).

Such drugs act by blocking the NMDA receptor at the PCP binding site as uncompetitive antagonists, an action that may induce anaesthetic activity for most of these substances at high doses [1; 5; 64-66]. These compounds are known to produce dissociative, hallucinogenic and schizophrenomimetic effects [64; 67-69]. The effects of these molecules are route and dose-dependent and diverse, generally inducing a mind-altering state, with sensory hallucinations, tactile distortions, euphoria, derealization and depersonalization [61; 70•].

Veterinary clinics are the typical sources of diverted 'K', which can be injected, snorted, smoked, or administered rectally; the dosage range being 25-300 mg. 'K' central 5-HT2A agonism [71], NMDA receptor antagonism [72], and high affinity for mu/delta/sigma opioid receptors [73] are thought to explain the hallucinogenic effects. 'K' psychoactive effects include near-death experiences (NDEs)/'out-of-body' sensations, such as the 'K-hole' [22; 74-76], as well. NDE include sensory deprivation [77], extreme joy, sense of travelling in the dark towards bright light, and communicating with deceased loved ones [78-79]. Physical adverse effects at times associated with NDEs include: hypovolaemia, septic shock, intra-cerebral haemorrhage, cerebral infarction, dyspnoea and cardiac arrest [80]. Chronic ketamine use can lead to dependence, tolerance, and a withdrawal syndrome; flashbacks typically taking the form of perceptual distortions and schizotypal symptoms. Flashbacks may persist after use has ceased, and are commonly reported [81]. About one-third of chronic 'K' users report either intestinal problems ('K cramps') [73] or urological issues ('K-bladder', i.e. abnormal bladder histology, decreased bladder capacity, dysuria, haematuria, hydronephrosis, and suprapubic pain) [82]. High ketamine consumption levels can cause toxicity leading to cardiovascular and respiratory

problems. Ketamine-related impaired perception of risk, muscle weakness and numbness can cause burns, falls and trauma, including fatal outcomes due to: death from hypothermia due to lying outside in winter, drowning, traffic accidents, and being a crime victim [76; 83]. Ketamine has a very rapid onset of action i.e. 30 seconds if injected intravenously, 5-30 minutes if taken intranasally and 20 minutes if ingested orally, with a duration of action of up to three hours [23].

Methoxetamine (MXE, 'Special M') entered the recreational drug market to avoid legislative sanctions through being a structural 'K' analogue [22]. MXE can be swallowed, taken sublingually, snorted/insufflated, injected or used rectally, with the dosage range being 5-100 mg [76; 84-86]. MXE presents with NMDA receptor antagonism activity, but also with dopamine-releasing and serotonin transporter inhibiting properties [73]. Users report changes in sensory perceptions expressed as intensified feelings (e.g. brighter colours and heightened imagery), euphoria, empathetic/entactogenic feelings, vivid hallucinations and improved mood [22]. MXE consumers often experience long-lasting dissociative effects, i.e. the 'M-hole' [19; 22]. Intense derealisation, detachment from one's own body, distorted perceptions of time and space, and disorientation are also reported [22]. Undesired effects include low mood, aphasia, cognitive impairment, dizziness, confusion, agitation and synaesthesia. After acute MXE intravenous injection, tachycardia, hypertension, confusion, agitation, stupor, ataxia, mydriasis and nystagmus have been reported [87]. Following chronic use, anxiety and suicidal ideation have been a reason of concern [21-22; 57]. Although MXE was marketed as 'bladder friendly', related pre-clinical studies [88] suggested both urological toxicity and unique cerebellar features [89]. Several analytically confirmed MXE-related fatalities have been reported [90-91].

PCP ('angel dust') produces distorted perceptions of sight and sound, dissociation from the environment, out-of-body feelings, and hallucinations. Acute symptoms may include: memory impairment; altered perception of time; slowness; anxiety; apathy; irritability; psychosis; stupor; coma; and violent behaviour. Chronic effects can comprise: memory and thinking impairment; mood shifts; anxiety disorders; suicidal thoughts; and dependence. PCP intake has been associated with cerebrovascular accidents and cardiac arrest [27]; catatonic states [92]; and delirium; the latter having led to the discontinuation of its research in the early 1960s [93-94]. Occasional deaths have been associated with the use of PCP [95-104].

Dextromethorphan

Dextromethorphan (DXM) is a cough suppressant and opioid derivative, being the dextroisomer of the codeine analogue levorphanol. At recommended dosages, DXM is considered a safe product. DXM is available as tablets, capsules, lozenges and syrups, in a variety of prescription and over-the-counter (OTC) cough and cold remedies, either alone or in combination with other ingredients like analgesics, antihistamines and expectorants [103]. Nonetheless, since its introduction in the '50s, DXM use has been abused for high-dosage related hallucinogenic and dissociative effects [5; 104-106]. DXM abuse seems to be popular among teens, in being considered a SMART choice, which is the acronym for: Stigma (unlike illicit street drugs, DXM purchase and assumption has no negative connotation); Money (DXM products are relatively inexpensive); Access (easy availability); Risks (low risk perception); and Testing (DXM is not detected by drug tests) [103]. DXM use may be associated with a high lifetime prevalence of mood, anxiety, and personality disorders [21; 106-107].

The drug is rapidly absorbed from the gastrointestinal tract, with duration of action ranging from 3 to 6 hours [108]. DXM effects depend on its metabolism by cytochrome CYP2D6 to dextrorphan and, due to the genetic polymorphisms of CYP2D6, extensive

metabolizers may be more prone to increase the dosage and suffer from neuropsychiatric manifestations [103; 107-109].

Similarly to PCP and ketamine, DXM acts as an NMDA receptor antagonist [103; 108; 110]. Nonetheless, it also shows an a3/b4 nicotinic receptors antagonism; a sigma1 and 2 opioid receptors agonism; and a serotonin reuptake inhibitory action. Like other dissociative agents, dextrorphan is also thought to exert adrenergic effects by inhibiting peripheral and central catecholamine reuptake [103; 108]. The long-term use of DXM can lead to dependence [103; 111], with the abrupt cessation of the drug resulting in a withdrawal syndrome [109].

DXM characteristics of the intoxication are dose-related. With up to 400mg, psychoactive effects include: trance-like euphoria, sense of well-being, profound empathy and social relaxation; but also, impairment of motor, cognitive, and perceptual functioning, with mild hallucinations, slurred speech, lethargy, ataxia and memory impairment. With higher dosages, a proper dissociative state (e.g. 'robo-ing', 'robo-copping', or 'robo-tripping'), is being observed, with 'out-of-body' experiences, bizarre/idiosyncratic/violent behaviour, paranoid thinking, perceptual distortion, and vivid auditory/visual hallucinations [103; 111].

Increase in body temperature (which may be a sign of a serotonergic syndrome) [21], tachycardia, hypertension, dyspnoea, restlessness, hyperreflexia, and respiratory depression may occur [103; 107-109; 111]. Fatal outcomes following the ingestion of even massive amounts of DXM alone are rare [112]. DXM intoxications can also exhibit signs of toxicity from concurrent compounds, including hepatotoxic effects from acetaminophen, anticholinergic effects from diphenhydramine, depressant effects from ethanol, and sympathomimetic effects from pseudoephedrine [103; 107-108; 111]. DXM is often marketed in cough and cold products as 'dextromethorphan hydrobromide'. Thus, there is the possibility of acute/chronic toxicity ('bromism') in association with substantial DXM ingestion [108; 111].

The combination of high doses of DXM with other serotonergic drugs, including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, St. John's Wort, and certain antibiotics (e.g., linezolid) may be associated with the development of a serotonin syndrome [108].

The possible therapeutic role for psychedelics and dissociatives

Psilocybin has been shown to uncouple synchronised activity in the posterior cingulate cortex and the medial prefrontal cortex. This suppression of regulated patterns of activity between different brain areas may characterise the 'psychedelic state' [113]. There might be a role for psilocybin for the alleviation of anxiety and depression in life-threatening illness [114-119]. The effect of varying of doses of oral psilocybin (100, 200, or 300 mg/kg) was tested in a small study on patients suffering from Obsessive Compulsive Disorder (OCD) [120], but only one subject had achieved long-term remission at the 6-month follow-up. There is some evidence for a possible role of psilocybin in the treatment of alcoholism or nicotine addiction [121-122], and according to Sewell et al. [123] psilocybin and LSD might also have a role in the treatment of cluster headache.

LSD has been studied as a possible treatment for depression for the last few decades [124]. Indeed, 5-HT1A and 5-HT2A receptors are implicated in the pathophysiology of dysfunctional emotional biases, with cortical 5-HT2A receptor expression being increased in postmortem samples of depressed and suicidal patients [125-127], and 5-HT2A binding decreased in the hippocampus of depressed patients [128]. Furthermore,

medication-free depressed patients with high pessimistic attitudes showed increased 5-HT2A receptor binding in the pre-frontal cortex compared with healthy control subjects [129-131]. There are also anecdotal reports of LSD being useful in the treatment of OCD [132], with a non-hallucinogenic LSD derivative, BOL-148 (2-bromo-LSD), shown to be an effective treatment of cluster headache [133].

Animal studies may suggest a possible role for DOI (2,5-Dimethoxy-4-iodoamphetamine), a nonselective 5-HT2A/2C agonist, as anti-anxiety [134-136].

Finally, over the last few years, and possibly because of the significant dopaminergic, serotonergic and glutamatergic actions of PCP-like compounds, research has focused on the possible antidepressant/antisuicidal clinical effects of both ketamine (for a thorough review, see [137] and methoxetamine/MXE [138].

Discussion

The present article offered an updated overview of the clinical and clinical pharmacological issues related to some of the most popular NPS categories, e.g. dissociatives and hallucinogens. Due to the rapid spread and wide availability of NPS, health professionals aim at being fully informed and updated, to be able to adapt their response to the potential new challenges that NPS may cause. Moreover, due to the difficulty in classifying NPS and their unknown long-term health harms, NPS can be considered a global problem, with public health, social and safety risks [139]. As a response, drug policies have enforced new regulatory approaches for NPS, focusing on their supply through legislative tools. Furthemore, in many European countries a range of effective public health responses, including prevention activities, drug demand and harm reduction intervention, have been increasingly implemented , [140].

Moreover, the parallel changes in drug scenarios, including the frequent polydrug use, the unknown toxicodynamics and toxicokinetics, and unusual presentation to emergency departments represent a challenge for psychiatry. In fact, the occurrence of both psychosis and remaining psychopathological issues has been related to [5; 28••]: a) increased central dopamine levels, associated with the intake of most of these substances, including novel psychedelic phenethylamines; b) 5-HT2A receptor activation, typically reported for all psychedelics and especially for NBOMe compounds; latest tryptamine derivatives; and hallucinogenic plants; and c) antagonist activity at NMDA receptors, described with all phencyclidine-like dissociatives.

Although the link between psychedelics, dissociatives, and mental health conditions is yet to be fully understood [52], one could argue that, when psychosis does develop and persist, this might be the result of a complex interaction between genetic predisposition and environment [141••-**142**].

From a psychopathological perspective, one could wonder about the similarities and differences between schizophrenia; the recreational drug-induced psychosis; the dissociative states; and the psychedelic-related psychopathological issues. Clinically, the psychotic symptom profiles between cannabis-induced psychotic disorder and acute schizophrenia may be very similar; however, cannabis users' cognition levels are less severely affected [141••]. Regarding the use of dissociatives and schizophrenia, there are valid and reliable animal models to investigate the neurobiological mechanism of psychosis in humans [143]. Furthermore, most recent research has confirmed that both occasional ketamine use and ketamine abuse or dependence are associated with increased psychotic symptoms [144]. In relation to the severity of the clinically observed abnormal beliefs, both patients with schizophrenia and those under the influence of ketamine show abnormal function of the right lateral prefrontal cortex or lesions with connectivity to this area [145].

According to De Gregorio et al. [146••], there are similarities between the acute hallucinogenic drug-induced states and the acute presentation of endogenous psychoses like schizophrenia. Conversely, it is more difficult to understand the chronic psychopathological issues observed in psychedelic users. To this respect, Bonhoeffer [147] developed a model of 'exogenous' psychosis that might help to understand what happens during and after the intake of psychedelic substances. This proposed model, known as 'lysergic psychoma', is described by the subjects as an external body, a sort of a 'tumour/mass', perceived to be persistently 'located' in the mind/ the brain after the use of psychedelics. Different from the pervasive schizophrenic experience, this may leave unaffected the remaining higher functions, including cognition and mood. In other words, the lysergic psychoma is conceptualized as a psychopathological experience in which the thinking Ego is still able to acknowledge and 'contain' the abnormal features (for a thorough review, see [148]).

Further reported reactions post-psychedelic treatment replicate or mimic the psychotic state, as is the case of the hallucinogen-persisting perception disorder (HPPD; replacing the term 'flashbacks'). HPPD includes afterimages, perception of movement in peripheral visual fields, blurring of small patterns, halo effects, and macro- and micropsia long after the drug has been used [13]. The main characteristic of these perceptual disturbances is that they profoundly affect a person's inner processes and the perception of the surrounding world, causing distress or impairment in their everyday life [4•]. These perceptual disturbances may be continuous or only occasional, and the only certain cause for HPPD is prior use of hallucinogens [4•; 26•; 149].

Psychedelics and dissociatives are being studied as well as potential treatment for certain psychiatric conditions, mainly treatment-resistant depression, anxiety and addiction disorders [150• -151]. Although it is still unclear if the psychedelic state is necessary for their therapeutic effects [141••], it has been suggested that both the identification of non-psychedelic compounds with similar serotonergic and glutamatergic receptor affinities as psychedelics, as would the identification of non-psychedelic analogues capable of promoting plasticity in the prefrontal cortex [141••; 146••) would constitute an important area for future research.

Treatment and management issues
Consumers of psychedelic and dissociate NPS may present to the Accident and Emergency Departments without providing vital information about the substances(s) ingested. Furthermore, standard drug tests will likely show negative results [2; 20]. It is possible that those patients with less severe symptoms may simply need reassurance, support, and monitoring. However, a medication may frequently be needed, e.g. to focus on decreasing levels of both self/outward-directed aggression and agitation. Due to the complex/unknown pharmacology of the substances arguably ingested, benzodiazepines may be the agents of choice, although this may be difficult with those intoxicated with alcohol. Where patients cannot be controlled with benzodiazepines alone, propofol and/or antipsychotics may be considered, although drugs such as haloperidol, olanzapine, or ziprasidone can lower seizure thresholds, limiting the levels of heat dissipation and contribute to dysrhythmias (for a full review, see [152••]). Hyperthermia, typically associated with phenethylamine psychedelics, needs to be evaluated and treated aggressively, and this typically involves cooling measures and i.v. fluid administration for rhabdomyolysis concern [28••]. The intake of serotonergic drugs (e.g. phenethylamines, hallucinogens, NBOMe compounds, etc.) may be

associated with the occurrence of the serotonin syndrome, to be managed using both benzodiazepines and cyproheptadine [28••].

Conclusions and recommendations

The online <mark>market</mark> of novel psychoactive substances is unfortunately developing far more rapidly than academic research. Apart from traditional webstores easily accessible by users, cryptomarkets have been recently developed. They are anonymous marketplaces operating on the so-called darknet, and accessible only via specially configured browsers [153]. Vulnerable subjects, including both children/adolescents and psychiatric patients, may be exposed to a plethora of 'pro drug' web pages, which provide direct drug purchase opportunities and/or drug information (e.g., description of the drug effects, dose, chemistry and intake experiences; [16]). Unfortunately, clinicians are not always aware of the type, effects and psychopathological risks related to NPS [154].

The onset of psychiatric symptoms after the use of these potent and highly rewarding drugs is extremely common, especially following repeated use. These episodes, sometimes characterized by significant psychotic features, are often self-limited and reversible; however, when the use is frequent, persistent, and at high dosages, the onset of full and long-lasting psychiatric disorders can be observed [148]. More clinical studies are needed to clarify these aspects and the importance of toxic psychosis and the complex link between NPS and psychiatric illnesses.

Compliance with Ethics Guidelines

All authors declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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