New / emerging psychoactive substances and associated psychopathological consequences

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Abstract

Background: The present paper provides an updated review of both the large number of new/novel/emerging psychoactive substances (NPS) and their associated psychopathological consequences. Focus was here given on identification of those NPS being commented in specialised online sources and the related short-/long-term psychopathological and medical ill-health effects.
Methods: NPS have been identified through an innovative crawling/navigating software, called the 'NPS.Finder®', created in order to facilitate the process of early recognition of NPS online. A range of information regarding NPS, including chemical and street names; chemical formula; three-dimensional image; and anecdotally reported clinical/psychoactive effects, were here made available.
Results: Using the 'NPS.Finder®' approach, a few thousands NPS were here preliminarily identified, a number which is about 4-fold higher than those figures suggested by European and international drug agencies. NPS most commonly associated with the onset of psychopathological consequences included here synthetic cannabinoids/cannabimimetics; new synthetic opioids; ketamine-like dissociatives; novel stimulants; novel psychedelics; and several prescription and over-the-counter medicines.
Conclusions: The ever-increasing changes in terms of recreational psychotropics' availability represents a relatively new challenge for psychiatry, as the pharmacodynamics and pharmacokinetics of many NPS have not been thoroughly understood. Health/mental health professionals should be informed about the range of NPS; their intake modalities; their psychoactive sought-after effects; the idiosyncratic psychotropics' combinations; and finally their medical and psychopathological risks.

Key words: new psychoactive substances; NPS; psychedelics; drug-induced psychosis; prescribing drug misuse; drug misuse.

Introduction

Several definitions of the term novel/new psychoactive substances (NPS) are in use, with the term 'new' not necessarily referring to new inventions but to substances that have recently been made available ([UNODC], 2013). Hence, 'new' can include a failed pharmaceutical or an old patent which has been 'rediscovered' and marketed for its potential use as a 'recreational' substance. Conversely, the term 'novel' can also express something newly created, or a compound that has come back into fashion after a period of absence from the recreational drug scene, or indeed a known NPS molecule being used in an innovative or unusual way, hence presenting with a 'novelty' appeal (Corkery et al., 2018a). Another distinction being made is between NPS and Emerging Psychoactive Substances (EPS), where the latter term captures all NPS as well as drugs that may not be newly invented, but have recently experienced a resurgence of, or increase in, use (Sutherland and Barratt, 2016).

Number and types of NPS in both real and online scenarios

Between 2009 and 2017, a total of 803 NPS were reported by 111 countries/territories (UNODC, 2018). In the EU, by the end of 2017 the number of NPS was over 670, of which 632 were notified after 2004 ([EMCDDA], 2018a); most molecules were synthetic cannabinoids, synthetic cathinones, phenethylamine derivatives; and synthetic opioids.

Both the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the United Nations Office on Drugs and Crime (UNODC), however, include an index NPS in their database only when the NPS is seized, chemically analysed and notified to them. However, one could argue that the NPS scenario is much larger than that formally identified by international agencies. Hence, an approach aiming at describing what is being discussed online by the web-based NPS enthusiasts 'e-psychonauts' (Orsolini et al., 2015) has been considered as potentially useful to identify in advance the NPS availability, market and diffusion. In fact, the *online* NPS scenario, with its related concerns, typically predicts the *real life* NPS scenario (Corazza et al., 2013). Consistent with this, a risk of violent behaviour associated with NPS intake has been identified in patients presenting to London (UK) acute mental health services (Shafi et al., 2017). Furthermore, both the psychopathological and aggression issues associated with the Ibiza clubbing scenario drug intake (Martinotti et al., 2017) had been somehow predicted by previous studies (Schifano et al, 2015; Schifano et al, 2016) based on the observation of the evolving 'e-psychonauts' scenario.

Aims

In this study, we aimed at: (a) identifying and describing the large number of NPS available as identified from a range of psychonauts', NPS-related, online sources; and (b) describing the short-/long-term clinical effects of the NPS most commonly associated with the onset of those psychopathological consequences which are of interest for mental health professionals. These NPS include: synthetic cannabinoids/cannabimimetics; new synthetic opioids;

ketamine-like dissociatives; novel stimulants and novel psychedelics; prescription; and over-the-counter (OTC) medicines (Schifano et al., 2015).

Methods

To facilitate the process of early recognition of the increasing dissemination of new substances online and the variability of information sources, a crawling/navigating software (i.e. the 'NPS.Finder®') was designed to automatically scan the open/surface web for new/novel/emerging NPS. This was meant to map on a 24/7 basis the large variety of psychoactive molecules mentioned/discussed within a range of major and representative online psychonaut web sites/fora (the full list of these sites is available upon request). The NPS.Finder® was designed to extract a range of information regarding NPS, including: chemical and street names; chemical formula; three-dimensional image; and anecdotally reported clinical/psychoactive effects. Resulting data were checked against the EMCDDA and UNODC NPS databases. The collection of further information was completed by consulting a range of open libraries and chemistry databases referring to the index item, if existing. These data were then automatically stored in an online, restricted access/password-controlled database located within firewall protected, highly secure, and consistently performing servers. After completion of proper piloting searches, a range of specific web scraper/crawler activities, to extract all accessible posts/entries from November 26th, 2017 and up to end of May 2019, were carried out. When any new item was detected during the automated web scan, the system sent an e-mail notification/alert to the core researchers' mailing list. Eventually, these data were screened for relevance and to exclude possible duplications. Finally, using chemical structure identification and published related data, researchers assigned each molecule to its NPS drug class (Schifano et al., 2015). Although the language most typically used by psychonauts was English, further languages here analyzed by NPS.Finder® included: Dutch, French, Turkish, Swedish, Spanish, German, Russian, and Italian.

To describe the medical and psychopathological issues most typically associated with the range of NPS intake, the Medline/PubMed database(s), were searched for papers using the terms 'new psychoactive substances', 'novel psychoactive substances', 'designer drugs', and 'emerging drugs of abuse'. A similar search was carried out for the main groups of pre-selected NPS molecules and related medical and psychopathological consequences.

Results

Preliminary data from the NPS.Finder® *web crawling activities*

After about 18 months of operation, the number of substances identified by the web crawler activities was 5922. By the time of writing, some 4,204 unique NPS molecules were included in the database and 1718/5922 (29.01%) remaining molecules resulted to be false positives/duplicates. Most popular NPS mentioned in the psychonauts' fora included: psychedelic phenethylamines (1262; 30%); synthetic cannabimimetics (1248; 29.7%); synthetic opioids (460; 10.9%); GABA-A/GABA-B receptor agonists (172; 4.1%); synthetic cathinones (171; 4.1%); prescribed/OTC medicinal

compounds (157; 3.7%); novel stimulants (82; 1.9%); novel psychedelics (38; 0.9%); and PCP/ketamine-like compounds (36; 0.8%).

Synthetic cannabinoids/cannabimimetics (SC)

Whilst low-dosage levels of synthetic cannabinoids (SC) produce similar psychoactive effects to cannabis/THC, with higher dosages auditory/visual hallucinations, anxiety, and intense feelings of paranoia often occur (Bonaccorso et al., 2018; Wessinger et al., 2015; Winstock and Barratt, 2013a). Other psychiatric and neurological effects include: behavioural dyscontrol and agitation (Brakoulias, 2012); mood swings (Celofiga et al., 2014); suicidal ideation, suicide attempts (Glue et al., 2013); panic attacks; thought disorganisation; and agitated/excited delirium (Schifano et al., 2017). A florid/acute/transient psychosis; relapse/worsening of a pre-existing psychosis and bipolar disorder (Oluwabusi et al., 2012; Ustundag et al., 2015); and the persistent psychotic disorder 'spiceophrenia' (Papanti et al., 2013; Schifano et al., 2016) have all been described. With synthetic cannabinoids, similar to what being described for a range of remaining NPS (Schifano et al, 2015), the total or partial recurrence of perceptual disturbances that appeared during previous hallucinogenic intoxications, typically known as Hallucinogen-Persisting Perception Disorder (HPPD), may occur (Martinotti et al., 2018).
The intoxication/acute toxic effects of SCs appear to be more akin to those experienced with sympathomimetic/stimulant drug use (Naviglio et al., 2015; Wood and Dargan, 2012). Typical medical untoward effects include: vomiting/nausea; hypertension and tachycardia; tachypnoea/dyspnoea; hyperglycaemia; mydriasis (Hermanns-Clausen et al., 2013; Schifano et al., 2015; Winstock and Barratt, 2013b); nystagmus; seizures (Hopkins and Gilchrist, 2013); encephalopathy (Louh and Freeman, 2014); coma; and stroke (Freeman et al., 2013; Mir et al., 2011; Rose et al., 2015). Ultimately, deaths have been associated with the use of synthetic cannabinoids, either on their own or in combination (Angerer et al., 2017; Corkery et al., 2014; Maeda et al., 2018; Olsen, 2018; Paul et al., 2018; Tait et al., 2015; Trecki et al., 2015). These may result from direct lethality of the molecule; behavioural dyscontrol; or suicide (Lászik et al., 2015; Patton et al., 2013; Rosenbaum et al., 2012; Shanks et al., 2012).
Finally, SC long-term use can give rise to dependence/tolerance phenomena (Gunderson et al., 2012; Spaderna et al., 2013); a withdrawal syndrome, characterized by: profuse sweating, tachycardia, tremor, diarrhoea, headache, drug craving, feelings of emptiness/depression, anxiety, irritability, mood swings, and insomnia/nightmares has been described (Macfarlane and Christie, 2015).

New Synthetic Opioids (NSOs)

New synthetic opioids (NSOs) emerged in recent years as part of the alarming worldwide opioid crisis (Armenian et al., 2018; [CDC], 2016; [CDC], 2018; Drummer, 2018; [EMCDDA], 2017; Graddy et al., 2018; Lucyk and Nelson, 2017; Prekupec et al., 2017; Suzuki and El-Haddad, 2017; Van Amsterdam and van den Brink, 2015). NSOs are a large group of narcotic analgesic drugs having structural similarities, but much greater potency of action and receptor

affinity, with respect to morphine (Marchei et al., 2018; Solimini et al., 2018; Tracy et al., 2017). This group includes compounds which were originally synthesized by pharmaceutical companies but never commercialised and then diverted into the illegal market, e.g. benzamide (U-47700, U-49900, AH-7921); acetamide (U-50488, U-51754); piperazine derivatives (MT-45) (Zawilska, 2017); and several illicitly manufactured fentanyl analogues, e.g. acetylfentanyl; carfentanyl; furanylfentanyl; 3-methylfentanyl; sufentanyl; etc. (Armenian et al., 2018; Marchei et al., 2018; Suzuki and El-Haddad, 2017). These molecules may be used alone; as adulterants in heroin; or as constituents of other illicit products or counterfeit medications (Abdulrahim and Bowden-Jones, 2018; Prekupec et al., 2017).

NSOs' toxicity includes drowsiness, sedation, disorientation, slurred speech, confusion, dizziness, nausea, miosis, slowed breathing and respiratory depression to coma (Suzuki and El-Haddad, 2017). Conversely, NSOs' psychotropic effects include: sedation; euphoria; feeling of relaxation; mood lift, dysphoric and dissociating effects (Solimini et al., 2018) (Table 1).

Due to their high potency, their continued use (or abuse) may induce tolerance, with the risk of overdose and death being elevated. Physical dependence and addiction may rapidly rise, and withdrawal symptoms occur if their use is rapidly reduced or suddenly stopped. These include symptoms similar to the traditional opioid withdrawal, such as restlessness, agitation, muscle and bone pain, insomnia, diarrhoea, vomiting, and cold flashes with goose bumps (Suzuki and El-Haddad, 2017; Zawilska, 2017).

Other compounds classified among NSOs are desomorphine ('krokodil'), mitragynine and 7-hydroxymitragynine (alkaloids found in "kratom"/*Mitragyna speciosa*; Liu et al., 2018; Corkery et al, in press), and salvinorin A, with its analogue herkinorin, which are the main *Salvia divinorum* components. Salvinorin A psychoactive effects include perceptual disturbances, psychosis, irritability, and anxiety (Ventura et al., 2018) (Table 1).

Ketamine-like dissociatives

Ketamine and phencyclidine (PCP) were both originally developed as general anaesthetics for veterinary and human use, but soon became street drugs. Despite the strong dissociative effects on post-operative patients, ketamine is used as anaesthetic mostly in veterinary practice, but also in emergency medicine (Baumeister et al., 2015). Ketamine ('special K') can be injected, snorted, smoked, or administered rectally, at a dosage range of 25-300 mg, inducing feelings of relaxation, dissociation, depersonalization, and psychotic experiences, with hallucinations lasting even longer than the anaesthetic effects.

Ketamine intoxication may include cardiovascular and respiratory symptoms and, due to its anaesthetic and dissociative effects, related risks may include trauma, drowning, death from hypothermia and traffic accidents (Schifano et al., 2015) (Table 1). The 'K-hole', which may result after the ingestion of large dosages of ketamine, is a typical out-of-body/near-death experience, with the user becoming trapped in a state of detachment from his/her physical presence. Residual symptoms, such as flashbacks and perceptual distortions, may follow.

Long-term ketamine use may present with both urological ('K-bladder') and intestinal ('K-cramps') symptoms (Schifano et al., 2015). Compared with ketamine, PCP ('angel dust') appears to determine much wider and unstable range of symptoms, with cerebrovascular accidents and cardiac arrest occurring (Baumeister et al., 2015). Chronic use of PCP may impair memory and thinking, and determine mood shifts, anxiety and suicidal thoughts ([DEA], 2013) (Table 1).
Further related dissociatives recently entered the market (Wallach et al., 2016), including: 4-MeO-PCP (Morris and Wallach, 2014); the 1,2-diarylethylamines (e.g. diphenidine, ephenidine, methoxydiphenidine and various analogues such as fluorolintane and N-ethyl-lanicemine); and the β-keto-arylcyclohexylamines (e.g. methoxetamine, deschloroketamine, and 2-fluoro-2-deschloroketamine) molecules (Wallach and Brandt, 2018). They primarily act as uncompetitive antagonists at glutamatergic NMDA receptors, but may also bind at opioid and monoaminergic receptors (Schifano et al., 2015). Their effects are diverse and dose-dependent, generally inducing a mind-altering state, with sensory hallucinations, tactile distortions, euphoria, derealization and depersonalization (Tracy et al., 2017; Wallach et al., 2016) (Table 1).

Novel stimulants and novel psychedelics, including psychedelic phenethylamines

Novel stimulant and novel psychedelic compounds include phenethylamines, cathinones, piperazines, tryptamines, pipradrols/piperidines, aminoindanes, benzofurans, and amphetamines; all of these present with varying levels of stimulant, entactogenic, and hallucinogenic effects. They exert an inhibitory action on the monoamine reuptake, increasing the quantity of noradrenaline/NA, dopamine/DA and serotonin/5-HT in the synaptic cleft (Miliano et al., 2016). Consistent with their pharmacological profile, those molecules that present with high serotonin:dopamine ratios may be considered analogous to entactogenic substances, such as MDMA. Conversely, high dopamine:serotonin ratios might predict a strong stimulant experience. Furthermore, high or low affinity to modulation of noradrenergic systems might be anticipated to be associated with varying sympathetic nervous system activation, whereas activation of 5-HT2A/1A receptors would more likely predict hallucinogenic effects (Baumeister et al., 2015) (Table 1).
Presenting with structural similarities to amphetamines (Feng et al., 2017), synthetic cathinones ([EMCDDA], 2017) are mostly inhibitors of the serotonin (SERT), dopamine (DAT) and noradrenaline (NET) transporters. These molecules can be further sub-categorised as: (1) cocaine/MDMA-like (3,4-methylenedioxy-N-alkylated cathinones e.g. butylone): these act as inhibitors at SERT, DAT and NET and as serotonin releasers; (2) methamphetamine-like (N-alkylated or ring-substituted cathinones e.g. buphedrone): these act as inhibitors at SERT, DAT and NET and as dopamine releasers; and (3) pyrovalerone-like cathinones (N-pyrrolidine cathinones e.g. MDPV (3,4-methylenedioxypyrovalerone): these are very potent at DAT and do not induce any monoamine substrate release (Simmler et al., 2013).

Apart from mephedrone (Dargan et al., 2010; De Sousa Fernandes Perna et al., 2016; Freeman et al., 2012; Karila et al., 2015; Karila et al., 2016; Prosser et al., 2012; Winstock, 2010; Winstock, 2011), the psychopathological consequences of most cathinones have not been fully studied. With mephedrone, low mood, loss of appetite, difficulty sleeping, levels of paranoid ideation, cognitive impairment, changes in perception, agitation, hallucinations, delusions, amnesia, confusion, violence and suicidal thoughts have been reported (Capriola, 2013; Herzig et al., 2013; Homman et al. 2018; John et al., 2017; Kaizer-Będkowska et al., 2018; Kehr et al., 2011; Lovrecic & Lovrecic, 2017). Users reported as well positive effects e.g. euphoria, improved psychomotor speed, alertness, and talkativeness (Cheng et al., 2012; Dargan et al, 2010; Mdege et al., 2017). Cathinone-induced acute intoxication may include symptoms of the serotonin syndrome, associated with aggression and hyperthermia, psychotic disorders, catatonia and excited delirium syndrome (Denysenko et al., 2015; Hohmann et al., 2014; Mugele et al., 2012; Otachbachi et al., 2010; Penders et al., 2012; Penders and Gestring, 2011; Warrick et al., 2013; Weaver et al., 2015). Other acute intoxication issues included dehydration, hypertension, tachycardia, kidney and liver impairment, electrolyte imbalance, metabolic toxicity, cerebral oedema, and death (Adebamiro & Perazella, 2013; Borek and Holstege, 2012; Imam et al., 2013). Suicides by hanging and deaths from firearm injuries have frequently been reported (Barrios et al., 2016; Marinetti and Antonides, 2013), as well as deaths from toxicity (Corkery et al., 2018b). Although long-term effects of synthetic cathinones' use are largely unknown, they may include insomnia, depression, anxiety, psychosis, and dependence (Capriola, 2013).
Phenethylamines are synthetic compounds available in tablets, capsules, and powder. They act on serotoninergic receptors, hence leading to psychedelic effects, but some of them inhibit the NA/DA reuptake as well. 3,4-methylenedioxy-methamphetamine (MDMA, *'ecstasy'*) is one of the most popular drugs among youngsters/clubbers, because of its stimulant effects. Recently the emergence of a range of other psychedelic phenethylamines, including: the 2-C and 2-D series drugs; the benzodifurans (e.g. 3-C-bromo - dragonfly), and others (e.g., 4-MTA, 6-APB, 4,4′-DMAR and PMA), has been reported (Miliano et al., 2016). Their psychoactive effects are dose-dependent, ranging from stimulant effects at lower doses, to hallucinogenic and entactogenic effects at higher doses. Phenethylamines' intake may be associated with loss of appetite, tachycardia, hypertension, anxiety, nausea, headache, dizziness, skin irritation, hyperthermia, convulsions, respiratory deficits, liver/kidney failure and death (Schifano et al., 2015). Psychotic symptoms are associated with a high dosage intake (Baumeister et al., 2015) (Table 1).
The lead compound in piperazines, N-Benzylpiperazine (BZP), has a typical central nervous system stimulant structure. Structurally similar to amphetamine and initially developed as an antidepressant, BZP triggers the release of DA and NA whilst inhibiting the uptake of DA, NA, and 5-HT (Miliano et al., 2016). Piperazines' toxicity causes hallucinations, seizures, hyponatraemia, serotonin syndrome, renal failure and ultimately death (Schifano et al., 2015) (Table 1).

Tryptamines, with the most common molecule being the lysergic acid diethylamide/LSD, are a group of monoamine alkaloids very similar to the endogenous neurotransmitter serotonin. They act both as 5-HT2A receptor agonists and serotonin reuptake inhibitors. A large range of novel tryptamines, including: 5-MeO-AMT, 5-MeO-DALT, 4-HO-DALT, 5-MeO-DIPT; and 5-MeO-DMT, have appeared on the drug scene (Miliano et al., 2016). Some of them are found in nature, e.g. Delosperma species plants (containing dimethyltryptamine/DMT; 5-MeO-DMT); hallucinogenic fungi (psilocin; 4-OH-DMT); and amphibians (bufotenin) (Schifano et al., 2015). 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. There are small numbers of tryptamine-related fatalities (Schifano et al., 2015) (Table 1).

Prescription and OTC drugs

Over the past decade the recreational use of several psychoactive pharmaceuticals has emerged in the NPS scene, including: antidepressants; antipsychotics; gabapentinoids; Z-drugs and designer benzodiazepines; and OTC drugs (Schifano et al., 2015; Schifano et al., 2018).

1 Antidepressants

Antidepressants emerged as being misused, raising public health concerns on their prescription control policies (Evans and Sullivan, 2014). Bupropion inhibits both the NA and DA reuptake (Schifano and Chiappini, 2018a) and, being a cathinone derivative, presents with stimulant activities (Baumeister et al., 2015; Evans and Sullivan, 2014). It may be consumed orally, insufflated, or injected, with high dosages provoking a 'high' similar to cocaine (Vento et al., 2013). Adverse effects range from nasal pain to irritability, agitation, cardiac toxicity, hallucinations and seizures. Vulnerable users are inmates and patients with past histories of substance misuse (Schifano and Chiappini, 2018a) (Table 1).

Amitriptyline anecdotally emerged as the most abused among tricyclic antidepressants giving, at high dosages, 'pleasant feelings' and euphoria. Its anticholinergic and antihistamine effects may contribute to its abuse liability (Evans and Sullivan, 2014). Tachycardia and cardiac conduction changes are common in patients ingesting high dosages of tricyclic antidepressants; overdoses may be fatal (Shenouda and Desan, 2013) (Table 1).

At high/supratherapeutic doses (e.g. 400-4,000mg/day), the phenylethylamine derivative venlafaxine ('baby ecstasy') inhibits the reuptake of serotonin, noradrenalin, and dopamine, particularly at the prefrontal cortex level (Francesconi et al., 2015). If suddenly discontinued, a withdrawal syndrome characterized by nausea, depression, suicidal thoughts, disorientation, stomach cramps, panic attacks, sexual dysfunction, headache, and occasional psychotic symptoms may develop (Table 1).

2 Antipsychotics

Quetiapine ([FDA], 2010) recently emerged on the drug scenario as being used for recreational purposes (Klein et al., 2017), which may have contributed to increased poisonings and related fatalities (Lee et al., 2018). Crushed quetiapine tablets can be self-administered through nasal insufflation, ingested, or injected (Chiappini and Schifano, 2018). The intentional abuse of quetiapine is associated with sedation and euphoria (Lee et al., 2018). Quetiapine is also abused concomitantly with other illicit substances, such as cocaine ('Q ball'; Lee et al., 2018). At high/supratherapeutic dosages, a quetiapine agonist activity on the DA system has been hypothesized (Chiappini and Schifano, 2018). Vulnerable subjects include inmates and those with a previous substance abuse history (Lee et al., 2018) (Table 1).
Olanzapine, at a dosage of up to 50 mg/day, has been anecdotally advised online as the 'ideal trip terminator' after a psychedelic drug binge. Moreover, it may be used to treat unwanted 'comedown' symptoms (depression, dysphoria, anxiety, and insomnia) from drug/alcohol intake (Chiappini and Schifano, 2018; Klein et al., 2017) (Table 1).

3 Gabapentinoids

A rise in pregabalin and gabapentin prescription rates has been registered worldwide, with an anecdotally growing black market (Parsons, 2018). Both gabapentinoids bind to the calcium channel, reducing the release of excitatory molecules. At therapeutic dosages, they are thought to possess GABA-mimetic properties, which may be behind the 'liking' (euphoric/relaxing high), but causing only limited rewarding ('wanting'), dopaminergic-related, properties (Berridge and Robinson, 2016; Bonnet and Scherbaum, 2017; Bonnet et al., 2018). A range of experiences may be associated with gabapentinoid high-dosage abuse, including euphoria, improved sociability, opiate-like sedation, entactogenic feelings/dissociation, and psychedelic effects (Schifano et al., 2015). Gabapentinoids may be ingested to cope with opiate/opioid withdrawal symptoms (Schifano et al., 2018). Unconventional routes of administration have been reported, e.g. intravenous; rectal – 'plugging"'; smoking; and 'parachuting', e.g. emptying the content of the capsule into a pouch (Al-Husseini et al., 2018; Chiappini and Schifano, 2016). A proper withdrawal syndrome, including: insomnia; headache; nausea; anxiety; and convulsions, can be associated with gabapentinoids' abrupt discontinuation (Baumeister et al., 2015; [WHO], 2017) (Table 1).

4 Z-drugs and designer benzodiazepines

The Z-drugs' (zolpidem, zopiclone and zaleplon) addictive potential has already been highlighted (Kapil et al., 2014; Schifano et al, 2019). Zolpidem and zopiclone seem to be the most involved in the diversion and abuse phenomena ([ACMD], 2013), and it is likely that the misusing phenomenon is currently underestimated (Hajak et al., 2003). A 20 mg to 300–400 mg/day zolpidem dosage has been associated with significant stimulating effects, hyperactivity and euphoria (Victorri-Vigneau et al., 2007) (Table 1). Polydrug consumption and history of drug misuse are frequently reported issues; both snorting and injection practices have been described. A withdrawal syndrome may develop after the abrupt cessation of Z-drugs' long-term, high-dosage, intake and

symptoms may include insomnia, anxiety, irritability, tremor, abdominal pain, hypertension, tonic-clonic seizures, and confusion.
Designer benzodiazepines recently emerged on the illegal drug scene ([EMCDDA], 2017; Graddy et al., 2018; Vårdal et al., 2019). Most of them are not approved for therapeutic use in any country (Baumeister et al., 2015; Moosmann et al., 2015) and may be easily acquired online (Vårdal et al., 2019). Whilst sharing clinical effects with 'traditional' molecules (Baumeister et al., 2015), some designer benzodiazepines (e.g. pyrazolam; phenazepam/'Zinnie') may be several times more potent than diazepam (Moosmann et al., 2015; Schifano et al., 2015; Tracy et al., 2017). Designer benzodiazepines' side-effects include amnesia, long-lasting (60 hours) confusion and disorientation, dizziness, loss of coordination, drowsiness, blurred vision, slurred speech and ataxia (Baumeister et al., 2015). Due to their high potency, molecules such as clonazolam or flubromazolam can cause strong sedation and amnesia at oral doses as low as 0.5 mg, hence they may be unintentionally overdosed (Moosmann et al., 2015). Etizolam, phenazepam, clonazolam, diclazepam, phenazolam, and flubromazolam have all been involved in fatalities ([UNODC], 2018) (Table 1).

5 OTC drugs
Over the last decade, clinicians have raised concerns relating to a range of OTCs being misused recreationally, with 'pharming' (e.g. shopping from a range of pharmacy shops) being an internationally recognized issue (Schifano and Chiappini, 2018b). OTC misuse may have developed due to their increased availability, affordability, and users' perceptions on their safety (Cooper, 2013; Sansgiry et al., 2016). Commonly abused medications include ephedrine and pseudoephedrine; codeine-containing antitussives; and dextromethorphan (Cooper, 2013). Codeine diversion has been reported to be associated with sedating effects, whilst its combination with promethazine is known as 'purple drank' (Cooper, 2013) (Table 1).
Dextromethorphan (DXM) is a cough suppressant opioid derivative, considered safe at recommended dosages, e.g. 120 mg in four divided doses per day (Linn et al., 2014). The psychotropic effects and addictive potential are associated with the intake of large dosages, typically administered through snorting or injecting practices. Psychotropic effects include trance-like euphoria/stupor, hyper excitability, depersonalization, dyskinesia, delayed response times, disordered speech, and vivid auditory/visual hallucinations (Romanelli and Smith, 2003). Due to the action of DXM's primary metabolite dextrorphan on the NMDA receptor, the compound may produce a ketamine-like dissociative state, known as 'robo-ing', 'robo-copping', or 'robo-tripping', after the DXM-containing cough syrup commercial name (Wilson et al., 2011). Moreover, DXM chronic abuse has been associated with psychosis (Linn et al., 2014). In addition to NMDA receptor antagonist activity, DXM and its metabolite dextrorphan are specific serotonin reuptake inhibitors. As a result, the acute DXM intoxication has been linked to a serotonin syndrome, especially if used together with remaining serotonergic agents (Linn et al., 2014) (Table 1).
Recently, the anti-diarrhoeal opiatergic compound loperamide has been reported for its euphoric effects (Lee et al., 2019;). At therapeutic dosages (2-

16mg/day), due to both rapid metabolism and poor blood–brain barrier penetration, it is considered safe. However, when self-administered at high dosages (e.g. >50mg), its μ-opioid receptors' agonist activities explain why 'lope', being anecdotally described as 'better than oxycodone', has been associated with euphoria, central nervous system depression, and fatal cardiotoxicity. Cytochrome inhibitors, such as cimetidine, omeprazole and grapefruit juice, as well as P-glycoprotein inhibitors, such as quinidine-quinine and pepper, may be concomitantly used to raise the drug blood levels (Baker, 2007; Schifano and Chiappini, 2018b) (Table 1).

Discussion

The present paper has provided an updated review of both the large number of NPS and their associated psychopathological consequences. In recent years, the large access to the web has led to a gradual, although partial, shift from a 'street' to a 'web' market (Corkery et al., 2017). Both the 'open' but also the 'deep web' and the 'dark net' (Orsolini et al., 2015), with their fora, blogs, social networks and chat rooms, are in a continuous development. These represent large-scale, international, shared platforms that facilitate the occurrence of confidential exchange of drug-related information, but which also directly/indirectly promote the acquisition of a range of new, emerging, and untested psychoactive substances (Schifano and Orsolini, 2015). This has facilitated the growth of a completely uncontrolled and 'quasi-legal' market for many psychoactive substances. The use of NPS is mostly self-experimental in nature, ad one could argue that the 'e-psychonauts' (Orsolini et al., 2015) are those who properly shape and influence current and possibly future drug scenarios. Indeed, the e-psychonauts seem to test, and at times synthesize, a range of drugs to achieve the state of consciousness they find most pleasurable (Orsolini et al., 2015). It is intriguing that, whilst navigating the online psychonauts' fora with NPS.Finder®, a few thousands NPS were here identified, a number which is about 4-fold higher than what identified by both the EMCDDA ([EMCDDA], 2018a) and the UNODC ([UNODC], 2018). Hence, it is here suggested that carrying out systematic web crawling activities may help in designing and developing a range of NPS-related early recognition and monitoring programmes. Further studies from our group will hopefully better identify: (a) which of the e-psychonauts' molecules will enter the future markets; and (b) which is the time gap, for an index NPS, between the start of the e-psychonauts' interest and the actual identification on the international drug scenarios.

The ever-increasing changes in terms of recreational psychoactives' availability represent a relatively new challenge for psychiatry. These molecules' intake may be risky, and the pharmacodynamics and pharmacokinetics of many NPS are still poorly understood (Schifano et al., 2016). Overall, the intake of these substances is typically associated with an imbalance of a range of neurotransmitter pathways/receptors, and consequently with the risk of psychopathological disturbances. The occurrence of psychopathological disturbances has been related here to the significant imbalance of a range of neurotransmitters/pathways: (a) increased central dopamine levels, mostly

associated with psychedelic phenethylamines and synthetic cathinones; (b) agonist/super agonist cannabinoid CB1 receptor activation, achieved with synthetic cannabimimetics; (c) 5-HT2A receptor activation, reported with latest tryptamine derivatives, DXM and hallucinogenic plants; (d) antagonist activity at NMDA receptors, described with phencyclidine-like dissociatives; and (e) k-opioid receptor activation, typically associated with Salvia divinorum intake. As NPS are presumably more often used in hedonistic and sporadic occasions, the acute physical and psychiatric complications are perhaps of special importance compared to the risk of addiction development observed with the traditional illicit psychoactive substances, which are more often used on a daily basis over an extended period of time.

It is difficult for mental health professionals to keep up-to-date with the growing number of NPS being made available. Clinicians are not always aware of the psychopathological risks relating to NPS intake, and, at the same time, they are not typically able to identify a potential NPS user (Simonato et al., 2013). This may be a reason for concern, especially for emergency mental health clinicians confronting with acute, and at times dramatic, clinical situations which are suspected of being drug-related but in which the standard urine specimen turns out to be negative. In fact, standard toxicity tests are able to identify just a few misused molecules and only expensive, lengthy, tests carried out in specialized settings are able to identify the vast range of NPS available (Smith et al., 2015). Hence, clinicians should be informed about the range of NPS; their intake modalities; their psychoactive sought-after effects; the idiosyncratic psychotropics' combinations; and finally, their psychopathological risks (Orsolini et al., 2015). Thus, further research studies should focus on drafting specific guidelines to better help clinicians in treating and managing the acute and long-term psychopathological consequences of NPS intake.

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Table 1: Main categories of Novel / New Psychoactive Substances (NPS) and their effects

SUBSTANCES	DESIRED EFFECTS	ADVERSE EFFECTS	
		Psychopathological symptoms	**Physical symptoms**
Synthetic cannabimimetics (SC)	Intense cannabis-like effects such as euphoric feelings and relaxation, associated with auditory/visual hallucinations	Acute: auditory/visual hallucinations, anxiety, intense feelings of paranoia, behavioural dyscontrol and agitation, mood swings, suicidal ideation, suicide attempts, panic attacks, thought disorganization, agitated/excited delirium, florid/acute transient psychosis, relapse/ worsening of a pre-existing psychosis, relapse of a pre-existing bipolar disorder. Chronic: persistent psychotic disorder, HPPD, 'Spiceophrenia'. SC use can give rise to dependence, tolerance and withdrawal (drug craving, feelings of emptiness/depression, anxiety, irritability, mood swings, and insomnia/nightmares).	Acute: Typical acute medical untoward effects include vomiting/nausea; hypertension and tachycardia; tachypnoea/ dyspnoea; hyperglycaemia; mydriasis, nystagmus; seizures, encephalopathy, coma; and stroke. Fatalities may occur. Chronic: Withdrawal symptoms may include diaphoresis, headache, tachycardia, tremor, diarrhoea, headache, insomnia.
New synthetic opioids (NSOs) (e.g., U-47700, U-49900, AH-7921, U-50488, U-51754, MT-45, acetylfentanyl, carfentanyl, furanylfentanyl)	Euphoria, sedation, feeling of relaxation, dissociating effects.	Acute: mood lift, dysphoric, dissociation, intense sedation, disorientation, confusion. Chronic: tolerance, addiction, withdrawal (similarly to the traditional opioid withdrawal, restlessness, agitation, insomnia).	Acute: Constipation, nausea, drowsiness, miosis, slurred speech, poor coordination, slowed breathing rate and respiratory depression, coma, death. Chronic: tolerance, addiction, withdrawal symptoms. Opioid toxicity effects, including death from overdose. Furthermore: damage of skin, blood vessels, bone and muscles surrounding the entry-point of the injection.
Desomorphine ('krokodil')	Morphine analogue with high potency due to high lipophilicity, fast onset of action, and short duration of effects. Euphoria, pleasure, relaxation.	Acute: mood lift, dysphoric mood and dissociation, sedation, disorientation, confusion. Chronic: tolerance, addiction, withdrawal (similarly to the traditional opioid withdrawal, restlessness, agitation, insomnia)	Acute: Constipation, nausea; risk of slowed breathing rate and respiratory depression, coma, death. Chronic: tolerance, addiction, withdrawal symptoms. Opioid toxicity effects, including death from overdose.
Mitragynine ('Kratom', 'kakuam', 'thang', 'ketum', 'biak')	In low doses, mild stimulant effects (euphoria, increased energy, relaxation)	At high dosages: sedative-narcotic effects, confusion.	Acute: severe nausea, vomiting, stomachache, and constipation associated with visual disturbances; death possible in combination with other substances and/or in association with underlying health conditions. Occasionally causes death on its own.

			Chronic: intrahepatic cholestasis and other liver disease, along with hypothyroidism; dependence and opioid-like withdrawal symptoms.
Salvinorin A (Salvia divinorum, hierba de Maria', 'Maria pastora', 'Sally-D', 'magic mint')	Potent hallucinogenic effects, with time distortion, vivid imagery; empathogenic effects.	Perceptual disturbances; psychosis; irritability; and anxiety, HPPD.	Deaths may occur as a result of the subject idiosyncratic behaviour.
Ketamine-like dissociatives			
Ketamine ('ket', 'special K', 'super K', 'kit-kat')	Dissociation, depersonalization, intense detachment and near-death experiences ('K-hole'), perceptual disorders, auditory and visual hallucinations.	Acute: anxiety, dissociation, depersonalization, perceptual distortions, auditory and visual hallucinations, flashbacks, 'K-hole'. Chronic: impairment of attention and recall, psychosis, perceptual disorders, HPPD, dependence can occur.	Acute: tachycardia, agitation, hypertension, nausea, slurred speech, dizziness, collapse. Accidental injury, risk of trauma, drowning, death from hypothermia and traffic accidents. Chronic: subtle visual anomaly, impairment of motor function, urological dysfunctions ('K-bladder'), rhabdomyolysis, intestinal symptoms ('K-cramps').
Phencyclidine (PCP, 'angel dust', 'supergrass', 'boat') and PCP-type substances (e.g., 3-MeO-PCE, 4-MeO-PCP)	Distorted perceptions of sight and sound, dissociation from the environment, out-of-body experiences, hallucinations.	Acute: cognitive changes, such as memory impairments, altered perception of time, slowness, anxiety, apathy, irritability, psychosis, stupor, coma, violent behaviour. Chronic: cognitive impairment, mood shifts, anxiety disorders, suicidal thoughts, dependence.	Acute: increase in breathing rate, elevated blood pressure, tachycardia, flushing and excessive sweating, nausea, vomiting, blurred vision, loss of balance, dizziness, kidney failure, seizures, cardiac arrest and cerebrovascular accidents. Chronic: dependence and withdrawal symptoms.
Methoxetamine ('mexxy', 'special M')	Relaxation, euphoria. Dissociative and sympathomimetic effects. More intense and longer lasting effects than ketamine ('M-hole': state of profound and long-lasting dissociation).	Acute: dissociation, hallucinations Chronic: neurocognitive deficits and deterioration in mood, perceptual distortions.	Acute: tachycardia, hypertension, cerebellar toxicity (loss of balance, slurred speech), seizures, nausea, vomiting, and diarrhoea, cardiac arrhythmias and blackouts; accidental deaths. Chronic: gastrointestinal symptoms (M-cramps), severe ulcerative cystitis and renal damage.
Novel Stimulants and novel psychedelics			
Synthetic cathinones (e.g., mephedrone, 'm-cat'; 'meow')	Stimulant (increased alertness, feeling 'high') effects, similar to amphetamine; euphoria, feeling of wellbeing and energy, feeling of self-confidence.	Acute: agitation, restlessness, anxiety, paranoid ideation, aggression and violence, insomnia. Chronic: insomnia, depression, anxiety, paranoid ideation,	Acute: tachycardia, hypertension, hyperthermia, anorexia, dizziness, headache, angina pectoris, myocarditis, abdominal pain, rhabdomyolysis, convulsions and death. Chronic: hypertension, tachycardia, kidney damage and failure, liver damage,

		psychosis, dependence and addiction.	muscle tissue damage, brain tissue damage
Psychedelic/empathogenic phenethylamines (e.g., 2C series; D series, such as DOI, DOC; benzodifurans, such as 'bromodragonfly'; others, such as PMA/PMMA)	Dose-dependent effects, ranging from mere stimulant effects (energy, euphoria, increased locomotor activity, talkativeness, disinhibition, alertness, sexual arousal) at low doses and psychedelic (hallucinations and dissociation) and/or empathogenic effects at higher dosages.	Acute: dysphoria, hallucinations. Chronic: cognitive impairment, depression, increased suicide risk.	Acute: hypertension, vomiting, hyperthermia, convulsions, hyponatraemia, anorexia, mydriasis, tachycardia, serotonin syndrome, collapse, dizziness, hallucinations, headache, sweating, delayed orgasm, erectile dysfunction, respiratory deficits, liver and kidney failure, and death Chronic: cognitive impairment, neurotoxicity.
Piperazines (e.g., BZP, mCPP, 'party pills', 'smileys')	Euphoric effects similar to amphetamines; hallucinogenic effects at higher doses.	Dissociation, perceptual distortion.	Hyperthermia, rhabdomyolysis, convulsions, serotonin syndrome and kidney failure; death has been reported at high doses.
Tryptamines (e.g., DMT, 5-MeO-DMT, 'magic mushrooms')	Mild stimulation, euphoria, intensified sensual or sexual feelings, visual hallucinations, alteration in sensory perception, depersonalization.	Acute: dysphoria, panic, paranoid feelings. Chronic: flashbacks, HPPD, dependence (rare).	Acute: agitation, tremor, tachycardia, hyperthermia, restlessness, gastrointestinal distress, muscle tension, rhabdomyolysis. Fatalities possible.
Prescription drugs with a misusing potential			
1. ANTIDEPRESSANTS:			
Bupropion	'High' similar to cocaine abuse at high dosages, but of lesser intensity.	Agitation, dysphoria, irritability, hallucinations	Tremor, agitation, vomiting, tachycardia, cardiac toxicity, hallucinations, seizures, death.
Amitriptyline	Pleasant feelings, sociability and euphoria at high dosages.	High dosages: Agitation, dysphoria	Tachycardia and cardiac conduction changes; nausea, vomiting, dry mouth, difficulty urinating, blurred vision, confusion, dizziness, dissociation, seizures, coma, death.
Venlafaxine ('baby ecstasy')	MDMA/amphetamine-like stimulant and psychedelic effects at high dosages.	Acute: Agitation, dysphoria, irritability Chronic: withdrawal symptoms, such as, depression, irritability, insomnia, suicidal thoughts, disorientation, panic attacks, and psychotic symptoms.	Acute: autonomic hyperactivity, tachycardia, hypertension, chest pain Chronic: if abruptly stopped, withdrawal symptoms, such as: nausea, tremors, insomnia, stomach cramps, sexual dysfunction, and headache can occur
2. ANTIPSYCHOTICS:			
Quetiapine ('Susie Q', 'Quell', and 'baby heroin'); 'Q ball' (quetiapine with cocaine); 'MaQ ball' (quetiapine and marijuana).	Intense sedation; euphoria.	Acute: sedation, perceptual distortion Chronic: withdrawal symptoms may occur if high-dosage/long-term intake abruptly stopped;	Acute: drowsiness, lethargy, hypotension, tachycardia, coma, respiratory depression, seizure, and death. Chronic: weight gain, increased risk of heart disease;

		agitation, anxiety, difficulty with concentration, insomnia, mood swings, psychotic symptoms, and suicidal thoughts or behavior can occur as a result.	withdrawal syndrome physical signs/symptoms may include nausea and vomiting, agitation, dizziness, irregular heartbeat, headache.
Olanzapine ('Lilly')	Relaxing and sedating effects; being anecdotally considered the 'ideal trip terminator' after a psychedelic drug binge or as a self-treatment of unwanted 'comedown' symptoms (depression, dysphoria, anxiety, and insomnia) from drug/alcohol intake.	Acute: relaxation, sedation Chronic: discontinuation symptoms after long-term usage: anxiety, dysphoria, insomnia.	Acute: drowsiness, slurred speech, confusion. Chronic: discontinuation symptoms after long-term usage, including irritability, dysphoria, insomnia, and nervousness.
3. GABAPENTINOIDS (pregabalin and gabapentin)	Abuse of high doses may cause: euphoria, improved sociability, opiate-like sedation, entactogenic feelings/dissociation, and psychedelic effects. Pregabalin action is more potent, with faster onset and greater bioavailability compared with gabapentin, hence characterized by potentially higher misusing potential.	Acute: anxiety; irritability, sedation, seizures. Chronic: dependence and withdrawal symptoms, suicidal behaviour.	Acute: clinical scenario similar to alcohol intoxication, with profound sedation and coma. Deaths may occur. Chronic: Gabapentinoid withdrawal syndrome may include insomnia; headache; nausea; and convulsions.
4. Z-DRUGS (zaleplon, zolpidem and zopiclone)	High dosages are associated with intense stimulating effects, hyperactivity and euphoria (>>>zopiclone).	Sedation	Withdrawal symptoms may include: insomnia, anxiety, irritability, tremor, restlessness, speech difficulties, abdominal pain, hypertension, tonic-clonic seizures, confusion/disorientation.
DESIGNER BENZODIAZEPINES (e.g., clonazolam, etizolam, flubromazepam, phenazepam ('Zinnie') and pyrazolam	Sedative, anxiolytic, hypnotic properties. May be ingested as 'self-medication' by users of stimulant and hallucinogenic drugs.	Sedation	Acute: drowsiness, confusion, unsteady walking, slurred speech, blurred vision, poor concentration, dizziness, amnesia, disorientation, sedation, slowed breathing, death. Chronic: impaired cognition, physiological and mental health sequelae consistent with traditional benzodiazepines; addiction and withdrawal symptoms, including seizures.

5. OVER-THE-COUNTER DRUGS:			
Codeine ('Purple drank' is a mix of codeine and promethazine)	Calming and euphoric effects.	Acute: Mood swings, irritability, anxiety, apathy, memory loss, delusions and hallucinations. Chronic: tolerance, withdrawal and dependence, typically developing as with other opioids	Acute: Sedation, drowsiness, dizziness, nausea and vomiting, decreased libido, constipation, seizures, and respiratory depression. Chronic: tolerance, withdrawal and dependence, typically developing as with other opioids
Loperamide	Euphoria ('Lope highs'), can occur after consuming large/very large dosages; may be used to alleviate opiate/opioid withdrawal (the 'poor man methadone').	Acute: sedation Chronic: addiction. As with traditional abused opioids, withdrawal symptoms, include anxiety, restlessness, depression, agitation.	Acute: unconsciousness, constipation, kidneys or liver dysfunction, respiratory depression, urinary retention, CNS depression and fatal cardiotoxicity, with high/very high QTc levels. Chronic: addiction. Similarly to other opioids, withdrawal symptoms include nausea, muscle cramps, excessive sweating, opioid cravings.
Dextromethorphan (DXM)	Dose-related effects, with trance-like euphoria or stupor, hyperexcitability, and vivid auditory/visual hallucinations; ketamine-like dissociative state ('robo-ing', 'robo-copping', or 'robo-tripping') possible.	Acute: dizziness, altered mental status, delayed response times, disordered speech, depersonalization, and dissociation. Chronic: psychosis, HPPD, tolerance and dependence. Withdrawal symptoms may include intense cravings, anxiety, panic attacks, irritability, insomnia and nightmares, memory issues, flashbacks.	Acute: nausea, vomiting, dyskinesia, seizures, liver failure, hyperthermia, respiratory depression, coma. The acute intoxication has been linked to the serotonin syndrome, especially if used together with molecules acting on the serotoninergic neurotransmission. Chronic: withdrawal syndrome may develop after a long-term use of high doses of DXM, and may consist of craving, fatigue, diaphoresis, nausea, hypertension, and tachycardia, gastrointestinal distress (vomiting, diarrhoea), insomnia.

DXM: Dextromethorphan, SC: Synthetic Cannabinoids, HPPD: Hallucinogen-Persisting Perception Disorder