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New/emerging psychoactive substances and associated psychopathological consequences‡

F. Schifano[1], F. Napoletano[2], S. Chiappini[1], A. Guirguis[3], J. M. Corkery[1], S. Bonaccorso[4], A. Ricciardi[4,5], N. Scherbaum[6] and A. Vento[7,8,9]

[1]Psychopharmacology, Drug Misuse, and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, UK; [2]Homerton University Hospital, London, UK; [3]Swansea University Medical School, Institute of Life Sciences 2, Swansea University, Singleton Park, Swansea, Wales; [4]Camden and Islington NHS Mental Health Foundation Trust, London, UK; [5]Department of Mental Health, ASL Roma 1, Rome, Italy; [6]LVR-Klinikum Essen, Klinik für Psychiatrie und Psychotherapie, University of Duisburg-Essen, Essen, Germany; [7]Addictions' Observatory (ODDPSS), Rome, Italy; [8]'Guglielmo Marconi' University, Rome, Italy and [9]Department of Mental Health, ASL Roma 2, Rome, Italy

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 thousand 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 represent 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.

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.*, 2018*a*). 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*a*; 2018*b*). In the EU, by the end of 2017 the number of NPS was over 670, of which 632 were notified after 2004 (EMCDDA, 2018); 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.

Invited Review

‡The original version of this article was submitted with an incorrect author affiliation. A notice detailing this has been published and the error rectified in the online PDF and HTML copies.

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Author for correspondence:
Stefania Chiappini, E-mail: stefaniachiappini9@gmail.com

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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, 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®', 2019) 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 26 November 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 analysed by NPS.Finder® (2019) 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 4204 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 (Winstock and Barratt, 2013*a*; Wessinger *et al.*, 2015; Bonaccorso *et al.*, 2018). 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) (Table 1).

The intoxication/acute toxic effects of SCs appear to be more akin to those experienced with sympathomimetic/stimulant drug use (Wood and Dargan, 2012; Naviglio *et al.*, 2015). Typical medical untoward effects include: vomiting/nausea; hypertension and tachycardia; tachypnoea/dyspnoea; hyperglycaemia; mydriasis (Hermanns-Clausen *et al.*, 2013; Winstock and Barratt, 2013*b*; Schifano *et al.*, 2015); nystagmus; seizures (Hopkins and Gilchrist, 2013); encephalopathy (Louh and Freeman, 2014); coma and stroke (Mir *et al.*, 2011; Freeman *et al.*, 2013; Rose *et al.*, 2015). Ultimately, deaths have been associated with the use of synthetic cannabinoids, either on their own or in combination (Corkery *et al.*, 2014; Tait *et al.*, 2015; Trecki *et al.*, 2015; Angerer *et al.*, 2017; Maeda *et al.*, 2018; Olsen, 2018; Paul *et al.*, 2018). These may result from direct lethality of the molecule; behavioural dyscontrol or suicide (Rosenbaum

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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 disorganisation, agitated/excited delirium, florid/acute transient psychosis, relapse/ worsening of a pre-existing psychosis, relapse of a pre-existing bipolar disorder.	*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: 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).	*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.	*Acute*: Constipation, nausea, drowsiness, miosis, slurred speech, poor coordination, slowed breathing rate and respiratory depression, coma, death.
		Chronic: tolerance, addiction, withdrawal (similarly to the traditional opioid withdrawal, restlessness, agitation, insomnia).	*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.	*Acute*: Constipation, nausea; risk of slowed breathing rate and respiratory depression, coma, death.
		Chronic: tolerance, addiction, withdrawal (similarly to the traditional opioid withdrawal, restlessness, agitation, insomnia)	*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, depersonalisation, intense detachment and near-death experiences ('K-hole'), perceptual disorders, auditory and visual hallucinations.	*Acute*: anxiety, dissociation, depersonalisation, perceptual distortions, auditory and visual hallucinations, flashbacks, 'K-hole'.	*Acute*: tachycardia, agitation, hypertension, nausea, slurred speech, dizziness, collapse. Accidental injury, risk of trauma, drowning, death from hypothermia and traffic accidents.

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Table 1. (*Continued.*)

Substances	Desired effects	Adverse effects	
		Psychopathological symptoms	Physical symptoms
		Chronic: impairment of attention and recall, psychosis, perceptual disorders, HPPD, dependence can occur.	*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.	*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: cognitive impairment, mood shifts, anxiety disorders, suicidal thoughts, dependence.	*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	*Acute*: tachycardia, hypertension, cerebellar toxicity (loss of balance, slurred speech), seizures, nausea, vomiting and diarrhoea, cardiac arrhythmias and blackouts; accidental deaths.
		Chronic: neurocognitive deficits and deterioration in mood, perceptual distortions.	*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.	*Acute*: tachycardia, hypertension, hyperthermia, anorexia, dizziness, headache, angina pectoris, myocarditis, abdominal pain, rhabdomyolysis, convulsions and death.
		Chronic: insomnia, depression, anxiety, paranoid ideation, psychosis, dependence and addiction.	*Chronic*: hypertension, tachycardia, kidney damage and failure, liver damage, 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.	*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, depression, increased suicide risk.	*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, depersonalisation.	*Acute*: dysphoria, panic, paranoid feelings. *Chronic*: flashbacks, HPPD, dependence (rare).	*Acute*: agitation, tremor, tachycardia, hyperthermia, restlessness, gastrointestinal distress, muscle tension, rhabdomyolysis. Fatalities possible.

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Table 1. (*Continued.*)

Substances	Desired effects	Adverse effects	
		Psychopathological symptoms	Physical symptoms
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	*Acute*: autonomic hyperactivity, tachycardia, hypertension, chest pain
		Chronic: withdrawal symptoms, such as, depression, irritability, insomnia, suicidal thoughts, disorientation, panic attacks and psychotic symptoms.	*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	*Acute*: drowsiness, lethargy, hypotension, tachycardia, coma, respiratory depression, seizure and death.
		Chronic: withdrawal symptoms may occur if high-dosage/long-term intake abruptly stopped; agitation, anxiety, difficulty with concentration, insomnia, mood swings, psychotic symptoms, and suicidal thoughts or behaviour can occur as a result.	*Chronic*: weight gain, increased risk of heart disease; 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	*Acute*: drowsiness, slurred speech, confusion.
		Chronic: discontinuation symptoms after long-term usage: anxiety, dysphoria, insomnia.	*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 characterised by potentially higher misusing potential.	*Acute*: anxiety; irritability, sedation, seizures.	*Acute*: clinical scenario similar to alcohol intoxication, with profound sedation and coma. Deaths may occur.
		Chronic: dependence and withdrawal symptoms, suicidal behaviour.	*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.

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Table 1. (*Continued.*)

Substances	Desired effects	Adverse effects	
		Psychopathological symptoms	Physical symptoms
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.	*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	*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	*Acute*: unconsciousness, constipation, kidneys or liver dysfunction, respiratory depression, urinary retention, CNS depression and fatal cardiotoxicity, with high/very high QTc levels.
		Chronic: addiction. As with traditional abused opioids, withdrawal symptoms, including anxiety, restlessness, depression, agitation.	*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, depersonalisation and dissociation.	*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: psychosis, HPPD, tolerance and dependence. Withdrawal symptoms may include intense cravings, anxiety, panic attacks, irritability, insomnia and nightmares, memory issues, flashbacks.	*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.

et al., 2012; Shanks *et al.*, 2012; Patton *et al.*, 2013; Lászik *et al.*, 2015) (Table 1).

Finally, SC long-term use can give rise to dependence/tolerance phenomena (Gunderson *et al.*, 2012; Spaderna *et al.*, 2013); a withdrawal syndrome, characterised 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) (Table 1).

New synthetic opioids (NSOs)

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

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and receptor affinity, with respect to morphine (Tracy *et al.*, 2017; Marchei *et al.*, 2018; Solimini *et al.*, 2018). This group includes compounds which were originally synthesised 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.*, 2017; Suzuki and El-Haddad, 2017; Marchei *et al.*, 2018). These molecules may be used alone; as adulterants in heroin; or as constituents of other illicit products or counterfeit medications (Prekupec *et al.*, 2017; Abdulrahim *et al.*, 2018).

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, depersonalisation 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, derealisation and depersonalisation (Wallach *et al.*, 2016; Tracy *et al.*, 2017) (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; Winstock, 2010; Winstock *et al.*, 2011; Freeman *et al.*, 2012; Prosser and Nelson, 2012; Karila *et al.*, 2015, 2016; De Sousa Fernandes Perna *et al.*, 2016), 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 (Kehr *et al.*, 2011; Capriola, 2013; Herzig *et al.*, 2013; John *et al.*, 2017; Lovrecic and Lovrecic, 2017; Homman *et al.*, 2018; Kaizer-Będkowska and Kucia, 2018). Users reported as well positive effects e.g. euphoria, improved

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psychomotor speed, alertness and talkativeness (Dargan *et al.*, 2010; Cheng *et al.*, 2012; 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 (Otachbachi *et al.*, 2010; Penders and Gestring, 2011; Mugele *et al.*, 2012; Penders *et al.*, 2012; Warrick *et al.*, 2013; Hohmann *et al.*, 2014; Denysenko *et al.*, 2015; Weaver *et al.*, 2015). Other acute intoxication issues included dehydration, hypertension, tachycardia, kidney and liver impairment, electrolyte imbalance, metabolic toxicity, cerebral oedema and death (Borek and Holstege, 2012; Adebamiro and Perazella, 2013; Imam *et al.*, 2013). Suicides by hanging and deaths from firearm injuries have frequently been reported (Marinetti and Antonides, 2013; Barrios *et al.*, 2016), as well as deaths from toxicity (Corkery *et al.*, 2018*b*). Although the 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-Methylenedioxymethamphetamine (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 of visual hallucinations, alterations in sensory perception, distortion of body image, depersonalisation, 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, 2018).

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, 2018*a*) and, being a cathinone derivative, presents with stimulant activities (Evans and Sullivan, 2014; Baumeister *et al.*, 2015). 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, 2018*a*) (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. 400–4000 mg/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 characterised by nausea, depression, suicidal thoughts, disorientation, stomach cramps, panic attacks, sexual dysfunction, headache and occasional psychotic symptoms may develop (Table 1).

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 hypothesised (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 (Klein *et al.*, 2017; Chiappini and Schifano, 2018) (Table 1).

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

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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 (Chiappini and Schifano, 2016; Al-Husseini *et al.*, 2018). 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).

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 h) 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*a*; 2018*b*) (Table 1).

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 recognised issue (Schifano and Chiappini, 2018*b*). OTC misuse may have developed due to their increased availability, affordability and users' perceptions of 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, depersonalisation, dyskinesia, delayed response times, disordered speech and vivid auditory/visual hallucinations (Romanelli and Smith, 2009). 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 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 (2–16 mg/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. >50 mg), 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, 2018*b*) (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 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 *et al.*, 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 synthesise, 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® (2019), a few thousand NPS were here identified, a number which is

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about 4-fold higher than what identified by both the EMCDDA (EMCDDA, 2018) and the UNODC (UNODC, 2018*a*; 2018*b*). 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 can identify just a few misused molecules and only expensive, lengthy, tests carried out in specialised 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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