Novel psychoactive substances (NPS): clinical and pharmacological issues

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Abstract

Purpose – *The purpose of this paper is to provide health professionals with novel psychoactive substances (NPS) clients with up to date information relating to the background, clinical pharmacology and, when possible, clinical management for each of these categories.*

Design/methodology/approach – *The world of NPS is complex and diverse, including a range of different molecules such as: psychedelic phenethylamines; synthetic cannabinoids, cathinone derivatives; novel stimulants; synthetic opiates/opioids; tryptamine derivatives; phencyclidine-like dissociatives; piperazines; GABA-A/GABA-B receptor agonists; a range of prescribing medications; psychactive plants/herbs; and a large series of performance and image-enhancing drugs. These molecules are sought by users for their psychactive effects.*

Findings – *The NPS categorization and classification provided here is an attempt to identify and better understand some of these substances. Given the vast range of medical and psychopathological issues associated with the NPS described it is crucial for health professionals to be aware of the effects and toxicity of NPS. The EU-MADNESS project aims to both better understand the pharmacology of the available/ forthcoming NPS and to disseminate the most current NPS-related information to practising and training health professionals.*

Research limitations/implications – *Further studies are required to identify a range of evidence-based, NPS-focused, clinical management and treatment strategies.*

Social implications – *The rapid pace of change in the NPS online market constitutes a major challenge to the provision of current and reliable scientific knowledge on these substances.*

Originality/value – *The present review will provide an overview of the clinical and pharmacological issues related to a few hundred NPS.*

Keywords *Categories and classification, Clinical issues, Novel psychoactive substances, Pharmacological issues, Synthetic substances, Training for health professionals*

Paper type *Research paper*

Introduction

The present paper will provide an overview of the clinical and pharmacological issues related to a few hundred novel psychoactive substances (NPS: Deluca *et al.*, 2012), grouped here for convenience in a range of categories (Schifano *et al.*, 2015), starting with the psychedelic phenethylamines' group (Schifano *et al.*, 2010; Schifano, 2011; Winstock and Schifano, 2009; Bersani *et al.*, 2014; Corazza *et al.*, 2011):

- in total, 179 "classical" PIA/phenethylamines/MDMA-like drugs; amphetamine-type substances (fluoroamphetamine, PMA, 2C-T, 2C-B, etc.);
- a dozen latest generation PIA derivatives: "Bromodragonfly"; NBOMe derivatives; indanes; benzofurans (5; 6-APB/APDB; 5-EAPB; 5-MAPB); "BenzoFury"; etc.; and
- in total, 126 psychedelic phenethylamines/stimulants from the Shulgin Index (Shulgin *et al.*, 2011); about 1,300 molecules being covered; including DMAA, etc.

MDMA/ecstasy misuse started at the end of the 1980s and steadily increased throughout the 1990s. The stimulant empathogenic (feelings of being closer to others) and entactogenic

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(improvement of one's own introspectiveness) properties of the molecule mean it is well-known on the club scene, in part because it allows consumers to dance frenetically for several hours. Consumers of ecstasy and related molecules typically only ask for help from specialized units, such as Accident & Emergency departments or Mental Health teams, when they show acute physical or psychiatric problems.

From the pharmacological point of view, MDMA is a 3,4-methylenedioxymethamphetamine, a molecule which shows similarities to both amphetamine, which has pure stimulant effects, and mescaline, a hallucinogenic drug. In 10 per cent of chronic ecstasy consumption cases, clear clinical pictures of dependency are observed. Following acute self-administration, different somatic sequelae have been described, including: tachycardia, hyperthermia, asystole, hypertension, metabolic acidosis, cerebral haemorrhages, convulsions, coma, rhabdomyolisis, midriasis, vomit, diarrhoea, thrombocytopoenia and acute renal failure. Hyperthermia can occur due to MDMA itself; the crowded environments; and intense physical activity in which clubbers are involved.

MDMA is only one of the different products which are derived from phenylethylamine. Others include: MDA (methylenedioxyamphetamine; "love drug", the parental compound of MDMA); MDEA (methylenedioxyethamphetamine; "Eve", which has effects similar to those of MDMA); MBDB (phenylbutanamine, "TNT"); 2-CB/"Nexus"; BOD (4-methyl-2,5,b-trimethoxyphenyl ethylamine); DOB; 4-MTA (4-methyltioamphetamine/"flatliners", a drug which has been responsible for at least four deaths in the UK; Corkery *et al.*, 2014).

Other very popular molecules include (Papanti *et al.*, 2013, 2014):

- Approximately 200 synthetic cannabimimetics ("spice"; "K2"; "Bonzai", etc.); including: AM-2201; AM-2233; AKB-48F; 5F-AB-PINACA; 5F-AKB-48; 5F-AMB; 5F-MN-18; 5F-PB22; 5F-SDB-005; 5F-SDB-006; AB-CHIMINACA; AB-FUBINACA; AB-PINACA; BB-22; EG-018; FAB-144; FDU-PB22; FUB-PB22; NM-2201; PB-22; THJ-018; THJ-2201, etc.

Synthetic cannabimimetics (SC; also called "synthetic cannabinoids")-based designer drugs are used as a legal alternative to cannabis for their very strong tetrahydrocannabinol (THC)-like effects. "Spice" has become a generic term to describe synthetic cannabinoids, possibly because this was in fact a brand name of an early SC blend. Spice are composed of a dried vegetal matrix, which mimics the "grass effect" of dried marijuana buds, and a mix of SC which is sprayed onto it. These drugs are primarily smoked, either in joints or using related paraphernalia such as "hookahs" or "bong" water pipes. The market for these drugs is global, with Spice available to purchase for either wholesale or retail purposes. Spice is usually labelled as "not for human consumption" to circumvent food, drug and medicine safety laws, with compounds frequently not listed on the packaging.

A range of SC compounds are typically identified within any given Spice batch. Even batches of the same brand can have a different composition and varying concentrations of SC in the mixture itself. SC show binding affinities between five and 10,000 times higher than THC for CB-rs. SC compounds are full agonists on the CB-rs, whilst THC is only a partial agonist. Hence, SC are more potent and possess higher dose-response efficacy levels than THC itself.

Several SC-metabolites retain high binding affinity and activity levels on CB-rs, while cannabis has just the one, less active, THC metabolite. As a consequence, this CB-rs' activation may be high enough to produce more severe physiological and psychological disturbances when compared to THC. Acute SC intoxication is usually characterized by elevated heart rate/blood pressure levels; visual/auditory hallucinations; mydriasis; agitation/anxiety; hyperglycaemia; hypokalaemia; dyspnoea/tachypnoea; nausea/vomiting; and seizures. Interestingly, nausea and seizures are very uncommon in marijuana misusers, which, it has been suggested, is due to the anticonvulsivant/antiemetic properties of cannabis.

Further popular molecules include (Corkery *et al.*, 2011, 2012; Loi *et al.*, in press; Schifano *et al.*, 2012):

- Approximately 30 synthetic cathinones; including: mephedrone "meow"; methedrone; methylone; 3-MeOMC; 3-MMC; 4-BMC; 4-MEC; 4-MeO-a-PVP; 4-MeO-PBP; 4-MeO-PV9; 4-MPD; 4F-PV8; 4F-PV9; 4F-PVP; a-PBT; a-PHP; a-PVT; Dibutylone; DL-4662; Ethylone; MDPPP; MOPPP; NEB; Pentedrone; PV-8 (crystals), etc.

All of these compounds are chemically similar to Khat/Catha Edulis, which is ingested by chewing the leaves. The psychostimulant effect of Khat can be accounted for by the mechanism of cathinone, which is considered to be its main active ingredient. Cathinones and derivatives stimulate the central nervous system, causing increased alertness, euphoria, occasional psychosis, and increased activity in the peripheral sympathetic nervous system leading to palpitations, increased blood pressure, dilated pupils and red eyes. Its acute effects include: abdominal pain, flushing, sweating (alternating with chills), tachycardia, restlessness and anxiety. Affective disturbances and paranoid ideation have been observed in some chronic users.

Other compounds possess a pharmacodynamic action comparable to that of amphetamine-type stimulants (ATS; Schifano *et al.*, 2010) and include:

- Novel stimulants; aminorex derivatives; 4,4-DMAR; diclofensine; methiopropamine.

Methamphetamine is frequently known as "speed", "meth" and "choke", and in its smokable form as "ice", "crystal", "crank" and "glass". After cannabis, ATS may be the most commonly used illegal substances worldwide. For recreational use, ATS can be swallowed, snorted, smoked, dissolved in water and injected. Similarly to cocaine, the clinical picture of stimulant intoxication is characterized by a sort of binge and crash cycle. Clinically, one can observe hyperactivity, anorexia and an increase in neurological arousal. The rush is the consequence of dopamine release from the pre-synaptic neurons in the mesolimbic dopaminergic system. High dosages can result in the occurrence of hyperthermia, convulsions and possibly death.

The most frequent psychopathological consequences of ATS ingestion include: violent and bizarre behaviour, anxiety, confusion, sleep disorders, psychotic disorders (paranoid type), aggression and tactile hallucinations (the sensation of having insects under the skin). Psychotic symptoms can persist for a long time after the consumer has stopped using the drug. Withdrawal symptoms include depression, anxiety, strong cravings and exhaustion. ATS use can be associated with a number of cardiovascular problems, and approximately 22 fatalities have been observed in the last couple of years in the UK following 4,4-DMAR/"serotoni" ingestion (Brandt *et al.*, 2014).

Over the last year or so, increasing reports of the following drug categories have been reported (Helander *et al.*, 2014):

- a few synthetic opiate/opioids, such as 4-fluorbutyrfentanyl; IC-26; MT-45; AH-7921; nortilidine; W15; W18, etc.; and
- three synthetic cocaine substitutes: RTI 111; RTI 121; RTI 126.

Furthermore, an increased interest in a range of hallucinogenic drugs has been recorded, with the most popular molecules including (Schifano, 2011):

- A few dozenstryptamine classical derivatives and five tryptamine derivatives such as 5-Meo-DALT; AMT; 5-Meo-AMT, etc.

Dymethyltryptamine (DMT) was first chemically synthesized in 1931, however it also occurs naturally in many species of plants which are used in South American shamanic practices. DMT has strong psychedelic properties, producing effects similar to those of LSD. Since DMT is inactive after oral administration, it must be injected, snorted, or smoked. It can produce powerful entheogenic (literally "God within", e.g. closeness to God) experiences, intense visual hallucinations and euphoria. If DMT is smoked, peak effects last for a short period of time (five to 30 minutes). The onset after inhalation is very fast (less than 45 seconds) and peak effects are reached within about a minute.

In some areas of London, the most popular recreational psychoactives may include GHB and remaining GABA-ergic molecules, such as (Schifano, 2011):

- A fewGABA-A/GABA-B receptor agonists: GHB-like drugs (GHB; Gamma-Butyrolactone (GBL); 1,4-BD); baclofen; phenibut; magnolols.

Since 1990, GHB use has been widespread in the USA due to its euphorising, sedative and anabolic properties (of which the latter is much vaunted by body builders). GHB is usually found

in the liquid form; however it is also possible to find GHB as a powder or in some tablets. The drug was initially developed as an anaesthetic but has also been used to treat narcolepsy and alcohol withdrawal. It can be produced in clandestine laboratories using a relatively simple synthesis, with readily available and inexpensive source materials.

GBL is an industrial chemical that is used in the illicit manufacture of GHB. GBL and 1,4-butanediol, another industrial chemical, are also used for their GHB-like effects. After ingestion, an increase in central dopamine levels has been recorded in users. Generally, the psychoactive properties of the molecule are observed ten to 20 minutes after administration, and last for about one to three hours (although its half-life is very short). Various hangover effects have been observed afterwards. Taken in small doses it lowers inhibition and induces feelings of calmness and euphoria. Higher dosages can cause severe drowsiness, whilst a dosage in excess of five grams can lead to a coma and a dosage higher than two grams per kilogram can result in death.

Tolerance to GHB and physical dependence may develop with chronic use. GHB withdrawal syndrome (which lasts for three to12 days and usually fades away without sequelae) is characterized by insomnia, muscular cramps, tremor and anxiety. Acute intoxication, which is more profound if the drug is taken together with other sedatives, includes vomit, profound sedation, dreamy states, muscular hypotonia, dizziness, respiratory distress and myoclonus.

Another class of NPS which is both popular and a cause for clinical concern includes the PCP/phencyclidine derivatives (Chiappini *et al.*, in press; Corazza and Schifano, 2010; Schifano *et al.*, 2008):

- A dozen of PCP-like drugs: PCP; ketamine; methoxetamine; PCE; 3-MeO-PCP; ethylketamine; 3-HO-PCP; 4-MeO-PCP; diphenidine; ; methoxyphenidine.

Phencyclidine was developed in the 1950s during a research programme targeting general anaesthetics. Patients anesthetized with PCP did not manifest the depression of vital cardiovascular and respiratory functions typical of classical general anaesthetic agents. Without overt loss of consciousness, patients were sharply dissociated from the environment. For this reason, PCP and related compounds were classified as “dissociative anaesthetics”. At the moment, PCP use has been reported only occasionally in Europe. Its clinical effects can vary according to the dosage: with a small dosage, derealization, slurred speech, motor incoordination, gait disturbances, sensations of strength/invulnerability and nystagmus can be observed. Visual and perceptual disturbances, affective disturbances, schizophrenia-like episodes, amnesia, serious episodes of violence and impulsivity have also been reported. The modification of the illicit chemical production can lead to the synthesis of drugs which are analogous to PCP itself, so that similar clinical and toxicological consequences can be observed.

Ketamine, also known as “special-K” or “K”, is in widespread use in a range of European countries, including the UK, Italy, France and Germany, often during illicit rave parties. Ketamine is usually diverted from the veterinarian market, since the product is used for surgical intervention in cats and dogs. When used in this way, ketamine can be injected, sniffed or smoked. Generally, the liquid itself is heated and the powder which results from this process is then snorted. Ketamine can be smoked in combination with marijuana or, in its liquid form, can be injected intravenously. At low doses, stimulant effects predominate. At higher doses, ketamine’s psychotropic effects range from referential thinking, dissociation and depersonalization to psychotic experiences, and include a sensation of feeling light, body distortion, absence of time sense, novel experiences of cosmic oneness and out-of-body experiences, often called the “K-hole”.

In long-term exposure, tolerance, dependence, withdrawal signs and flashbacks are described. Schizotypal symptoms and perceptual distortions may persist after cessation of ketamine use. Due to its sympathomimetic activity, it causes mild stimulation of the cardiovascular system, pupil dilation and bronchodilation and does not suppress respiration or gag reflex. Conversely, administration of the drug in high doses can cause cardiovascular and respiratory toxicity. Recreational ketamine users may experience numbness of the limbs, analgesia, change in body temperature and vomiting. Difficulty with balance, combined with numbness, muscle weakness

and impaired perception can result in falls, trauma or burns. Risks from the setting have also included drowning, death by hypothermia from lying outside in winter, traffic accidents and becoming a victim of crime. With chronic ketamine ingestion, both urological (k bladder) and intestinal ("k cramps") problems have been reported (Middela and Pearce, 2011).

Piperazines, including:

- A few piperazines: BZP; TFMPP.

May act as weak amphetamine-type substances, and especially in the past BZP was included in "fake" ecstasy/MDMA tablets.

Increasingly popular nowadays are a number of plants and herbs, including:

- Herbs/plants: *Salvia divinorum*; *Mytragina speciosa/kratom*; *Tabernanthe iboga/ibogaine*; *Kava Kava*; *Psychotria viridis/Ayahuasca*; *hydrangea*; *Rhodiola rosea*; *Datura stramonium*; etc.
- In youth culture, a number of different herbal products (the so-called "ecological" drugs) are becoming increasingly popular. These compounds can be purchased quickly and conveniently from dedicated web sites. "Ayahuasca" contains both DMT and beta carbolines. DMT has strong psychedelic properties, producing effects similar to those of LSD. DMT, which is broken down by the digestive enzyme monoamine oxidase, is practically inactive if taken orally, unless combined with a monoamine oxidase inhibitor/MAOI, such as beta carbolines. Taken orally with an appropriate MAOI, DMT produces a long lasting (over three hours), slow and intense psychedelic experience.

Recently there has been increasing concern, both in the UK and in the EU, about the misuse of a range of medicinal products, including (Schifano *et al.*, 2011; Schifano, 2014):

- A number of medicinal products: tramadol, oxycodone, and remaining opiates/opiods; anticonvulsants (gabapentin and pregabalin); antiseptics (benzydamine); DXM; benzodiazepines/sedatives (phenazepam "Zinnie"; methaqualone; diclazepam; etizolam flubromazepam); stimulants (ethylphenidate; camfetamine); antiparkinsonian/anticholinergics: selegiline; tropicamide); chloroquine; antiretrovirals/"whoonga"; xylazine.

Gabapentinoids (e.g. pregabalin and gabapentin) are widely used in neurology and psychiatry, but are increasingly being reported as having a potential for misuse. Potent binding of pregabalin/gabapentin at the calcium channel results in a reduction in the release of excitatory molecules. Furthermore, gabapentinoids are thought to possess GABA-mimetic properties whilst possibly leading to direct/indirect effects on the dopaminergic "reward" system. Overall, pregabalin is characterized by higher potency, quicker absorption rates, and greater bioavailability levels than gabapentin.

Although at therapeutic dosages gabapentinoids may present with low addictive liability levels, the perception amongst misusers that these molecules constitute a valid substitute for most common illicit drugs may be a cause for concern. Typical gabapentinoids users are individuals with a history of recreational polydrug misuse, who self-administer with dosages clearly in excess (e.g. up to three to 20 times) of those which are clinically advisable.

Finally, there is the group of performance and image-enhancing drugs (PIED) which seem to be increasingly popular amongst the general population (Minervini *et al.*, 2012; Corazza *et al.*, 2014):

- A number of PIEDs: minikikke/super strength caffeine tablets; DNP; testosterone booster concoctions such as Tribulus terrestris-containing products; cognitive enhancers (aniracetam; piracetam); melanotans, etc.

These compounds include drugs, nutrients, drinks, vitamins, vegetable extracts and potions from a range of different origins. The distributors and proponents of these compounds emphasize their capacity to increase intelligence, attention and concentration, as well as improve memory function.

In particular, there is increasing concern in the UK regarding the misuse of the slimming aid/molecule dinitrophenol/DNP, which has been associated with a number of fatalities in the UK (Grundlingh *et al.*, 2011).

Conclusions

Health professionals are being increasingly concerned and aware of the number of clients self-administering with NPS coming to the attention of relevant organizations and agencies. The NPS categorization and classification here provided is an attempt to identify and better understand some of these substances. As a result of their emergence, treatment agencies and others need to consider their responses (D'Agnone, 2015) in the light of the knowledge here provided.

Although current surveys suggest relatively low levels of NPS use in Europe and in the UK, at least if compared with classical scheduled substances such as THC, cocaine and heroin, this may change. Indeed, since the NPS online market is by far more rapid than scientific research (Deluca *et al.*, 2012), a major challenge remains the lack of reliable NPS-related scientific knowledge, which is in comparison developing too slowly. In particular, further studies are required to identify a range of proper, NPS-focused, clinical management/treatment strategies.

Given the vast range of medical and psychopathological issues associated with the NPS here described, it is crucial for health professionals to be aware of the effects and toxicity of NPS. Indeed, the 2014-2016 European Commission-funded EU-MADNESS project, with the Author is this review being the Principal Investigator, aims at both better understanding the pharmacology of the available/forthcoming NPS and at sharing/disseminating of proper NPS-related knowledge to practising/in training health professionals.

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