Novel psychoactive substances of interest for psychiatry

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Novel psychoactive substances include synthetic cannabinoids, cathinone derivatives, psychedelic phenethylamines, novel stimulants, synthetic opioids, tryptamine derivatives, phencyclidine-like dissociatives, piperazines, GABA-A/B receptor agonists, a range of prescribed medications, psychoactive plants/herbs, and a large series of performance and image enhancing drugs. Users are typically attracted by these substances due to their intense psychoactive effects and likely lack of detection in routine drug screenings. This paper aims at providing psychiatrists with updated knowledge of the clinical pharmacology and psychopathological consequences of the use of these substances. Indeed, these drugs act on a range of neurotransmitter pathways/receptors whose imbalance has been associated with psychopathological conditions, including dopamine, cannabinoid CB1, GABA-A/B, 5-HT2A, glutamate, and k opioid receptors. An overall approach in terms of clinical management is briefly discussed.

Key words: Novel psychoactive substances, legal highs, smart drugs, research chemicals, substance abuse, dual diagnosis, psychedelic phenethylamines, synthetic cannabimimetics, phencyclidine-like drugs, cathinones, tryptamines

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In parallel with a decrease/stabilization of the use of internationally controlled drugs (1), the market of novel psychoactive substances is on the rise year on year. The diffusion of these substances has been identified in 94 countries/territories (2), with some 5% of 19-24 years old European people having already experimented with them. The web plays a major role in shaping this unregulated market (3), with users being attracted by these substances due to both their intense psychoactive effects and likely lack of detection in routine drug screenings (4).

Overall, novel psychoactive substances are defined as new narcotic/psychotropic drugs which are not controlled by the United Nations' 1961 Narcotic Drugs/1971 Psychotropic Substances Conventions, but which may pose a public health threat (5). However, "novel" will not necessarily mean here a new development, but will refer to substances that have recently become popular/available, constituting a reason of current/potential public health concern.

In particular, there are increasing levels of concern about the onset of acute/chronic psychopathological manifestations associated with the intake of a range of novel psychoactive substances (3,6,7). Here we provide an overview of the clinical pharmacology of the few hundred substances available (4,8,9) and the psychopathological disturbances they can produce.

We searched Medline/PubMed for studies using the terms "new psychoactive substances", "novel psychoactive substances", "legal highs", "designer drugs", "research chemicals", "smart drugs", and "emerging drugs of abuse". A similar search was carried out for the main groups of substances and associated psychiatric manifestations. Where no information relating to the index substances was available from the peer reviewed literature, specific websites were identified by typing the index substance keywords on Google, with selection and analysis of fora posts/threads.

SYNTHETIC CANNABIMIMETICS

Synthetic cannabimimetic (SC) preparations are composed by a dried plant, marijuana-like, base and a sprayed mixture of SCs. Oral/e-liquid/injectable SC formulations are also available (10-12). Within any given "Spice" package, usually a range of different SC molecules (13) and/or further psychoactives (14-20) can be identified. Batches of the same brand may possess highly variable SC concentrations (21).

It is likely that a few hundreds of SC molecules are currently available (8,9). SCs possess high/very high cannabinoid receptor binding affinity levels, with a significantly higher dose-response efficacy than tetrahydrocannabinol itself (22,23). In addition to this, some SCs show further pharmacodynamic actions (24) which may *per se* be a reason of clinical concern, such as N-methyl-D-aspartate (NMDA) receptor antagonism (25) and/or monoamine oxidase (MAO) inhibitory properties (26). Furthermore, almost all SCs possess indole-derived structures, which may in itself facilitate 5-HT2A receptor dysfunction, typically associated with both hallucinations/psychosis (27-30) and the serotonin syndrome (31). Further, the recent trend of SC fluorination may increase the compounds' lipophilicity, hence enhancing the absorption through biological membranes/blood brain barrier (32,33).

Acute SC intoxication is characterized by agitation/anxiety and visual/auditory hallucinations (34-36), together with tachycardia, hypertension, mydriasis, hyperglycaemia, dyspnoea, vomiting and seizures. Further SC-related medical complications may include stroke, encephalopathy, myocardial infarction and acute kidney injuries (37-40).

A number of analytically confirmed accidental deaths/suicides have been related to SC ingestion, either on their own or in combination with other compounds (41-51).

Long-term SC misuse may be associated with both tolerance/dependence (35,52) and a severe/prolonged withdrawal syndrome (53-56). A risk of developing psychosis in chronic marijuana users has repeatedly been described, and a correlation with the dosage ingested has been reported (57). Similarly, SC intake has been associated with the occurrence of florid/acute transient psychosis, relapse/worsening of a pre-existing psychosis, persisting psychotic disorders/"spiceophrenia" (6), and manic-like symptoms or relapse of pre-existing bipolar disorder (58,59).

SYNTHETIC CATHINONES

Synthetic cathinones have been first detected by our web-mapping research group in 2008 (4). They are beta-ketophenethylamines structurally similar to amphetamines/catecholamines, with subtle variations that alter their chemical properties, potency, pharmacokinetics and pharmacodynamics. Their popularity was driven by the lack of availability or the poor purity of cocaine or 3,4-methylenedioxy-methamphetamine (MDMA, "Ecstasy"), combined with little, if any, legal restrictions (3).

Typically, synthetic cathinones are snorted or ingested orally or injected. For mephedrone, the half-life is as short as one hour, hence the re-dosing risk (60). Each synthetic cathinone has variable effects and potency levels on serotonin, dopamine and noradrenaline pathways, but all typically possess sympathomimetic/amphetamine-like effects (8,9).

Cathinone-related psychoactive effects include increased alertness, euphoria, excited delirium, hallucinations, agitation and aggression, associated with tachycardia, hypertension and dilated pupils. Abdominal pain, flushing, sweating, chills, restlessness and anxiety can be observed as well (8,9,61). Mood disturbances and paranoid ideation have been observed in chronic users (61-64). Additional reported mephedrone serious effects include hyperthermia, rhabdomyolysis, renal failure and seizures.

Fatalities have been associated with mephedrone (47,61,62), methylone and butylone (65). A significant proportion of synthetic cathinones' users report tolerance, dependence or withdrawal symptoms (66). Abstinent methcathinone users may present with decreased striatal dopamine transporter density on positron emission tomography scans, suggesting the potential risk for long-term psychiatric problems (67).

NOVEL DERIVATIVES OF "CLASSICAL" PSYCHEDELIC PHENETHYLAMINES/ MDMA-LIKE DRUGS

MDMA ("Ecstasy") is only one of the psychedelic phenethylamine products. Recent and popular appearances into the drug scenario include a few 2C molecules, such as 2,5-dimethoxy-4-bromophenethylamine (2-CB, "Nexus") (68), 2,5-dimethoxy-4-iodophenethylamine (2C-I) (69), and 2,5-dimethoxy-4-ethylphenethylamine (2C-E) (70). Most 2C drugs show affinity for 5-HT2A receptors, whilst some of them inhibit the dopamine/noradrenaline/serotonin reuptake as well (3). They may be purposefully or unintentionally ingested as MDMA substitutes.

With MDMA-like drugs, enhanced mood, increased energy, openness and perceptual alterations are typically reported, together with a range of serotonergic and sympathomimetic toxicity effects, including tachycardia, hypertension, metabolic acidosis, convulsions, rhabdomyolysis, mydriasis, vomiting, diarrhoea and thrombocytopenia. Acute renal failure and hyperthermia are a reason of particular concern (3,7,71,72).

3C-bromo-Dragonfly ("B-Fly") has been described as a powerful/long lasting (up to 3 days of psychoactive effects) drug, associated with long-standing hallucinations, mood elevation, paranoid ideation, confusion, anxiety and flashbacks (73).

25C-NBOMe ("N-bomb", "Pandora") (74) is one of the most popular NBOMe compounds, a group of high potency drugs which are currently a reason of public health concern (8,9). Sold online as legal lysergic acid and typically ingested orally or sublingually, "N-bomb" is a partial agonist of 5-HT2A receptors. Its effects include stimulation, hallucinations, dissociation, anxiety, aggression and unpredictable violent episodes (74).

"B-Fly", "N-bomb", para-methoxyamphetamine (PMA, "Dr. Death"), 4-methyltioamphetamine (4-MTA, "flatliners") and 6-(2-aminopropyl) benzofuran (6-APB, "Benzofury") have all been implicated in a number of acute toxicity events and fatalities (47,73,74).

NOVEL STIMULANTS

4,4'-dimethylaminorex (4,4'-DMAR, "Serotoni") is a derivative of aminorex (75,76) which has been associated in 2013/2014 with some 30 deaths in Europe (77). Similar to amphetamine-type stimulants (71), "Serotoni" is a potent dopamine/noradrenaline releaser whilst inhibiting the serotonin transporter as well (78). It may be snorted or ingested (79-81). It produces euphoria, alertness and agitation lasting several hours (80). Hyperthermia and cardiorespiratory problems have also been described (82).

Although synthesized some 70 years ago, methiopropamine (MPA, "Blow"), a methamphetamine analogue, started to be recently advertised online as a "research chemical" (83-85) to be smoked, ingested or snorted. Being a selective noradrenaline/dopamine reuptake inhibitor (86), it produces euphoria, hallucinations, alertness and sexual arousal. This may be associated with loss of appetite, tachycardia, anxiety, nausea, headache, dizziness, skin irritation, difficulty urinating and hangover effects (87).

SYNTHETIC OPIOIDS

These compounds share with morphine most of their clinical pharmacological effects, including analgesia, sedation, euphoria and risk of respiratory depression.

AH-7921 ("doxylam") is equipotent to morphine (88). Although first synthesized some 45 years ago, it is now available online in powder form to be snorted or ingested. A few related fatalities have recently been identified (82).

Although never marketed as such, MT-45 was developed in the early 1970s as a potential analogue of the analgesic lefetamine (89). Being a mu/delta/sigma opioid receptor agonist (90), it is currently a popular compound, either on its own or in combination with synthetic cathinones ("Wow") (82). MT-45 intake has been associated with respiratory depression, loss of consciousness and ototoxicity (91) and a number of fatalities as well (82).

Further popular drugs include nortilidine, which is an NMDA receptor antagonist and dopamine reuptake inhibitor equipotent to morphine (92); the high potency mu-opioid agonists W15 and W18 (93); 4-fluoro-butyrfentanyl ("4FBF") and IC-26 ("methiodone"), a methadone analogue.

SYNTHETIC COCAINE SUBSTITUTES

RTI-111 is a potent stimulant acting as an inhibitor of serotonin, dopamine and noradrenaline reuptake (94). RTI-121, developed in the 1990s, is a potent/long-lasting stimulant acting as selective dopamine reuptake inhibitor (95). RTI-126 (96) may present with a potency 5-fold higher than cocaine (97). When snorted, these compounds are associated with alertness, euphoria, talkativeness, insomnia and prolonged residual tension/anxiety (87).

NOVEL TRYPTAMINE DERIVATIVES

Synthetic tryptamines appeared on illicit drug markets throughout the 1990s (98), to be replaced over the last few years by cathinones, phenethylalamines and piperazines (82,99).

Nevertheless, novel tryptamines (e.g., N-diallyl-5-methoxytryptamine, 5-MeO-DALT; alpha-methyltryptamine, AMT; 5-methoxy-alpha-methyltryptamine, 5-MeO-AMT; N,N-diallyl-4-hydroxytryptamine, 4-HO-DALT; 5-methoxy-diisopropyltryptamine, 5-MeO-DIPT; 5-methoxy-N,N-dimethyltryptamine, 5-MeO-DMT; N,N-diethyltryptamine, DET; 5-(2-aminopropyl)indole, 5-IT) continue to appear on the online drug scenario (2,82,100,101).

Most exogenous tryptamines are psychoactive hallucinogens found naturally (102-106), notably in Delosperma species plants (dimethyltryptamine, DMT; 5-MeO-DMT), hallucinogenic fungi (psilocin; 4-OH-DMT), and amphibians (bufotenin). Endogenous bufotenin and DMT have been detected in humans as well (107-109), even though their biological functions remain unclear.

The predominant clinical effects of tryptamines, associated with both agonist activities at 5-HT2A receptors and serotonin transporter inhibition (110-117), consist in visual hallucinations, alterations in sensory perception, distortion of body image, depersonalization, marked mood lability and anxiety/panic (98,118). Untoward effects include agitation, tachyarrhythmia and hyperpyrexia (111). There are small numbers of confirmed post-mortem toxicology reports on tryptamines, mainly relating to AMT (47).

Bufotenin (119) is found on the skin of various species of the toad Bufo genus, in Amanita mushrooms, and in Anadenanthera peregrina/Piptoderma peregrina plants (120). Its psychoactive effects are mainly due to its enzymatic conversion to 5-MeO-DMT. Typically, consumers smoke the crystals obtained by drying the liquid taken from the frogs, but both oral and intravenous use have been recently reported as well.

AMT is available mainly from the web, in tablet and liquid formulations. Visual illusions and euphoria have been reported (121). 5-MeO-AMT and 5-MeO-DMT have a structure similar to amphetamine, hence explaining their sympathomimetic effects (98,99). 5-IT, a positional AMT isomer and a substituted phenethylamine, has been made available since 2012. It possesses both hallucinogenic and stimulant effects (98,99).

GABA-A/B RECEPTOR AGONISTS

Currently used in some countries to treat narcolepsy and alcohol withdrawal (122), gamma-hydroxybutyric acid (GHB, "liquid Ecstasy") was developed as an anaesthetic some 50 years ago. It can be produced in clandestine laboratories using a relatively simple synthesis with readily available and inexpensive source materials. It is typically ingested orally. Gamma-butyrolactone (GBL) and 1,4-butanediol, both industrial chemicals, are also currently used for their GHB-like effects, with GBL being a high lipophilicity/high potency GHB pro-drug.

GHB intake is associated with both increased central dopamine levels and activation of GABA-A/B receptors (123). GHB elimination half-life is 27 minutes, hence the re-dosing risk (124). Euphoria and calmness are initially observed after ingestion. A low/moderate oral dose of 10 mg/kg (0.75 g) can produce short-term amnesia, hypotonia, lowering of inhibitions and libido increase. Higher dosages lead to drowsiness, nausea, vomiting, muscle stiffness, dizziness, confusion, delirium, hallucinations, convulsions and cardiopulmonary depression.

GHB is highly addictive (125), with its withdrawal syndrome being characterized by insomnia, muscular cramping, tremor and anxiety (126). Initial UK data indicate that there have been 159 GHB/GBL-associated fatalities reported over the last two decades. Most deaths (79%) were accidental and GHB/GBL alone was implicated in 37% of cases (127).

Baclofen is a GABA-B agonist (128) showing both anxiolytic and analgesic properties whilst exerting some beneficial alcohol, cocaine and nicotine anti-craving effects (129-132). It can also be used for GHB/GBL withdrawal/detoxification (133). Most typically, misusers present with a history of substance abuse/self-medication with other substances and start taking large dosages after being regularly prescribed with baclofen for medical reasons (134).

Although signs of toxicity may be identified with as little as 100 mg of baclofen (135), misusers report the intake of higher dosages in order to achieve the desired effects, including euphoria, relaxation and anxiety obliterating/antidepressant-like effects, similar to those reported after GHB and pregabalin intake (80,136).

Several deaths after baclofen overdose have occurred (137). The acute intoxication is characterized by severe hypotonia, delirium, sedation, respiratory depression, cardiac conduction abnormalities, and possibly coma. Baclofen should always be withdrawn gradually (138). Common presenting withdrawal features are muscular hyperactivity, hyperthermia, metabolic derangements, rhabdomyolysis, convulsions and delirium, with issues similar to the serotonin syndrome (139).

Phenibut ("PB") is being used in Russia and Latvia for the treatment of anxiety/alcohol withdrawal symptoms and as a nootropic (140). As a dietary supplement, it is freely available online. When misused, it is typically taken orally in dosages (e.g., 1-3 g) notably superior to the therapeutic ones, thus leading to a risk for overdose. At these dosages, it acts as agonist at GABA-A/B receptors, whilst stimulating dopamine/serotonin neurotransmission as well (141,142).

Its use may rapidly lead to dependence/tolerance (143), with related withdrawal symptoms being managed with baclofen (144). Withdrawal signs/symptoms may include visual and auditory hallucinations, psychomotor agitation, derealization, depersonalization, increased light and sound sensitivity, muscle pain/twitches, tachycardia, nausea, tremor and insomnia (145). Acute intoxication is characterized by tachycardia, visual hallucinations, tremor, nausea and vomiting, with the possible occurrence of the serotonin syndrome (146,147).

PHENCYCLIDINE-LIKE DISSOCIATIVE DRUGS

Dissociative drugs are both popular and a cause of clinical concern (148-150). Ketamine hydrochloride ("special K") is of widespread use worldwide.

Ketamine is usually diverted from veterinary clinics, where it is used for surgical interventions. Its hallucinogenic effects are related to central 5-HT2A agonism (151), NMDA receptor antagonism (152), and high affinity for mu/delta/sigma opioid receptors (153).

When misused, ketamine can be injected or snorted or smoked or administered rectally, in a dosage range of 25-300 mg. Its psychotropic effects include referential thinking, dissociation, depersonalization, psychotic experiences and out-of-body/near death experiences (e.g., the "K-hole", 150). In the long term, tolerance, dependence, withdrawal signs and flashbacks are described, with schizotypal symptoms and perceptual distortions possibly persisting after cessation (154).

Approximately one third of patients with long-term recreational ketamine use present with both urological ("k bladder", e.g., dysuria, suprapubic pain, haematuria, decreased bladder capacitance, abnormal bladder histology, hydronephrosis) (155) and intestinal ("k cramps") (153) problems. High dosage self-administration may be associated with both cardiovascular and respiratory toxicity. Numbness, muscle weakness and impaired perception can result in falls, trauma or burns. Risks have also included drowning, death from hypothermia due to lying outside in winter, traffic accidents and becoming a crime victim (47,150).

Methoxetamine (MXE, "Special M") has recently entered the market as a structural analogue of ketamine in order to elude legislative sanctions (149). It may be swallowed or insufflated or injected or used rectally or sublingually at a dosage range of 5-100 mg (9,80,87,136).

MXE possesses NMDA receptor antagonism, dopamine releasing and serotonin transporter inhibiting activities (153). Most users report long-lasting dissociative effects (e.g., the "M-hole", 156). Although having been marketed as "bladder friendly", initial preclinical studies are a reason of clear concern (157), with cerebellar features and seizures being unique to "special M" intoxications (158). A number of analytically confirmed MXE-related fatalities have been described (148).

Diphenidine (DND) and methoxphenidine (MXP) are novel lefetamine derivatives acting as NMDA receptor antagonists (159), serotonin transporter inhibitors, dopamine agonists, and opioid agonists (87). They can be ingested or insufflated or injected at a dosage range of 50-150 mg, with a duration of effects of 8-12 hours (87). Interestingly, a range of serotonin syndrome signs/symptoms have been associated with DND/MXP high dosage ingestion (80,87,136).

Dextromethorphan (DXM) is an over-the-counter antitussive lacking strong mu-opioid agonist properties but acting as an NMDA receptor antagonist (159) whilst possessing serotonin transporter inhibiting activities (160). With long-term DXM abuse, psychotic disturbances can be observed (8,9). Abrupt DXM cessation has been associated with withdrawal symptoms (e.g., vomiting, diarrhoea, myalgias, restlessness, night sweats, insomnia, anxiety, but also hallucinations and flashbacks) (161). DXM high dosage ingestion may be associated with occurrence of the serotonin syndrome (160).

PIPERAZINES

Benzylpiperazine (BZP) was initially trialled as an antidepressant some 40 years ago, but never entered the market.

Especially in the past, it was included in "fake" Ecstasy tablets. It is an 5-HT2A receptor agonist, which explains its hallucinogenic effects at higher doses.

Piperazines have become popular to mimic Ecstasy effects, with the recently introduced "Molly" being typically an MDMA/piperazine combination (162). Their effects are similar to those of amphetamine, but less intense (8,9,162). Their ingestion is typically associated with stimulant effects, but at higher dosages hallucinations can be reported as well. Seizures can occur in as many as one in five patients presenting with piperazine toxicity, with hyponatremia, serotonin syndrome and renal failure having been described as well (162).

Meta-chlorophenylpiperazine (mCPP) is the main trazodone/nefazodone metabolite. Its high dosage ingestion can produce euphoria, hypertension and tachycardia.

HERBS/PLANTS

Salvia divinorum ("Sally-D") has a long history as a divinatory psychedelic. Its current use includes smoking or chewing the dried leaves containing salvinorin A and B, both k-opioid receptor agonists (163). At high dosages, time distortion, vivid imagery and empathogenic effects have been anecdotally reported (80,87,136). When smoked, its clinical effects occur within 20-60 seconds and last 5-15 minutes. Its intake may be associated with perceptual disturbances, psychosis, headache, irritability and anxiety (80,87,136). Dependence and tolerance have not been reported.

Sceletium tortuosum ("Kanna") is a traditional Southern Africa entheogen (164) currently available as extract, dried-powdered herb, tincture, tea bags and seeds. It may be snorted, smoked, chewed or swallowed (80,87,136). Desired effects include euphoria, reduction of tension, libido enhancement and appetite suppression. The mood-elevating action is due to the serotoninergic activity of its alkaloids (165), e.g., mesembrine, mesembrenone, mesembrenol and tortuosamine. Common side effects reported are hypertension, headache and nausea, associated with anxiety, irritability and insomnia. A serotonin syndrome can occur if Kanna is associated with selective serotonin reuptake inhibitors (SSRIs) or MAO inhibitors (MAOIs) (80,87,136).

Mitragyna speciosa ("Kratom") is a tree native to some Asian countries whose leaves contain mitragynine, mitraphylline, 7-hydroxymitragynine and O-desmethyltramadol. Mitragynine ("biak-biak") is a partial agonist of the mu/delta opioid receptors. 7-hydroxymitragynine is a mu-opioid agonist 30-fold more potent than mitragynine. Mitraphylline acts both on mu/delta opiate receptors and as an NMDA receptor antagonist (119). Kratom may be smoked or brewed or ingested as an extract. Users report either an opiate-like sedation, particularly at higher dosages, or a cocaine-like stimulation at lower dosages (80,87,136). Other clinical effects include severe nausea and vomiting associated with visual disturbances. Regular use may lead to dependence and opioid-like withdrawal symptoms upon discontinuation. A few related fatalities have been reported (47).

Piper methysticum ("Kava Kava") is a social/ceremonial drink in many South Pacific Islands, with kavalactones and kavapyrones being its active constituents (8,9,119). Out of these, desmethoxy-yangonin is a reversible MAOI-B, able to increase as well dopamine levels in the nucleus accumbens (166). Kavain is a N-terminal acetyltransferase (NAT) inhibitor, supposedly with serotonin reuptake inhibition and NMDA receptor activation properties (167). Yangonin acts as a cannabinoid CB1 agonist (168). Kava roots are also available in liquid form, tinctures, extracts and tablets. Kava confers a rapid onset, long-term sedation (119). There are several reports of associated liver damage or failure (169).

Ayahuasca is a psychedelic South American brew, traditionally made from Banisteriopsis caapi vine (containing beta-carboline harmala alkaloids, possessing reversible MAOI-A properties) and Psychotria viridis, a DMT-containing plant (8,9,119). Being metabolized by the digestive MAO, DMT is practically inactive if taken orally, unless combined with a MAOI. Effects may last 2-6 hours, and include intense visual hallucinations, euphoria, paranoid ideation and entheogenic sensations, associated with vomiting and/or diarrhoea (8,9,119).

Ibogaine is a hallucinogenic alkaloid extracted from the root bark of the Western African shrub Tabernanthe iboga, traditionally used as a sacrament (8,9,119). It is an 5-HT2A agonist, dopamine agonist, NMDA receptor antagonist and k-opioid receptor agonist (170). Its ingestion is associated with visual hallucinations and entheogenic effects, possibly associated with ataxia, nausea, vomiting and arrhythmias (171).

A recent increase in online discussions relating to the possible misuse of magnolols has been identified by our research group (172). The bark extract of Magnolia officinalis is typically used in traditional oriental medicine for the treatment of insomnia, anxiety and allergies (173). Honokiol and magnolol, the main constituents of its extracts, are both weak cannabinoid CB2 and GABA-A receptor agonists (174). Magnolol is then metabolized into its 20-fold more potent metabolite tetrahydromagnolol, active at cannabinoid CB1/CB2 receptors (174). Cannabis- and benzodiazepine-like effects (e.g., sedation, reduced attention and concentration, headache) are being reported (80,87,172).

Hydrangea paniculata/Hortensia is a common ornamental plant. Its misuse may be associated with a range of cannabis-like effects, e.g., euphoria, sedation, confusion, dizziness and headache (80,87,136). It may be smoked, or ingested in capsules, extracts, teas or sugar syrup.

Datura stramonium is another common plant well known for its mind-altering properties (e.g., hallucinations, delusions, bizarre behavior and euphoria) associated with xerostomia, severe mydriasis/photophobia, confusion, disorientation, tachycardia, and amnesia (8,9,80,87,119). Related fatal medullary paralysis, arrhythmias and cardiovascular collapse events have been reported (47).

Nauclea latifolia is a flowering, tramadol-containing, sub-Saharan plant (175), used recreationally to obtain pain relief, sedation and anxiolytic effects (80,87).

PRESCRIBED PRODUCTS

Pregabalin is approved in Europe for the treatment of epilepsy/partial seizures, neuropathic pain and generalized anxiety disorder. The molecule is however also often prescribed off-label for a range of psychiatric conditions, including bipolar disorder, alcohol/narcotic withdrawal states and attention-deficit/hyperactivity disorder. In parallel with increasing prescribing levels, a growing black market is currently being observed (8,9,176,177).

Potent binding of pregabalin and gabapentin at the calcium channel results in a reduction in the release of excitatory molecules. Furthermore, they are thought to possess GABA-mimetic properties and direct/indirect effects on the dopaminergic "reward" system (177). Overall, pregabalin is characterized by higher potency, quicker absorption rates and greater bioavailability than gabapentin (176).

Typical misusers of these compounds are individuals with a history of recreational polydrug use. A range of experiences may be associated with gabapentin abuse, including euphoria, improved sociability, opiate-like sedation and psychedelic effects (176). Similarly, pregabalin is considered an "ideal psychotropic drug" to achieve specific mindsets, including sedative effects mixed with euphoria and dissociation.

Misuse of pregabalin, at dosages up to 3-20 times higher than the maximal dosage indicated (176), mostly seems to occur orally, but intravenous use, rectal "plugging" and smoking have been reported as well. A few drugs are reportedly misused in combination with pregabalin or gabapentin, including cannabis, alcohol, lysergic acid, amphetamine and GHB (176,177).

Phenazepam ("Zinnie") is an old benzodiazepine, currently prescribed in the Russian Federation for the treatment of a range of neurological disorders as well as for alcohol withdrawal/anxiety, and as a surgery premedication (178). Easily accessible online at low prices, it is considered five times more powerful than diazepam (179). It can be ingested, snorted or injected, either on its own or in combination with other substances, with euphoric effects having been described (8,9). Reported side effects include amnesia, dizziness, loss of coordination, drowsiness, blurred vision, slurred speech and ataxia. Deaths by respiratory arrest due to its misuse in combination with other sedatives have been reported (180).

Olanzapine is being anecdotally advised online as the "ideal trip terminator" after a psychedelic drug binge (181). The molecule is self-prescribed, and for a few days only, at daily dosages up to 50 mg/die.

Quetiapine ("Q ball") is similarly anecdotally considered to "come off the psychedelic trip" (181), with typical misusers being clients with a previous substance abuse history. Vulnerable subjects (e.g., adolescents, inmates) may be particularly at risk (182). Reasons for abuse of atypical antipsychotics may include the desire of "feeling mellow" (183).

There are anecdotal reports of misuse of venlafaxine, particularly in combination with other substances (80,87,136), possibly related to the increase it produces in dopamine neurotransmission (184,185), particularly at the level of the prefrontal cortex (186).

Recent concerns relating to orphenadrine (an anticholinergic drug) misuse have been reported (187). Similarly, misuse of tropicamide (an ophthalmic anticholinergic compound producing short-acting mydriasis and cycloplegia) has been recently described (188). When misused, tropicamide is typically injected intravenously, often in combination with other psychoactives. Tropicamide-related psychoactive effects include hallucinations, "open eye dreams" and dysphoria, associated with slurred speech, persistent mydriasis, hyperthermia, tremor, convulsions, psychomotor agitation, tachycardia and suicidal ideation (188).

PERFORMANCE AND IMAGE ENHANCING DRUGS

Increasing consumption levels of substances known as performance and image enhancing drugs (PIEDs) have been recorded (8,9,189). PIEDs are drugs, nutrients, drinks, vegetable extracts or potions from a range of different sources.

Among image enhancers, there are increasing levels of concern regarding the misuse of the slimming aid dinitrophenol (DNP), whose intake has been implicated in a number of UK fatalities (47,190). DNP is offered online as a metabolism booster to bodybuilders and dieters. Its ingestion may be associated with euphoria, energy increase, nausea and headache (8,9).

Typically identified in dietary supplements, 1,3-dimethylamylamine (DMAA) intake is associated with euphoria and mild stimulant effects, together with hypertension, headache, nausea, and vomiting (80,87,111). In parallel with concerns about DMAA's health risks, including deaths (191), new synthetic stimulants, including beta-methylphenylethylamine (BMPEA), N,alpha-diethylphenylethylamine (DEPEA) and more recently 1,3-dimethylbutylamine (DMBA) have been offered to online customers looking for alternative "natural" dietary supplements. With DMBA, effects such as restlessness, mood enhancement, increased focus, nausea, flushing and tachycardia have been reported (80,87,192).

Melanotan synthetic tanning agents are largely available online, aiming at promoting melanogenesis and hair-skin pigmentation. Melanotan user groups include aesthetically driven women, body dysmorphics and male bodybuilders. Sexual arousal, flushing, nausea, weight loss and immune response alterations have been reported (193,194).

A range of natural products available online, such as those containing Tribulus terrestris, are becoming popular

because of their alleged powerful pro-testosterone, muscular strength enhancer formula. Both increased sexual arousal (80,87) and psychotic episodes (associated with long-term ingestion) (189) have been described.

Among cognitive enhancers, piracetam, aniracetam and centrophenoxine have been reported to be abused by healthy individuals with the hope to improve their performance in study and work-related activities (195). Piracetam is a GABA derivative, originally marketed in 1971 as a nootropic (196), due to restored neurotransmission and increased brain oxygen consumption (197). With the ingestion of high dosages of these substances, hallucinations and mood alterations have been reported (80,136,196).

"Natural" sexual performance enhancers are advertised online as "safer" alternatives to pharmaceutical phosphodiesterase type 5 inhibitors. The most popular compounds include yohimbine, Maca, Epimedium and Ginkgo Biloba. Their ingestion has been associated with anxiety, irritability, hypomanic reactions and inappropriate behaviour (80,87, 136,198).

DISCUSSION

The ever-increasing number of novel psychoactive substances emerging worldwide (2,8,9,101) and the parallel changes in drug scenarios represent a challenge for psychiatry. In fact, the intake of these substances is typically associated with the imbalance of a range of neurotransmitter pathways/receptors, and consequently with the risk of psychopathological disturbances.

The occurrence of psychosis has been related to: a) increased central dopamine levels (199), associated with the intake of most of these substances, including novel psychedelic phenethylamines, synthetic cathinones and 4,4'-DMAR; b) cannabinoid CB1 receptor activation (200), achieved with synthetic cannabimimetics; c) 5-HT2A receptor activation (201), reported with NBOMe compounds, latest tryptamine derivatives, lefetamine derivatives, DXM and hallucinogenic plants; d) antagonist activity at NMDA receptors (202), described with phencyclidine-like dissociatives; and e) k-opioid receptor activation (203), typically associated with Salvia divinorum intake.

Vulnerable subjects, including both children/adolescents and psychiatric patients, may be exposed to a plethora of "pro drug" web pages, which provide direct drug purchase opportunities and/or drug information (e.g., description of the drug effects, dose, chemistry and intake experiences). Advanced levels of knowledge related to novel psychoactive substances are typically provided by drug fora/blog communities' members (e.g., the "e-psychonauts", 4).

It is arguably inappropriate to trust information obtained online without independent verification, and only large scale, adequately controlled clinical studies can give a clear indication of drug characteristics and adverse effects. However, previous studies from our group (4,176) have clearly suggested that an increase in online trafficking/debate about a specific psychoactive drug typically precedes the occurrence of clinical incidents at the population level.

Consumers of novel psychoactive substances may self-refer overnight to accident and emergency departments, when concerned with acute medical or psychiatric problems, without disclosing their substance intake and showing negative results at the standard drug tests (8,9). It is clearly difficult to draw a detailed and universal management plan to cope with the behavioural and psychopathological disturbances related to the intake of the virtually few hundreds of substances currently available (8,9,162).

Given the complex or unknown pharmacology of the substances possibly ingested by the client, benzodiazepines may be agents of choice (3). They may, however, need frequent re-dosing/high dosages to achieve adequate sedative effect, and this may be a problem if clients have co-ingested alcohol (3). Where patients cannot be controlled with benzodiazepines alone, propofol and/or antipsychotics may be considered (8,9,162), although this may further contribute to the acute toxicity effects of the abused substances.

Treatment of hyperthermia needs to be aggressively planned, and this typically involves cooling measures and intravenous fluid administration for rhabdomyolysis concern (3). Serotonin syndrome is managed using benzodiazepines and cyproheptadine (204). Inpatient admission, possibly to intensive care units, may at times be needed (8,9,162).

The increasing levels of misuse of a range of medicinal products, otherwise representing a valuable asset in the pharmacological repertoire of psychiatry/addiction medicine (177), are a reason of further concern. Possible sources of this acquisition may either be diversion of regularly prescribed medicines or online/"rogue" pharmacies (205).

Psychiatrists/physicians who consider prescribing a psychoactive molecule possessing a potential for misuse (e.g., pregabalin or gabapentin for neurological/psychiatric disorders) should carefully evaluate a possible previous history of drug abuse. Furthermore, they should be able to promptly identify signs of misuse, and provide assistance in tapering off the index medication (177).

The online market of novel psychoactive substances is unfortunately developing far more rapidly than academic research (4). We believe that mental health professionals need to be aware of the psychopathological effects of these substances. We hope that the present paper may represent a useful contribution in this respect.

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