Novel psychoactive substances of interest for psychiatry

Fabrizio Schifano[1], Laura Orsolini[1,2], G. Duccio Papanti[1,3], John Corkery[1]

[1]School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Herts, UK; [2]United Hospital and Academic Department of Experimental and Clinical Medicine, Polytechnic University of Marche, Ancona, Italy; [3]Medical School, University of Trieste, Trieste, Italy

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 as well.

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 (25,30) 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).

The 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, previously 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).

Para-methoxyamphetamine (PMA, "Dr. Death"); 4-methyltioamphetamine (4-MTA, "flatliners"); 6-(2-aminopropyl) benzofuran (6-APB, "Benzofury"); "B-Fly"; and "N-bomb" have all been implicated in a number of related 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-butyr-fentanyl ("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). Lastly, 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-methoxy-tryptamine, 5-MeO-DALT; alpha-methyltryptamine, AMT; 5-methoxy-alpha-methyltryptamine, 5-MeO-AMT; N,N-diallyl-4-hydroxytryptamine, 4-HO-DALT; 5-methoxy-diisopropyl-tryptamine, 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 (DMT, 5-MeO-DMT), hallucinogenic fungi (psilocin, 4-OH-DMT), and amphibians (bufotenin). Endogenous bufotenin and dimethyltryptamine (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 own 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 decade. 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 both GHB/GBL and phenibut 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 phenibut, 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, PB 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,

PB 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 the 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 the legislative sanctions (149). MXE 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 methoxetamine analytically confirmed 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 of 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 1 in 5 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 it is associated with selective serotonin reuptake inhibitors (SSRIs) or MAO inhibitors (MAOIs) (80,87,136).

Mytragina speciosa ("Kratom") is a tree native to some Asian countries whose leaves contain mitragynine, mitraphylline, 7-hydroxymitragynine and O-desmethyltramadol. Mytragynine ("biak-biak") is a partial agonist of the mu/delta opioid receptors. 7-hydroxymitraginine 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 SSRI 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), but 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 the 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 the 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 associated with anti-cholinergic peripheral/central effects (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 in alternative to the prescribed medication itself 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). Different from current medical guidelines, however, the molecule is being 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 may present with addictive liability levels and its ingestion may be associated with euphoria, energy increase, nausea and headache (8,9). DNP is proposed online as a metabolism booster to bodybuilders and dieters.

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-methyl-phenylethylamine (BMPEA), N,alpha-diethylphenylethylamine (DEPEA) and more recently 1,3-dimethylbutylamine (DMBA) have been proposed 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, such as those containing Tribulus terrestris, are available online. They are particularly popular because of their alleged powerful pro-testosterone, muscular strength enhancer, natural 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 recently been reported to be abused by healthy individuals with the hope to enhance their functions in study and work-related performances (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 high dosage cognitive enhancers' ingestion, 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. 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 activities at both the NMDA and mGlu2/3 receptors (202), described with phencyclidine-like dissociatives; and e) k-opioid receptors' 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 as well (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.

Acknowledgements

References

1. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). European drug report 2014: trends and developments. Lisbon: EMCDDA, 2014.

2. United National Office on Drugs and Crime (UNODC). Global synthetic drugs assessment. Vienna: UNODC, 2014.

3. Nelson ME, Bryant SM, Aks SE. Emerging drugs of abuse. Emerg Med Clin N Am 2014;32:1-28.

4. Deluca P, Davey Z, Corazza O et al. Identifying emerging trends in recreational drug use; outcomes from the Psychonaut Web Mapping Project. Prog Neuropsychopharmacol Biol Psychiatry 2012;39:221-6.

5. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Hallucinogenic mushrooms: an emerging trend case study. Lisbon: EMCDDA, 2006.

6. Papanti D, Schifano F, Botteon G et al. 'Spiceophrenia': a systematic overview of 'Spice'-related psychopathological issues and a case report. Hum Psychopharmacol 2013;28:379-89.

7. Schifano F. Drugs: treatment and management. In: Ghodse AH, Herrman H, Maj M et al. (eds). Substance abuse: evidence and experience. Chichester: Wiley-Blackwell, 2011:53-74.

8. Schifano F. NPS: clinical and pharmacological issues. Drug and Alcohol Today (in press).

9. Schifano F. Novel psychoactive substances also known as 'legal highs'. In: Davies SC (ed). Annual report of the Chief Medical Officer 2013, Public mental health priorities: investing in the evidence. London: Department of Health, 2014:259.

10. Lonati D, Buscaglia E, Papa P et al. MAM-2201 (analytically confirmed) intoxication after "synthacaine" consumption. Ann Emerg Med (in press).

11. Aranda E, Sala E, Navarro M et al. Use of novel psychoactive substances (NPS): a description of a harm reduction center in Barcelona. Res Adv Psychiatry 2014;1(Suppl. 1):36.

12. Vandrey R, Dunn KE, Fry JA et al. A survey study to characterize use of Spice products (synthetic cannabinoids). Drug Alcohol Depend 2012; 120:238-41.

13. Kikura-Hanajiri R, Uchiyama N, Kawamura M et al. Changes in the prevalence of synthetic cannabinoids and cathinone derivatives in Japan until early 2012. Forensic Toxicol 2013;31:44-53.

14. Ogata J, Uchiyama N, Kikura-Hanajiri R et al. DNA sequence analyses of blended herbal products including synthetic cannabinoids as designer drugs. Forensic Sci Int 2013;227:33-41.

15. Park Y, Lee C, Lee H et al. Identification of a new synthetic cannabinoid in a herbal mixture: 1-butyl-3-(2-ethoxybenzoyl)indole. Forensic Toxicol 2013;31:187-96.

16. Uchiyama N, Kawamura M, Kikura-Hanajiri R et al. URB-754: a new class of designer drug and 12 synthetic cannabinoids detected in illegal products. Forensic Sci Int 2013;227:21-32.

17. Uchiyama N, Shimokawa Y, Matsuda S et al. Two new synthetic cannabinoids, AM-2201 benzimidazole analog (FUBIMINA) and (4-methylpiperazin-1-yl) (1-pentyl-1H-indol-3-yl)methanone (MEPIRAPIM), and three phenethylamine derivatives, 25H-NBOMe 3,4,5-trimethoxybenzyl analog, 25B-NBOMe, and 2C-N-NBOMe, identified in illegal products. Forensic Toxicol 2014;32:105-15.

18. Uchiyama N, Matsuda S, Kawamura M et al. Two new-type cannabimimetic quinolinyl carboxylates, QUPIC and QUCHIC, two new cannabimimetic carboxamide derivatives, ADB-FUBINACA and ADBICA, and five synthetic cannabinoids detected with a thiophene derivative a-PVT and an opioid receptor agonist AH-7921 identified in illegal products. Forensic Toxicol 2013;31:223-40.

19. Dresen S, Ferreiros N, Putz M et al. Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. J Mass Spectrom 2010;45:1186-94.

20. Wurita A, Hasegawa K, Minakata K et al. A large amount of new designer drug diphenidine coexisting with a synthetic cannabinoid 5-fluoro-AB-PINACA found in a dubious herbal product. Forensic Toxicol 2014;32:331-7.

21. Choi H, Heo S, Choe S et al. Simultaneous analysis of synthetic cannabinoids in the materials seized during drug trafficking using GC-MS. Anal Bioanal Chem 2013;405:3919-63.

22. Fattore L, Fratta W. Beyond THC: the new generation of cannabinoid designer drugs. Front Behav Neurosci 2011;21:1-11.

23. Brents LK, Prather PL. The K2/spice phenomenon: emergence, identification, legislation and metabolic characterization of synthetic cannabinoids in herbal incense products. Drug Metab Rev 2014;46:72-85.

24. Pertwee RG. Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. Curr Med Chem 2010;17:1360-81.

25. Papanti GD, Orsolini L, Francesconi G et al. 'Noids'; what you (don't) want to know about synthetic cannabinoids. Adv Dual Diagn 2014;7:137-48.

26. Fisar Z. Inhibition of monoamine oxidase activity by cannabinoids. Naunyn Schmiedebergs Arch Pharmacol 2010;381:563-72.

27. Morgan D, Kondabolu K, Kuipers A et al. Molecular and behavioral pharmacology of two novel orally-active 5HT2 modulators: potential utility as antipsychotic medications. Neuropharmacology 2013;72:274-81.

28. Halberstadt AL. Recent advances in the neuropsychopharmacology of serotonergic hallucinogens. Behav Brain Res (in press).

29. Wells DL, Ott CA. The new marijuana. Ann Pharmacother 2011;45:414-7.

30. Yip L, Dart CR. Is there something more about synthetic cannabinoids? Forensic Toxicol 2014;32:340-1.

31. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005; 352:1112-20.

32. Ismail F. Important fluorinated drugs in experimental and clinical use. J Fluor Chem 2002;118:27–33.

33. Wilkinson SM, Banister SD, Kassiou M et al. Bioisosteric fluorine in the clandestine design of synthetic cannabinoids. Aust J Chem (in press).

34. Hermanns-Clausen M, Kneisel S, Szabo B et al. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. Addiction 2013;108:534-44.

35. Spaderna M, Addy PH, D'Souza DC. Spicing things up: synthetic cannabinoids. Psychopharmacology 2013;228:525-40.

36. Winstock AR, Barratt MJ. The 12-month prevalence and nature of adverse experiences resulting in emergency medical presentations associated with the use of synthetic cannabinoid products. Hum Psychopharmacol 2013;28:390-3.

37. Freeman MJ, Rose DZ, Myers MA et al. Ischemic stroke after use of the synthetic marijuana 'spice'. Neurology 2013;81:2090-3.

38. Freeman WD, Jacksonville FL, Louh IK. "Spice encephalopathy". Response to "Ischemic stroke after use of the synthetic marijuana 'spice'". Neurology 2014;81:2090-3.

39. Mir A, Obafemi A, Young A et al. Myocardial infarction associated with use of the synthetic cannabinoid K2. Pediatrics 2011;128:e1622-7.

40. Centers for Disease Control and Prevention (CDC). Acute kidney injury associated with synthetic cannabinoid use – multiple states, 2012. MMWR Morb Mortal Wkly Rep 2012;62:93-8.

41. Saito T, Namera A, Miura N et al. A fatal case of MAM-2201 poisoning. Forensic Toxicol 2013;31:333-7.

42. Shanks KG, Dahn T, Terrell AR. Detection of JWH-018 and JWH-073 by UPLC–MS-MS in postmortem whole blood casework. J Anal Toxicol 2012;36:145-52.

43. Schaefer N, Peters B, Bregel D et al. A fatal case involving several synthetic cannabinoids. Toxichem Krimtech 2013;80:248-51.

44. Savasman CM, Peterson DC, Pietak BR et al. Two fatalities due to the use of synthetic cannabinoids alone. Presented at the 66th Annual Scientific Meeting of the American Academy of Forensic Sciences, Seattle, February 2014. Denver: Publication Printers Inc., 2014:316.

45. Patton AL, Chimalakonda KC, Cindy L et al. K2 Toxicity: fatal case of psychiatric complications following AM2201 exposure. J Forensic Sci 2013; 58:1676-80.

46. Behonick G, Shanks KG, Firchau DJ et al. Four postmortem case reports with quantitative detection of the synthetic cannabinoid, 5F-PB-22. J Anal Toxicol 2014;38:559-62.

47. Corkery J, Claridge H, Loi B et al. Drug related deaths in the UK. NPSAD Annual Report 2013. London: International Centre for Drug Policy, St. George's University of London, 2014.

48. Elliott S, Evans J. A 3-year review of new psychoactive substances in casework. Forensic Sci Int 2014;243:55-60.

49. Kronstrand R, Roman M, Andersson M et al. Toxicological findings of synthetic cannabinoids in recreational users. J Anal Toxicol 2013;37:534-41.

50. Rosenbaum CD, Scalzo AJ, Long C et al. K2 & Spice abusers: a case series of clinical and laboratory findings. Presented at the North American Congress of Clinical Toxicology, Washington, September 2011.

51. Wikstrom M, Thelander G, Dahlgren M et al. An accidental fatal intoxication with methoxetamine. J Anal Toxicol 2013;37:43-6.

52. Gunderson EW, Haughey HM, Ait-Daoud N et al. 'Spice' and 'K2' herbal highs: a case series and systematic review of the clinical effects and biopsychosocial implications of synthetic cannabinoid use in humans. Am J Addiction 2012;21:320-6.

53. Nacca N, Vatti D, Sullivan R et al. The synthetic cannabinoid withdrawal syndrome. J Addict Med 2013;7:296-8.

54. New Zealand Ministry of Health. Revoked interim product approvals. www.health.govt.nz.

55. Rominger A, Cumming P, Xiong G et al. Effects of acute detoxification of the herbal blend 'Spice Gold' on dopamine D2/3 receptor availability: a [18F]fallypride PET study. Eur Neuropsychopharmacol 2013;23:1606-10.

56. Zimmermann US, Winkelmann PR, Pilhatsch M et al. Withdrawal phenomena and dependence syndrome after the consumption of 'spice gold'. Dtsch Arztebl Int 2009;106:464-7.

57. Di Forti M, Sallis H, Allegri F et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophr Bull (in press).

58. Celofiga A, Koprivsek J, Klavz J. Use of synthetic cannabinoids in patients with psychotic disorders: case series. J Dual Diagn 2014;10:168-73.

59. Oluwabusi OO, Lobach L, Akhtar U et al. Synthetic cannabinoid-induced psychosis: two adolescent cases. J Child Adolesc Psychopharmacol 2012;22:393-5.

60. Farre M, Papaseit E, Pérez-Mañá C et al. Human pharmacology of mephedrone: a dose-finding pilot study. Presented at the College on Problems of Drug Dependence Meeting, San Juan, June 2014.

61. Schifano F, Corkery J, Ghodse AH. Suspected and confirmed fatalities associated with mephedrone (4-methylmethcathinone; 'meow meow') in the UK. J Clin Psychopharmacol 2012;32:710-4.

62. Corkery JM, Schifano F, Ghodse AH. Mephedrone-related fatalities in the United Kingdom: contextual, clinical and practical issues. In: Lazinica A (ed). Pharmacology. Rijeka: InTech, 2012.

63. Corkery JM, Schifano F, Oyefeso A et al. 'Bundle of fun' or 'bunch of problems'? Case series of khat-related deaths in the UK. Drugs Educ Prev Policy 2011;18:408-25.

64. Loi B, Claridge H, Goodair C et al. Deaths of individuals aged 16-24 in the UK after using mephedrone. Hum Psychopharmacol (in press).

65. Warrick BJ, Wilson J, Hedge M et al. Lethal serotonin syndrome after methylone and butylone ingestion. J Med Toxicol 2012;8:65-8.

66. Schifano F, Albanese A, Fergus S et al. Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. Psychopharmacology 2011;214:593-602.

67. McCann UD, Wong DF, Yokoi F et al. Reduced striatal dopamine transporter density in the abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C]WIN-35,428. J Neurosci 1998;18:8417-22.

68. Ambrose JB, Bennett HD, Lee HS et al. Cerebral vasculopathy after 4-bromo-2,5-dimethoxyphenethylamine ingestion. Neurologist 2010;16:199-202.

69. Bosak A, LoVecchio F, Levine M. Recurrent seizures and serotonin syndrome following "2C-I" ingestion. J Med Toxicol 2013;9:196-8.

70. Topeff JM, Ellsworth H, Willhite LA et al. A case series of symptomatic patients, including one fatality, following 2C-E exposure. Clin Toxicol 2011;49:526.

71. Schifano F, Corkery J, Naidoo V et al. Comparison between amphetamine/methylamphetamine and ecstasy (MDMA, MDEA, MDA, 4-MTA) mortality data in the UK (1997-2007). Neuropsychobiology 2010;61:122-30.

72. Winstock A, Schifano F. Disorders relating to the use of ecstasy, other 'party drugs' and khat. In: Gelder M, Andreasen N, Lopez-Ibor JJ et al (eds). New Oxford textbook of Psychiatry. Oxford: Oxford University Press, 2009:494-502.

73. Corazza O, Schifano F, Farrè M et al. Designer drugs on the Internet: a phenomenon out-of-control? Analysis of anecdotal online reports relating to the hallucinogenic drug Bromo-Dragonfly. Curr Clin Pharmacol 2011;6:125-9.

74. Bersani FS, Corazza O, Albano G et al. 25C-NBOMe: preliminary data on pharmacology, psychoactive effects and toxicity of a new potent and dangerous hallucinogenic drug. Biomed Res Int (in press).

75. Davis FT, Brewster ME. A fatality involving U4Euh, a cyclic derivative of phenylpropanolamine. J Forensic Sci 1988;33:549.

76. Brewster ME, Davis FT. Appearance of Aminorex as a designer analog of 4-methylaminorex. J Forensic Sci 1991;36:587-92.

77. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). 4,4'-DMAR. Europol Joint Report on a new psychoactive substance: 4,4'-DMAR (4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine). Lisbon: EMCDDA, 2014.

78. Brandt SD, Baumann MH, Partilla JS et al. Characterization of a novel and potentially lethal designer drug, (±)-cis-para-methyl-4-methylaminorex (4,4'-DMAR, or 'Serotoni'). Drug Test Anal 2014;7:684-95.

79. Chemrus.com. www.chemrus.com.

80. Drugs-forum.com. www.drugs-forum.com.

81. Serotoni.info. www.serotoni.info.

82. European Monitoring Centre for Drugs and Drug Addiction (EUROPOL-EMCDDA). Dangerous synthetic drugs hit the EU market. www.emcdda.europa.eu.

83. Blicke FF, Burckhalter JH. α-thienylaminoalkanes. J Am Chem Soc 1942;64:477.

84. Angelov D, O'Brien J, Kavanagh P. The syntheses of 1-(2-thienyl)-2-(methylamino) propane (methiopropamine) and its 3-thienyl isomer for use as reference standards. Drug Test Anal 2011;5:145-9.

85. Bouso ED, Gardner EA, O'Brien JE et al. Characterization of the pyrolysis products of methiopropamine. Drug Test Anal 2013;6:676-83.

86. Iversen L, Gibbons S, Treble R et al. Neurochemical profiles of some novel psychoactive substances. Eur J Pharmacol 2012;700:147-51.

87. Bluelight.com. www.bluelight.com.

88. Tyers MB. A classification of opiate receptors that mediate antinociception in animals. Br J Pharmacol 1980;69:503-12.

89. Umemoto S, Nagatsuka T, Nakamura H. N-(1,2-Diphenylethyl)piperazine derivatives. Japanese patent, Jpn. Tokkyo Koho, JP 47049071 (19721209), 1972.

90. Matsuno K, Senda T, Kobayashi T et al. Reduction of 4-cyclohexyl-1-[(1R)-1,2-diphenylethyl]-piperazine-induced memory impairment of passive avoidance performance by σ1 receptor agonists in mice. Meth Find Exp Clin Pharmacol 1998;20:575-80.

91. Lindeman E, Bäckberg M, Personne M et al. MT-45 – en livsfarlig och potentiellt ototoxisk internetdrog. Lakartidningen 2014;111.pii:CZR4.

92. Brayfield A. Tilidine hydrochloride. The complete drug reference. Martindale: Pharmaceutical Press, 2013.

93. Knaus EE, Warren BK, Ondrus TA. Analgesic substituted piperidylidene-2-sulfon(cyan)amide derivatives. US Patent 4468403. CA 1255680 A1. Canadian Patents & Development Limited, 1982.

94. Carroll FI, Gao Y, Rahman P et al. Synthesis, ligand binding, QSAR, and CoMFA study of 3β-(p-substituted phenyl)tropane-2β-carboxylic acid methyl esters. J Med Chem 1991;34:2719-25.

95. Fleckenstein AE, Kopajtic TA, Boja JW et al. Highly potent cocaine analogs cause long-lasting increases in locomotor activity. Eur J Pharmacol 1996;311:109-14.

96. Carroll FI, Blough BE, Nie Z et al. Synthesis and monoamine transporter binding properties of 3-(3',4'-disubstituted phenyl)tropane-2-carboxylic acid methyl esters. J Med Chem 2005;21:2767-71.

97. Clarke RL, Daum SJ, Gambino AJ et al. Compounds affecting the central nervous system. 4. 3β-phenyltropane-2-carboxylic esters and analogs. J Med Chem 1973;16:1260-7.

98. Shulgin A, Shulgin A. TiHKAL. The continuation, 1997. www.erowid.org.

99. Sanders B, Lankenau SE, Bloom JJ et al. 'Research chemicals': tryptamine and phenylamine use among high-risk youth. Subst Use Misuse 2008;43:389-402.

100. Arunotayanun W, Dalley JW, Huang XP et al. An analysis of the synthetic tryptamines AMT and 5-MeO-DALT: emerging 'novel psychoactive drugs'. Bioorg Med Chem Lett 2013;23:3411-5.

101. United Nations Office on Drugs and Crime (UNODC). www.unodc.org.

102. Cimino G, De Stefano S. Chemistry of Mediterranean gorgonians. Simple indole derivatives from Paramuricea chamaeleon. Comp Biochem Physiol C Toxicol Pharmacol 1978;61:361-2.

103. DeKorne J. Ayahuasca analogs and plant-based tryptamines. Sacramento: The Entheogen Review, 1996.

104. Collins M. Some new psychoactive substances: precursor chemicals and synthesis-driven end-products. Drug Test Anal 2011;3:404-16.

105. Koike Y, Wada K, Kusano G et al. Isolation of psilocybin from Psilocybe argentipes and its determination in specimens of some mushrooms. Lloydia 1981;44:362-5.

106. Mckenna DJ, Towers GHN. Biochemistry and pharmacology of tryptamines and beta-carbolines: a minireview. J Psychoactive Drugs 1984;16:347-58.

107. Guichhait RB. Biogenesis of 5-methoxy-N,N-dimethyltryptamine in human pineal gland. J Neurochem 1976;26:187-90.

108. Barker SA, Monti JA, Christian ST. N,N-dimethyltryptamine: an endogenous hallucinogen. Int Rev Neurobiol 1981;22:83-110.

109. Kärkkäinen J, Räisänen M, Naukarinen H et al. Urinary excretion of free bufotenin by psychiatric patients. Biol Psychiatry 1988;24:441-6.

110. Lessin AW, Long RF, Parkes MW. Central stimulant actions of α-alkyl substituted tryptamine in mice. Br J Pharmacol 1965;24:49-67.

111. Dargan PI, Wood DM. Novel psychoactive substances: classification, pharmacology and toxicology. London: Academic Press/Elsevier, 2013.

112. Cozzi NV, Gopalakrishnan A, Anderson LL. Dimethyltryptamine and other hallucinogenic tryptamines exhibit substrate behavior at the serotonin uptake transporter and the vesicle monoamine transporter. J Neural Transm 2009;116:1591-9.

113. Fantegrossi WE, Murnane KS, Reissig CJ. The behavioural pharmacology of hallucinogens. Biochem Pharmacol 2008;75:17-33.

114. Nichols DE. Hallucinogens. Pharmacol Ther 2004;101:131-81.

115. Fontanilla D, Johannessen M, Hajipour AR et al. The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. Science 2009;323:934-7.

116. Psychonautwiki.com. http://wiki.tripsit.me.

117. Ray TS. Psychedelics and the human receptorome. PLoS One 2010; 5:e9019.

118. Sogawa C, Sogawa N, Tagawa J et al. 5-methoxy-N,N-diisopropyltryptamine (Foxy), a selective and high affinity inhibitor of serotonin transporter. Toxicol Lett 2007;170:75-82.

119. Ujvary I. Psychoactive natural products: overview of recent developments. Ann Ist Super Sanità 2014;50:12-27.

120. Lyttle T, Goldstein D, Gartz J. Bufo. Toads and bufotenine: fact and fiction surrounding an alleged psychedelic. J Psychoactive Drugs 1996;28:267-90.

121. Wilcox J. Psychoactive properties of alpha-methyltryptamine: analysis from self reports of users. J Psychoactive Drugs 2012;44:274-6.

122. Gallimberti L, Schifano F, Forza G et al. Clinical efficacy of gamma-hydroxybutyric acid in treatment of opiate withdrawal. Eur Arch Psychiatry Clin Neurosci 1994;244:113-4.

123. Brennan R, Van Hout MC. Gamma-hydroxybutyrate (GHB): a scoping review of pharmacology, toxicology, motives for use, and user groups. J Psychoactive Drugs 2014;46:243-51.

124. Palatini P, Tedeschi L, Frison G et al. Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. Eur J Clin Pharmacol 1993;45:353-6.

125. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Report on the risk assessment of GHB in the framework of the joint action on new synthetic drugs. Lisbon: EMCDDA, 2002.

126. Galloway GP, Frederick SL, Staggers F Jr. Physical dependence on sodium oxybate. Lancet 1994;343:57.

127. Corkery JM, Loi B, Clardige H et al. The evolution and characteristics of UK deaths involving GHB and its analogues. Presented at the 3rd International Conference on Novel Psychoactive Substances, Rome, May 2014. Red Adv Psychiatry 2014;1(Suppl.1):16.

128. Peng CT, Ger J, Yang CC et al. Prolonged severe withdrawal symptoms after acute-on-chronic baclofen overdose. J Toxicol Clin Toxicol 1998;36:359-63.

129. Breslow MF, Fankhauser MP, Potter RL et al. Role of gamma-aminobutyric acid in antipanic drug efficacy. Am J Psychiatry 1989;146:353-6.

130. Franklin TR, Harper D, Kampman K et al. The $GABA_B$ agonist baclofen reduces cigarette consumption in a preliminary double-blind placebo-controlled smoking reduction study. Drug Alcohol Depend 2009;103:30-6.

131. Haney M, Hart CL, Foltin RW. Effects of baclofen on cocaine self-administration: opioid- and nonopioid-dependent volunteers. Neuropsychopharmacology 2006;31:1814-21.

132. Shoptaw S, Yang X, Rotheram-Fuller EJ et al. Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for

individuals with chronic patterns of cocaine use. J Clin Psychiatry 2003;64:1440-8.

133. Schep LJ, Knudsen K, Slaughter RJ et al. The clinical toxicology of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol. Clin Toxicol 2012;50:458-70.

134. Kapil V, Green JL, Le Lait MC et al. Misuse of the γ-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. Br J Clin Pharmacol 2014;78:190-1.

135. Lee TH, Chen SS, Su SL et al. Baclofen intoxication: report of four cases and review of the literature. Clin Neuropharmacol 1992;15:56-62.

136. Erowid.org. www.erowid.org.

137. Haubenstock A, Hruby K, Jager U et al. Baclofen (Lioresal) intoxication report of four cases and review of the literature. Clin Toxicol 1983;20:59-68.

138. Coffey RJ, Edgar TS, Francisco GE et al. Abrupt withdrawal from intrathecal baclofen: recognition and management of a potentially life-threatening syndrome. Arch Phys Med Rehabil 2002;83:735-41.

139. Meythaler JM, Roper JF, Brunner RC. Cyproheptadine for intrathecal baclofen withdrawal. Arch Phys Med Rehabil 2003;84:638-42.

140. Helander A, Bäckberg M, Beck O. MT-45, a new psychoactive substance associated with hearing loss and unconsciousness. Clin Toxicol 2014;52:901-4.

141. Lapin I. Phenibut (beta-phenyl-GABA): a tranquilizer and nootropic drug. CNS Drug Rev 2001;7:471-81.

142. Nurmand LB, Otter MI, Vasar EE. Effect of structural analogs of gamma-aminobutyric acid on serotonin- and dopaminergic mechanisms. Farmakol Toksikol 1980;43:288-91.

143. ReDNet Research Group. Phenibut full report. London: King's College London, Institute of Psychiatry, 2012.

144. Samokhvalov AV, Paton-Gay CL, Balchand K et al. Phenibut dependence. BMJ Case Rep 2013;2013.

145. Högberg L, Szabó I, Ruusa J. Phenibut yielded withdrawal symptoms and psychosis. Drugs for cosmonauts – now marketed as dietary supplements online. Lakartidningen 2013;110:825-7.

146. Schmitt C, Gégu C, Spadari M et al. Use of phenibut in France: report of two cases. Therapie 2013;68:123-4.

147. Ronn M. Serotonin syndrome or phenibut overdose: a case study. J Am Pharm Assoc 2003;53:e151-70.

148. Chiappini S, Claridge H, Corkery J et al. Special M related fatalities in the UK. Res Adv Psychiatry 2014;1(Suppl. 1):38.

149. Corazza O, Schifano F, Simonato P et al. Phenomenon of new drugs on the Internet: the case of ketamine derivative methoxetamine. Hum Psychopharmacol 2012;27:145-9.

150. Schifano F, Corkery J, Oyefeso A et al. Trapped in the 'K-hole'; overview of deaths associated with ketamine misuse in the UK (1993-2006). J Clin Psychopharmacol 2008;28:114-6.

151. Waelbers T, Polis I, Vermeire S et al. 5-HT2A receptors in the feline brain: 123I-5-I-R91150 kinetics and the influence of ketamine measured with micro-SPECT. J Nucl Med 2013;54:1428-33.

152. Nishimura M, Sato K. Ketamine stereoselectively inhibits rat dopamine transporter. Neurosci Lett 1999;274:131-4.

153. Advisory Council on the Misuse of Drugs (ACMD). Ketamine: a review of use and harm. London: ACMD, 2013.

154. Morgan CJ, Monaghan L, Curran HV. Beyond the K-hole: a 3-year longitudinal investigation of the cognitive and subjective effects of ketamine in recreational users who have substantially reduced their use of the drug. Addiction 2004;99:1450-61.

155. Luciano RL, Perazella MA. Nephrotoxic effects of designer drugs: synthetic is not better! Nat Rev Nephrol 2014;10:314-24.

156. Corazza O, Schifano F. Ketamine-induced 'near-death experience' states in a sample of 50 misusers. Subst Use Misuse 2010;45:916-24.

157. Dargan PI, Tang HC, Liang W et al. Three months of methoxetamine administration is associated with significant bladder and renal toxicity in mice. Clin Toxicol 2014;52:176-80.

158. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Risk assessments. Methoxetamine. Report on the risk assessment of 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine) in the framework of the Council Decision on new psychoactive substances. Lisbon: EMCDDA, 2014.

159. Morris H, Wallach J. From PCP to MXE: a comprehensive review of the non-medical use of dissociative drugs. Drug Test Anal 2014;6:614-32.

160. Chyka PA, Erdman AR, Manoguerra AS et al. Dextromethorphan poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol 2007;45:662-77.

161. Miller SC. Dextromethorphan psychosis, dependence and physical withdrawal. Addict Biol 2005;10:325-7.

162. Kersten BP, McLaughlin ME. Toxicology and management of novel psychoactive drugs. J Pharm Pract (in press).

163. Munro TA, Duncan KK, Xu W et al. Standard protecting groups create potent and selective kappa opioids: salvinorin B alkoxymethyl ethers. Bioorg Med Chem 2008;16:1279-86.

164. Gericke N, Viljoen AM. Sceletium – a review update. J Ethnopharmacol 2008;119:653-63.

165. Abe N, Ali Z, Khan IA. Structure of novel alkaloids from Sceletium tortuosum. Planta Med 2013;79:P34.

166. Baum SS, Hill R, Rommelspacher H. Effect of kava extract and individual kavapyrones on neurotransmitter levels in the nucleus accumbens of rats. Prog Neuropsychopharmacol Biol Psychiatry 1998;22:1105-20.

167. Seitz U, Schüle A, Gleitz J. [3H]-monoamine uptake inhibition properties of kava pyrones. Planta Med 1997;63:548-9.

168. Ligresti A, Villano R, Allarà M et al. Kavalactones and the endocannabinoid system: the plant-derived yangonin is a novel CB_1 receptor ligand. Pharmacol Res 2012;66:163-9.

169. Sarris J, LaPorte E, Schweitzer I. Kava: a comprehensive review of efficacy, safety, and psychopharmacology. Aust N Zeal J Psychiatry 2011;45:27-35.

170. Bulling S, Schicker K, Zhang YW et al. The mechanistic basis for noncompetitive ibogaine inhibition of serotonin and dopamine transporters. J Biol Chem 2012;287:18524-34.

171. Vlaanderen L, Martial LC, Franssen EJ et al. Cardiac arrest after ibogaine ingestion. Clin Toxicol 2014;52:642-3.

172. Baccarin J. Esiste un potenziale di misuso dei Magnololi? Analisi qualitativa dei report online. MD dissertation. University of Padua, 2014.

173. Lee WT, Lin MH, Lee EJ et al. Magnolol reduces glutamate-induced neuronal excitotoxicity and protects against permanent focal cerebral ischemia up to 4 hours. PLoS One 2012;7:e39952.

174. Rempel V, Fuchs A, Hinz S et al. Magnolia extract, magnolol, and metabolites: activation of cannabinoid CB2 receptors and blockade of the related GPR55. ACS Med Chem Lett 2012;4:41-5.

175. Taïwe GS, Bum EN, Talla E et al. Nauclea latifolia Smith (Rubiaceae) exerts antinociceptive effects in neuropathic pain induced by chronic constriction injury of the sciatic nerve. J Ethnopharmacol 2014;151:445-51.

176. Schifano F, D'Offizi S, Piccione M et al. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother Psychosom 2011;80:118-22.

177. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS Drugs 2014;28:491-6.

178. Rafstedt K, Hultén P, Brusiu K. Phenazepam as a drug of abuse – high frequency of prolonged symptoms. Presented at the 29th International Congress of the European Association of Poison Centers and Clinical Toxicologists, Stockholm, May 2009. Clin Toxicol 2009;47:436-510.

179. Johnson B. New "old" drug: phenazepam (fenazepam). ToxTalk (SOFT) 2010;34:17-8.

180. Corkery J, Schifano F, Ghodse AH. Phenazepam abuse in the UK: an emerging problem causing serious adverse health problems, including death. Hum Psychopharmacol 2012;27:254-61.

181. Valeriani G, Corazza O, Bersani FS et al. Olanzapine as the ideal 'trip terminator'? Analysis of online reports relating to antipsychotics' use and misuse following occurrence of novel psychoactive substance-related psychotic symptoms. Hum Psychopharmacol (in press).

182. Klein-Schwartz W, Schwartz EK, Anderson BD. Evaluation of quetiapine abuse and misuse reported to poison centers. J Addict Med 2014;8:195-8.

183. Malekshahi T, Tioleco N, Ahmed N et al. Misuse of atypical antipsychotics in conjunction with alcohol and other drugs of abuse. J Subst Abuse Treat (in press).

184. Shang Y, Gibbs MA, Marek GJ et al. Displacement of serotonin and dopamine transporters by venlafaxine extended release capsule at steady state: a [123I]2beta-carbomethoxy-3beta-(4-iodo-phenyl)-tropane single photon emission computed tomography imaging study. J Clin Psychopharmacol 2007;27:71-5.

185. Weikop P, Kehr J, Scheel-Krüger J. The role of alpha1- and alpha2-adrenoreceptors on venlafaxine-induced elevation of extracellular serotonin, noradrenaline and dopamine levels in the rat prefrontal cortex and hippocampus. J Psychopharmacol 2004;18:395-403.

186. Stahl SM. Essential psychopharmacology. Neuroscientific basis and pratical applications, 4th ed. Cambridge: Cambridge University Press, 2013.

187. Gallegos A. The EU early warning system: NPS. Presented at the 16th World Congress of Psychiatry, Madrid, September 2014.

188. Bersani FS, Corazza O, Simonato P et al. Drops of madness? Recreational misuse of Tropicamide collyrium: early warning alerts from Russia and Italy. Gen Hosp Psychiatry 2013;35:571-3.

189. Minervini L, Antonielli Romanini F, Solmi M et al. Acute psychotic episode associated with the intake of a testosterone-enhancer herbal mixture purchased online. Psychother Psychosom 2012;81:248-9.

190. Grundlingh J, Dargan PI, El-Zanfaly M et al. 2,4-dinitrophenol (DNP): a weight loss agent with significant acute toxicity and risk of death. J Med Toxicol 2011;7:205-12.

191. Cohen PA. DMAA as a dietary ingredient. JAMA Intern Med 2012;173:1038-9.

192. Cohen PA, Travis JC, Venhuis BJ. A synthetic stimulant never tested in humans, 1,3-dimethylbutylamine (DMBA), is identified in multiple dietary supplements. Drug Test Anal (in press).

193. Brennan R, Van Hout MC, Wells J. Heuristics of human enhancement risk: a little chemical help? Int J Health Promot Educ (in press).

194. Van Hout MC, Brennan R. An in-depth case examination of an exotic dancer's experience of melanotan. Int J Drug Policy 2014;25:444-50.

195. Corazza O, Bersani FS, Brunoro R et al. Performance and image enhancing drugs: the abuse of cognitive enhancer piracetam. Subst Use Misuse (in press).

196. Winblad B. Piracetam: a review of pharmacological properties and clinical uses. CNS Drug Rev 2005;11:169-82.

197. Jordaan B, Oliver DW, Dormehl IC et al. Cerebral blood flow effects of piracetam, pentifylline, and nicotinic acid in the baboon model compared with the known effect of acetazolamide. Arzneimittelforschung 1996;46:844-7.

198. Corazza O, Martinotti G, Santacroce R et al. Sexual enhancement products for sale online: raising awareness of the psychoactive effects of

yohimbine, Maca, Horny Goat Weed and Ginkgo Biloba. BioMed Res Int (in press).

199. Brisch R, Saniotis A, Wolf R et al. Corrigendum: The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue. Front Psychiatry 2014;5: 110.

200. Hajós M, Hoffmann WE, Kocsis B. Activation of cannabinoid-1 receptors disrupts sensory gating and neuronal oscillation: relevance to schizophrenia. Biol Psychiatry 2008;63:1075-83.

201. Selvaraj S, Arnone D, Cappai A et al. Alterations in the serotonin system in schizophrenia: a systematic review and meta-analysis of postmortem and molecular imaging studies. Neurosci Biobehav Rev 2014;45:233-45.

202. Genius J, Geiger J, Dölzer AL et al. Glutamatergic dysbalance and oxidative stress in in vivo and in vitro models of psychosis based on chronic NMDA receptor antagonism. PLoS One 2013;8:e59395.

203. Ranganathan M, Schnakenberg A, Skosnik PD et al. Dose-related behavioral, subjective, endocrine, and psychophysiological effects of the κ opioid agonist Salvinorin A in humans. Biol Psychiatry 2012;72:871-9.

204. Mugele J, Nanagas KA, Tormoehlen LM. Serotonin syndrome associated with MDPV use: a case report. Ann Emerg Med 2012;60:100-2.

205. Littlejohn C, Baldacchino A, Schifano F et al. Internet pharmacies and online prescription drug sales: a cross-sectional study. Drugs – Educ Prev Polic 2005;12:75-80.