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The "Legal Highs" of Novel Drugs of Abuse

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Abstract

The abuse of drugs is a widespread and growing issue, both in United States and Europe, as a number of synthetic drugs have raised popularity over the past years for recreational use. Moreover, the nature of addiction is often debated as either a *lifestyle choice* that may underline a *physiological vulnerability,* or a chronic brain disease with remarkable epigenetic, neurodevelopmental and sociocultural components. Consciousness and treatment of new drugs of abuse give challenges for health care practitioners primarily due to a lack of quantitative reports. As law enforcements struggle to ban these often referred as "legal highs", new compounds are produced. Also, a major problem in tracking these drugs is that they are easily available through head shops, the web and other sources, therefore giving rise to a high risk of suspected intoxication. The aim of this article is to highlight the pharmaco-toxicological features of some common drugs of abuse such as central nervous system stimulants as synthetic cannabinoids, synthetic cathinones, gabapentin, acetyl fentanyl, phenethylamine called NBOMe, hallucinogenic mushrooms, piperazines, tryptamines, salvia, methoxetamine, kratom and performance-enhancing drugs. The tremendous heterogeneity of these drugs results in variable pharmacokinetic and pharmacodynamic effects, thus suspected intoxication is a priority diagnosis in order to ensure safety of patients and needs to be handled with the guide of the patient's symptoms through specific and detailed urine and blood analysis.

Keywords: Drugs of abuse; Cannabinoids; Cathinones; Salvia; Kratom; Gabapentin

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Introduction

Drugs of abuse are currently a growing problem, especially in the most westernized countries, whereas novel drugs have become increasingly popular. Drug addiction is described as a progression from impulsive to compulsive behavior, ending in chronic, relapsing drug taking. Patients with impulse control disorders experience an increasing sense of tension or arousal before committing an impulsive act; pleasure, gratification or relief at the time of committing the act; and then regret, selfreproach or guilt after the act [1]. The nature of addiction is often debated as either a *lifestyle choice* that may underline a *physiological vulnerability.* The development of the aversive emotional state that drives the negative reinforcement of addiction is termed the 'dark side' of addiction [2].

A brief description of the mechanisms of action through which drugs of abuse exert their reinforcing effects is that they trigger supraphysiologic surges of dopamine in the nucleus accumbens that activate the direct striatal pathway via Dopamine 1 (D1) receptors and inhibit the indirect striato-cortical pathway via Dopamine D2 (D2) receptors [3].

Drugs modulate the expression of genes involved in neuroplasticity via epigenetic and RNA modifications, thus altering intracellular cascades and the neuronal circuits whose dysfunction have been implicated in the long-lasting changes associated with addiction [4, 5]. It is important for health care practitioners to keep up with "the latest" of the drugs of abuse, especially due to lack of quantitative reporting and surveillance and to recognize substance use disorders in order for patients to be transitioned to the most appropriate recovery hospital or clinic. Patient management is primarily driven by the symptoms and basic laboratory screenings are important to help diagnosis and organ damage [6]. Many of these novel drugs have similar effects and respond well to careful supportive management. On the other hand, typical toxic symptoms are not precipitated equally by many of these agents, because most new designer drugs are not detected with conventional drug testing. A quick look into

the epidemiology shows that in 2015 in Europe an estimated 5,7% of young adults (15-34 years old) have used cannabinoids, a 1% have used cocaine, a 0,5% and 0,6% amphetamine and ecstasy respectively, whereas a 1,3 millions of adults (15-64 years old) have consumed opioids [7]. On the other hand, an estimated 23,9 million Americans (12 years old or older) are currently under illicit abuse drugs. In this case the illicit drugs routinely surveyed include hashish, cocaine, hallucinogens, marijuana [8]. So far with the most known abuse substances, but there is an increasing evidence of a over-the-counter drug abuse and misuse, such as weight control drugs (some of them may contain pseudoephedrine, banned by the WADA (World Antidoping Agency) [9]. The majority of the new drugs are synthetic cannabinoids, amphetamine-like stimulants, opioid-like substances, or hallucinogens [10, 11]. In this article the pharmacology and clinical effects of these drugs are described.

Performance-enhancing drugs

Currently, these compounds can not be considered drugs of abuse *per se*, but the popularity and the repetitive use, especially among athletes, may eventually lead to tolerance and addiction with consumption at higher doses. Performance-enhancing drugs, whether they are prescription-based such as anabolic steroids or growth hormone or sold in sport nutrition shops, are becoming more popular among athletes as pre and post-workout supplements, based upon the drive and incentive to perform at always higher levels. They may then represent putative drugs of abuse, as long as they may exert reinforcing effect by activating reward circuits in the brain. Initial drug assumption is largely a voluntary behavior, but continued drug use may impair brain function by interfering with the capacity to exert self-control over drug-taking behavior, thus rendering the brain more sensitive to stress and eventually to negative moods [3-12].

NBOME

Newer drugs, such as NBOMe have gained popularity over the past years. They are phenethylamine derivatives of the 2C group of hallucinogen. The most common of these drugs is 25C-NBOMe which has legally replaced the lysergic acid (LSD) [13-15]. Administration route may include buccal, sublingual, nasal, oral, parenteral, rectal and inhalation [12]. They show both a stimulatory and hallucinogen clinical effect [16, 17]. Their symptoms may include nausea, vomiting, dizziness, diarrhea, headaches, body aches, depression confusion and hallucination [18].

Hallucinogenic mushrooms

Also various "magic mushrooms" have also long been used for inducing hallucinations experiences and show a large variation in potency. Species of Psilocybe produce the alkaloid psilocybin (4-phosphoryloxy-N, Ndimethyltryptamine), which is hydrolysed to psilocin in the gut. Psilocybin is an agonist of several serotonin subreceptors (5-HT), including 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C, and it binds to these receptors with various degrees of affinity (for a review, see [19]).

This compound mimics a serotonin uptake inhibitor, invokes psychotropic experiences and have similar effects to DMT and other hallucinogenic compounds [20]. There are 22 species of mushrooms in the genus Psilocybe that contain psilocybin in the United States and Canada [21], as well as a number of species in other genera that contain psilocybin [22]. There is little information regard potential synergistic and/or antagonist impacts on humans if different drugs are taken in combination. However it may be speculated that alcohol may enhance the adverse effects induced by "magic mushrooms". Infact both psilocine and psilocybine are rapidly inactivated by the enzyme MAO (mono amine oxidase, which catalyses the oxidative deamination of biogenic amines). Acetaldehyde, the primary metabolite of ethanol, reacts with endogenous biogenic amines thereby producing the MAO-inhibitors tetrahydroisoquinolines and b-carbolines (tryptolines) (see review [23]). Also tobacco use is associated with lowered levels of MAO in the brain and peripheral organs [24, 25]. Tobacco smokers may therefore experience more pronounced desired and adverse effects of magic mushrooms compared to non-smoker (see review [23]).

Synthetic cathinones

Stimulants are a variety of substances able to enhance focus and wakefulness, mood, and ultimately decrease ingestive behavior. Well known are nicotine, methylxanthines and amphetamines. More recently, cathinones, also known as bath salts, have been added. They were marketed as “legal highs” as central nervous system (CNS) stimulants and “not for human consumption” to avoid regulatory oversights [26]. Their mechanism of action is similar to other stimulants, therefore changing monoamine transporters through which serotonin, dopamine and norepinephrine are taken from central synaptic clefts, resulting in increased postsynaptic neurotransmission [27].

They are found in the leaves of the khat plant (*Catha edulis*) which also contains norephedrine [28, 29]. Many are the routes of administration for bath salts, varying from insufflating (snorting) to oral ingestion, but also intravenous, intramuscular and per-rectum administration [30-32]. Stimulants are strongly searched after as they show psychoactive effects such as increased energy, decreased appetite and decreased sleep. Therefore, their use could be as rewarding as drinking caffeine or chewing khat or coca leaves for cognitive enhancing performaces, but it may also result in severe addiction or psychiatric disorders, especially paranoia and hallucinations [33, 34]. Cardiovascular effects may also be related to the stimulant effects of cathinones, with symptoms including chest pain, palpitations, hypertension and tachycardia [30, 31]. Furthermore, long-term effects of bath salts are still unknown.

Synthetic cannabinoids

Synthetic cannabinoids (SC) refer to a growing of man made chemicals and represent one the most illicit substances both worldwide and in the United States, that are either sprayed on dried, shredded plant material, so they can be smoked as herbal incense or sold in liquid form to be vaporized and inhaled in e-cigarettes [35]. They have similar psychotropic

effects to marijuana that contains the active component Δ9-tetrahydrocannabinol (THC) [36-38]. These products may be found in "head shops", convenience stores, and over the Internet as herbal incense or air fresheners and were marketed as "not for human consumption" [39]. Many substances compose SC and "K2" and "Spice" are the most common. They act through cannabinoid receptors with a large number of biologic targets. A high density of CB1 receptors are present in the brain and modulate gamma-aminobutyrric acid (GABA) and glutamate transmission, whereas CB2 receptors are found in the CNS and in peripheral tissues (spleen and immune cells) and mediate immunosuppression [26-40]. Onset and duration appear to be similar to marijuana but vary based on the product ingested [41]. Clinical effects of SC comprise a variety of target organs, such as CNS, heart, gut, kidney, eye. Other effects are on metabolism and hyperthermia, tolerance, withdrawal and dependence. Adverse effects include anxiety, paranoia, hallucinations, sedation, psychosis and seizures [26-39]. Cardiovascular effects include hypertension and tachycardia [42, 43]. Other adverse effects may include nausea, vomiting, and acute kidney injury [44-46]. Long-term and chronic effects of SC use are difficult to characterize and unknown. Nevertheless, long-term users may be at increased risk for new-onset and relapse of psychosis and reduced brain volume and emotional processing [47, 48]. Moreover, cognitive deficits and memory impairment were reported with chronic marijuana use [49].

Gabapentin

Gabapentin was approved in the United States in 1993 for the treatment of seizure disorder, but since that time, it has increasingly been prescribed for a number of other conditions. It is a analog that is structurally related to GABA, but it does not bind to the GABA receptors or affect GABA binding, uptake, or degradation. Nevertheless, blockinging voltage-dependent calcium channels, Gabapentin results to affect CNS [50]. Because of its CNS effects, recent findings have shown that Gabapentin might become a drug of abuse. So far, it may have benefit for some anxiety disorders and has clearer efficacy for alcohol craving and withdrawal symptoms and may play a role in adjunctive treatment of opioid dependence. More recently, it has been shown that gabapentin is increasingly used by patients in methadone maintenance programs to get "legal highs". It is apparently effective and safe, but comes with the potential for misuse and negative sequelae (Joseph Insler, Medscape Medical News). Eight case reports show the abuse and dependence of gabapentin, occurring in patients with a previous history of drug abuse or dependence [51]. Also it has been demonstrated that abuse of gabapentin is associated with opioid addiction [52]. Further research is required to better clarify the association with abuse.

Kratom

Kratom is an opioid-like tropical tree from Southest Asia, traditionally used by dwellers from Thailand and Malaysia to alleviate musculoskeletal pain and to increase energy, appetite, sexual desire [53, 54]. Other claimed beneficial effects of Kratom include antipyretic antihypertensive, antinflammatory, antidiarrheal and hypoglicemic effects [26]. Recently it has gained recognition in Western countries as a "natural alternative" for self treated chronic pain and a remedy for opioid withdrawal [55]. Kratom is readily available on the Internet and gained popularity in its use and abuse [56]. Most commonly it is use for the hallucinogenic effects but also, to a lesser extend, for management of opioid withdrawal. Kratom contains more than 40 alkaloids that interact with opioid and monoaminergic receptors, even though it is not related to opioids [57]. Mitragynine is responsible for its opioid-like effects [55]. The drug is usually smoked, but it can also be ingested after being brewed into a tea. Onset of effect occurs 5-10 min after assumption and it lasts for about 2 to 5 h [58, 59]. Toxicological effects are rare and only occurs in high dosages [55]. Adverse effects are similar to opioids and include nausea, vomiting, constipation, respiratory depression, itching, dry mouth, increased urination, anorexia and palpitations [53].

Acetyl Fentanyl

Acetyl fentanyl (N-[1-phenethylpiperidin-4-yl]-Nphenylacetamide) is one of countless novel psychoactive substances that have been linked to several recent deaths in Rhode Island, Pennsylvania, North Carolina, and Louisiana [60, 61].This drug is an opioid analgesic, chemically similar to the medicinally used fentanyl, but it is not approved for therapeutic uses. Studies suggest that it is 5 to 15 times more potent than heroin [62], approximately 6 times as potent as morphine [63]. Although the pharmacological effects of Acetyl Fentanyl have not been specifically investigated clinically in humans, fentanyl-like substances have been generally associated with euphoria, altered mood, drowsiness, miosis, cough suppression, constipation and respiratory depression [64]. Moreover Fentanyl and its analogs are typically lipophilic, readily cross the blood–brain barrier and accordingly, display a rapid onset of analgesic effects [65].

Acetyl fentanyl is typically administered in transdermal patch or intravenous injectable formulations, as a direct substitute or mixed with heroin or other substances among dependent users [64]. However, acetyl fentanyl exists in a legal gray area: it is considered illicit if intended for human consumption, but it evades regulation if packaged with the qualifier "not for human consumption" [66]. In comparison with traditional drugs of abuse, medical doctors have greater difficulty with the diagnosis. In fact clinicians should suspect acetyl fentanyl was the causal agent if a patient unresponsive to standard naloxone doses was revived by a megadose or responds to naloxone but screens negative for heroin [67]. Thus regulatory challenges are really need, maybe with the elimination of the exemption for products containing an analogue of a controlled substance when labeled "not for human consumption".

Salvia

Salvia is derived from the ethnomedical plant *Salvia divinorum*. Recently it has become more readily available to consumers due to distribution through head shops and the Internet. It is endorsed with potent hallucinogen properties in humans. The active

compound, salvironin A is a selective high efficacy kappa-opioid receptor (KOPr) agonist, including mu-opioid receptor (MOPr), the target of opioid alkaloids, such as morphine [68, 69] and it is pharmacologically distinct from other known hallucinogens in humans. Salvinorin A causes sedative-like and locomotor-decreasing effects in rodent and non-human primate models (including unresponsiveness to environmental stimuli) [70-72]. These effects are qualitatively similar to those of synthetic KOPr agonists, and are sensitive to KOPr antagonism [70-72]. KOPr agonist have neuroendocrine effects, primarily mediated by KOPr at different hypothalamic sites, including prolactin release and also stimulation of Hypothalamus-Hypophysis-Axis (HPA), Adrenocorticotropin hormone (ACTH) and cortisol [73-76]. Salvironin A also results in anhedonia in intracranial self-stimulation (ICSS) assays and depressant-like effects in the forced swin test, similarly to synthetic KOPr agonists [77, 78]. These findings may explain that prolonged high efficacy signaling, through KOPr, results in behavioral and neurobiological effects associated with human neuropsychiatric conditions, especially depression-like and anxiety-like states, and specific addictions. Carefully controlled studies in human, initially experienced hallucinogen or Salvia Divinorum users, characterized the effects of salvinorin A smoking (0,75.21 µg/kg), the effect being of rapid onset, peaked by 2 min after inhalation and declined by 30 min [79, 80]. Under these carefully monitored conditions, volunteers reported robust hallucinogenic-like effects, depersonalization and derealization, but no robust dysphoria or aversion [79]. It is unknown if effects in a different population (i.e., non-hallucinogen users) would show a more robust dysphoria/aversion signal, consistent with effects observed in preclinical rodent models [71-77], or dysphoric effects reported with synthetic KOPr agonists in humans [81-84]. A separate study with smoked salvinorin A (in volunteers with previous self-exposure to *Salvia divinorum*) reported dose-dependent and reversible psychomimetic effects, dissociation, and neuroendocrine effects (increases in serum cortisol and prolactin) [84]. A further study examined the effects of *Salvia divinorum* smoking, and characterized subjective experiences including cognitive alterations, which were also robust and time-dependent [85]. Therefore, based upon these cited studies Salvinorin A act as a potent and fast-acting high efficacy KOPr agonist. Still unclear are the potential harm and degree of dependence in humans from recreational use of Salvia. The most common symptoms recognized were confusion or disorientation, hallucinations, giddiness, dizziness, flushed sensation and tachycardia.

Methoxetamine

Methoxetamine has recently become available via the Internet and is marked as “legal ketamine” that was specifically created in 2010 for sale on the gray market as a ‘bladder-safe’ substitute for the dissociative anaesthetic ketamine, from which it is also derived [86, 87]. Preclinical data highlighted a stimulatory effect of Methoxetamine on dopamine neurotransmission within the mesolimbic pathway such as, mood enhancement with hallucinogenic, dissociative aspects and it may have high addictive potential [88]. At higher doses a profoundly altered state of consciousness [89, 90] and psychomotor agitation, anxiety, paranoid and psychotic reactions, disorientation, somatic reactions, cerebellar symptoms as well as acute cerebellar toxicity [91]. It appears to have similar clinical effects to its parent drug and seems not to have a specific type or class of users. A study carried out in south-east London reported that Methoxetamine as used by 315 individuals, mostly men aged 18–59 years [92]. Specifically, 6.4% of users reported using Methoxetamine occasionally, but data by the end of 2012 reported a slight reduction (<3%) in the occasional use of Methoxetamine by clubbers in the UK, which was likely because of local temporary control measures [93]. In fact the secretary of state in the UK made a Temporary Class Drug Order under the Misuse of Drugs Act, 1971, (SI2012/980) for methoxetamine and its simple derivatives, recognizing their potential toxicity without having no legitimate medical or industrial use [94].

Emergency evaluation and patient management

Safety is a major concern and priority, when assessing a patient under the influence of these novel drugs of abuse. Many of them may have an altered sensorium and may be unable to provide a robust history surrounding the ingestion. Once safety is established, initial approach consists of ensuring a patient airway and adequate breathing. Much like treating many emergency patients, the management of the poisoned patient consists of common sense and supportive care. The standard A, B, C (Airway, Breathing, Circulation) approach is the common framework to utilize when treating an intoxicated subject. Also profound CNS depression can result in the loss of protective airway reflexes and intubation may be required in case a patient cannot handle reflex of secretions. Naloxone administration should be considered in patients with CNS and respiratory depression, as well as benzodiapezines may be indicated for seizures having a toxicologic cause. Circulatory status can be assessed through evaluation of the patient's vital signs and perfusion status. Hypertension and hypotension have both been diagnosed in intoxicated patients and these two conditions require appropriate intervention. Sedation can also be required in case of an acutely agitated patient. In spite of the classical pharmacological therapy with haloperidol, diphenhydramine and lorazepam, which have overall some disadvantages, benzodiazepines have been proved effective in the management of agitation whether the cause is a drug of abuse or withdrawal syndromes. At present, benzodiazepines are the drugs of choice in the treatment of alcohol withdrawal syndrome but also non-benzodiazepine anticonvulsants carbamazepine and oxcarbazepine [95], topiramate [96], valproic acid demonstrate effective and safe (see review [97]).

Moreover, once the initial recovery has been completed, a more thorough assessment should occur, tracing back the history that elicited the substance of abuse. In this case, laboratory tests may be useful in the evaluation of a patient with altered mental status. Blood testing, such as CBC, prothrombin time, liver profile, metabolic profile and creatine phosphokinase level are useful tools to highlight an end-organ complications from acute or chronic drug abuse.

Conclusion

New drugs and drug use trends often shows up on the scene very rapidly, raising a worldwide problem whose rate of development outpaces that of legislation. Due to the large availability on the market, healthcare professionals should be continuously aware of the newest trends in synthetic drugs abuse and the physiologic and psychiatric consequences of intoxication. Patients, especially those with a history of addiction, should be educated about the dangers of substances. The general population, especially parents, should take notice to help deter experimentation and subsequent addiction, physical injury, and therefore possible death.

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