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Novel Psychoactive Substances—Recent Progress on Neuropharmacological Mechanisms of Action for Selected Drugs

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A feature of human culture is that we can learn to consume chemical compounds, derived from natural plants or synthetic fabrication, for their psychoactive effects. These drugs change the mental state and/or the behavioral performance of an individual and can be instrumentalized for various purposes. After the emergence of a novel psychoactive substance (NPS) and a period of experimental consumption, personal and medical benefits and harm potential of the NPS can be estimated on evidence base. This may lead to a legal classification of the NPS, which may range from limited medical use, controlled availability up to a complete ban of the drug form publically accepted use. With these measures, however, a drug does not disappear, but frequently continues to be used, which eventually allows an even better estimate of the drug's properties. Thus, only in rare cases, there is a final verdict that is no more questioned. Instead, the view on a drug can change from tolerable to harmful but may also involve the new establishment of a desired medical application to a previously harmful drug. Here, we provide a summary review on a number of NPS for which the neuropharmacological evaluation has made important progress in recent years. They include mitragynine ("Kratom"), synthetic cannabinoids (e.g., "Spice"), dimethyltryptamine and novel serotonergic hallucinogens, the cathinones mephedrone and methylone, ketamine and novel dissociative drugs, γ-hydroxybutyrate, γ-butyrolactone, and 1,4-butanediol. This review shows not only emerging harm potentials but also some potential medical applications.

Keywords: Kratom, synthetic cannabinoids, dimethyltryptamine, serotonergic hallucinogens, mephedrone, ketamine, γ-hydroxybutyrate

INTRODUCTION

It appears to be a human trait to constantly seek for new psychoactive substances and to explore potential use of them. As long as human record keeping dates back, humans consume psychoactive plant preparations. Since centuries they isolated single compounds yielding "natural drugs," while since decades synthetic chemistry allowed the innovation of completely new compounds that are not

available from natural resources (1, 2). Despite the risk of being toxic upon single or chronic consumption, there are constantly new drugs that find their way into drug-taking communities (3).

Novel stimuli and novel information about the external world have an incentive salience and maintain seeking behavior in animals and in humans (4, 5). The search for novel external stimuli may translate to novel "mental states," as an experience of new interoceptive states. Human brains generate distinct working modes that are subjectively perceived as mental states. This is at the neurobiological side believed to be organized by the summatory tonic activity of modulatory transmitter systems. Mental states can determine how an organism perceives, processes, and stores external and internal information. It also affects how efficiently behavior is generated (6–8). Mental states change spontaneously or as a consequence of environmental influences, thereby some mental states are perceived as more pleasurable and useful for goal-directed behavior than others. The rewarding value of novelty may, thus, be expanded to novel mental states, which have never been incurred by natural means. Psychoactive substances can induce and maintain a desired mental state. Some of them may also provoke novel mental states. Only a few of the well-established psychoactive substances induce "euphoria" or a sense of "well-being," which directly reinforces drug-seeking and consumption behaviors. Most psychoactive substances, however, induce mental states that are primarily useful for other purposes. In that, they exert complex reinforcing effects during drug instrumentalization (6–10). Thus, the mental state that is induced by a psychoactive drug and for which humans develop a memory (11) may facilitate other behaviors with positive or negative reinforcing outcome, such as the facilitation of social interaction, mating behavior, coping with stress, and cognitive enhancement (9, 12–16). When a new drug is discovered and experimentally used, the new user may not only judge the novelty and emotional impact of the newly experienced mental state but subsequently decide for what purposes this new mental state may serve (17, 18). Once a new drug is made available, an experimental consumption starts that determines individual subjective effects as well as context and possibility of instrumentalization. This may not only work in humans but also for a newly experienced psychoactive drug in animals (19).

A major factor that fuels continuous search for new psychoactive drugs is the need to replace existing ones in routine use. Once a long known drug has been criminalized and banned, availability of the drug becomes limited. Legal control imposes punishment on drug possession, trade, and use, which limits its instrumentalization for frequently performed behavior, such as coping with stress (20). If the drug was useful for this behavior, e.g., to better relax after stressful work, users may start looking for a legal replacement of the banned drug and, thus, be motivated for testing new drugs (21).

Novel psychoactive substances (NPSs) had been defined by the United Nations as new narcotic or psychotropic drugs that are not controlled by the United Nations' 1961 Single Convention on Narcotic Drugs or by Psychotropic Substances Conventions (22). NPSs are by definition those psychoactive drugs used for intoxication which are not already prohibited by UN Single Convention on Narcotic Drugs or Misuse of Drugs Act (23), thereby "novel" does not necessarily mean that the drug has been developed completely new recently. It may also refer to substances that have lately become popular and/or more widely available, constituting a reason of current or potential public health concerns (24).

The way of a NPS in society, from its introduction, experimental use, instrumentalization, habitual abuse, up to its legal control, depends essentially on the relationship of adverse side effects and potential medical use. The adverse side effects are those effects of the drug that threaten the physiological integrity and behavioral repertoire of the whole organism, beyond the desired psychoactive action. Many known psychoactive drugs are strong toxins and harm the user. This can occur after acute consumption or after chronic intake (3). Humans establish cultural rules for the consumption and the control of side effects of psychoactive drugs (25). This keeps even highly dangerous drugs, such as alcohol, legal and limits their harm potential when incorporated in cultural activities (26). But establishing those initially "non-written" rules requires a certain amount of experience and a user/non-user discourse. One result of this discourse is the possibility of legal control, and a "written down" law on where, when, and how a psychoactive substance can be used. Drugs can be labeled as addictive drugs and made illicit. However, many new substances are at the same time tested for a potential beneficial application, e.g., to treat pain, or even as substitutes for well-known addictive drugs, thereby the verdict may be that a NPS might have some addiction- and harm potential but also beneficial effects, which may actually dominate the use profile. There is occasionally also a reversal of the discourse decision in that addictive drugs may receive an additional medical application, e.g., ketamine, which was discussed as an abuse drug (27, 28), but is now also considered as a useful treatment for depression (29).

Newly introduced psychoactive substances do not usually arise from controlled pharmacodevelopment. In that, these drugs initially have the status of a "legal high" and virtually everybody is allowed to possess, distribute, and consume them. Only when after consumption accidents with physical- and/or behavioral impairments occur, or in the worst case drug fatalities, a NPS can be classified and legally controlled or its medical use defined (21). However, the drug discourse requires evidence, ideally scientific, arising from controlled experimentation. This evidence should go well beyond the accumulation of single cases. Quite naturally, during the information collecting period, the NPS is used, and thus, not brand new anymore. What is new afterward is the certainty with which sufficiently reliable statements about the drug can be made (30).

It has to be admitted that the legal status discourse is in practice way more complicated and also culturally selective, which shall not be the focus of this review that rather focuses on the neurobiological evidence that feeds into this discourse. In this article, we review the state of knowledge on a number of NPS for which now a considerable penetration of society has developed in distinct cultural or geographical regions and for which sufficient evidence has been gathered to allow for evidence-based statements. This should provide a comprehensive overview on some of the currently most relevant NPS, thereby the choice of substances discussed was driven by the perceived progress in the understanding of their neuropharmacological action by the

authors. In that, the review does not provide a complete coverage of all currently available NPS.

KRATOM AND MITRAGYNINE

Mitragyna speciosa Korth. (*M. speciosa*), from the Rubiaceae family, is a tropical medicinal plant native to Southeast Asia (31, 32). In Malaysia, *M. speciosa* leaves are known as Ketum or Biak (31, 32), and in Thailand as Kratom (33, 34). *M. speciosa* has been historically used in Southeast Asia as a stimulant drug and in its traditional context as a remedy for various symptoms (33, 34). Previous studies mainly described the traditional uses of Kratom among rural folk, peasants, and laborers in Southeast Asia (33, 35, 36). More recently, studies on Kratom use are emerging from Europe and the US (37–40). They suggest that Kratom is now also used outside its traditional context. In the West, it is still considered a "safe" herbal drug with potential medicinal application (38, 39, 41, 42).

In Southeast Asia, manual laborers commonly chew fresh Kratom leaves and ingest brewed Kratom tea/juice to reduce fatigue, promote work desire, and enhance physical tolerance to debilitating work (32, 33, 43, 44). Kratom leaves are also used as an opium substitute to treat morphine addiction in Malaysia and Thailand (31, 45). Because of its unique healing properties, rural inhabitants use Kratom leaves to treat various medical conditions such as cough, fever, pain, diarrhea, diabetes, and hypertension (32, 44, 46). However, Kratom is potentially addictive and chronic users find it difficult to refrain from prolonged Kratom use (33, 36, 43). The common side effects of long-term use include constipation, weight loss, hyperpigmentation, dehydration, fatigue, insomnia, and increased urination (33, 36, 46). The majority of Kratom users believe its use is not as harmful as those of other illicit substances, such as methamphetamine and heroin, and that Kratom dependence carries little or no health risks (45–47). So far, there have been no deleterious incidents directly related to Kratom use in Southeast Asia. Only one study from Thailand has reported Kratom poisoning cases, with palpitation, seizure, and nausea. However, these effects may have been arisen from coadministration of other illicit substances (48).

Regular users are more likely to increase the quantity and frequency of Kratom use over time. In Thailand, traditional users often chew fresh or powdered Kratom leaves (33, 44). In Malaysia, Kratom users commonly ingest brewed Kratom tea/juice (25, 36, 47, 49). In the US and in Europe, Kratom is primarily used as a natural alternative to self-medicate for chronic pain and as an opioid withdrawal treatment (37, 50, 51). Kratom is marketed as a "legal high" and can be easily obtained in different forms, such as powder extracts, tablets, capsule, or liquids, through the Internet (38, 52). As a consequence of the rise in Kratom mortality and toxicity cases in the West, regulatory agencies have begun to view Kratom negatively (39, 53, 54). The US Drug Enforcement Administration intends to regulate Kratom use in the US (51). However, it appears that most, if not all of the Kratom-induced medical complications in the West were triggered by the use of adulterated Kratom products (53, 54).

About 40 alkaloids have been identified in *M. speciosa* leaves. The alkaloid content in the leaves varies, depending on geographical location and season of harvest (55). Mitragynine and 7-hydroxymitragynine are the principal psychoactive constituents of *M. speciosa* and were shown to induce morphine-like effects in animal models (31, 55, 56). The synthesis of the mitragynine was reported by Takayama et al. (57) and later by Ma and colleagues (58, 59). However, a synthesis of mitragynine is with 18–23 steps rather laborious, time-consuming, not economical, and has only a low yield of 3–13% (60). Thus, direct isolation of mitragynine from the leaves is much more efficient and cost-effective.

A comprehensive pharmacokinetic description of mitragynine in rats was provided by Parthasarathy et al. (61) after intravenous (i.v.) and oral administration. The blood concentration peaked at 1.2 h with 2.3 μg/mL followed by biphasic elimination with a half-life of 2.9 h and a clearance of 0.09 L/h/kg after administration of 1.5 mg/kg mitragynine (i.v.). The volume of distribution was rather small with 0.79 L/kg, suggesting that mitragynine is not widely distributed into tissue compartments (62). The oral absorption of mitragynine was shown to be lengthy and incomplete, with an absolute oral bioavailability of around 3%. Several studies revealed that after oral application of 20–50 mg/kg mitragynine, a volume distribution of 37–89 L/kg and clearance of 1.6–7 L/h (per kg) was reached (61–63), which supports the low bioavailability and poor absorption of mitragynine.

Mitragynine is a lipophilic alkaloid with poor water solubility (64). Mitragynine has a biphasic metabolism. The first phase produces seven identified metabolites, thereby mitragynine is processed through hydrolysis of methyl ester in position 16 and O-demethylation of the 9-methoxy- and of the 17-methoxy groups (65). The second phase involves further oxidation to carboxylic acids or reduction to alcohols and the combinations of some steps *via* the intermediate aldehydes. Four metabolites were additionally conjugated to glucuronides and to sulfates in rats and humans (65). Abuse of mitragynine and related compounds can be detected through gas chromatography or liquid chromatography with mass spectrometry, respectively (65–67).

Mitragynine shows the highest affinity to κ-opioid receptors followed by μ- and δ-opioid receptors (68). It acts as a receptor agonist at μ-opioid receptors and possibly as an antagonist at κ-opioid receptors (56, 69–71). At cellular level, mitragynine blocks neuronal Ca^{2+} channels (72). It was also found to inhibit forskolin-stimulated cyclic adenosine monophosphate (cAMP) formation *in vitro* in an opiate receptor-dependent way (73, 74). A study by Fakurazi et al. (75) showed that repeated exposure to mitragynine attenuated the expression of cAMP and cAMP response element-binding protein.

Mitragynine was extensively investigated for its antinociceptive effects. A study by Reanmongkol et al. (76) found prolonged antinociceptive effects in the hot plate test, but not in the tail flick test. Another study showed prolonged antinociceptive effect in both tests (77). Intraperitoneal administration also yielded positive antinociceptive results in the hot plate, formalin-, and acetic-acid tests (78). Mitragynine's antinociceptive effects were comparable to those of oxycodone suggesting an abuse potential (79, 80).

In animal models, mitragynine induces anxiolytic effects after acute treatment in several test paradigms (81). This may be mediated by its effects on Fos expression in dorsal raphe nucleus (82), and the activation of δ-opioid receptors (83). Withdrawal from

chronic mitragynine induces anxiety-related behavior in rats (84). There have been conflicting reports of mitragynine affecting cognitive function. Apryani et al. (85) found that mitragynine i.p. administration can impair object location memory in mice. Another study, however, showed no impairment of short-term memory in the Y-maze task. The mice, however, were given *M. speciosa* extract through oral administration (86). In rats, a study showed an increase in learning ability when given *M. speciosa* extract in a passive- and an active avoidance task. However, mitragynine alone did not have significant effects on long-term memory consolidation in both tasks (87). A recent study using a passive avoidance task showed independent impairments of learning, memory consolidation, as well as memory retrieval after acute mitragynine administration at a dose ≥10 mg/kg (i.p.) in rats. In parallel, mitragynine-treated rats showed a disrupted low frequency rhythm (delta and theta) in the electroencephalogram (EEG), which may account for the learning and memory impairments (84).

Chronic administration of mitragynine at a dose of ≥10 mg/kg (i.p.) may cause addiction-like behaviors in animal models (56, 84, 88). Mitragynine (15 mg/kg, i.p.) shows discriminative stimulus properties in rats. It fully substituted for a morphine (5 mg/kg) stimulus, and partially for a cocaine cue (10 mg/kg, i.p.) (89). Thus, mitragynine likely possess both opioid and psychostimulant effects. Mitragynine at doses ≥10 mg/kg (i.p.) shows rewarding properties in rodents as measured by conditioned place preference. These effects are opiate receptor dependent and can be blocked by the opiate receptor antagonist naloxone (56). Subchronic administration of mitragynine increased the expression of dopamine transporter- and dopamine (DA) receptor-regulating factor mRNA in the limbic system of the brain (84) indicating a critical role of DA in the rewarding effects of mitragynine, thereby the dose of mitragynine may be crucial, given that addiction-like behaviors were only observed at doses ≥10 mg/kg (i.p.) in rodents. Those are considerably higher than reported maximum doses of mitragynine consumed by humans, which are usually in the range of <3 mg/kg (p.o.) per day.

Altogether, Kratom and its main psychoactive ingredient mitragynine are drugs that are widely used in Southeast Asia with an increasing appearance in Western countries. Experimental studies in animals have now shown that mitragynine has an addictive potential, however, only at higher doses. Human users in countries of frequent use with a traditional context report a rather low daily consumption with only mild side effects. Kratom and mitragynine can be instrumentalized to enhance physical work power and endurance. A major reason for Kratom consumption is its reported efficacy to replace opiates in chronic users. This makes the Kratom plant preparation and also the isolated compound mitragynine interesting options to treat opiate addiction.

SYNTHETIC CANNABINOIDS

The abuse of herbal preparations spiked with synthetic cannabinoids is still increasing. A hallmark of this consumption is the use of an inhomogeneous group of substances that occur on the market with different names, such as Spice, Spice gold, diamond-spice, chill X, abyss, Pandora's box, exodus, annihilation, fire, smoke, sence, chillX, chillys, highdi's, earth impact, and many more (90, 91). Synthetic cannabinoid preparations are frequently mislabeled as research chemicals, herbal incenses, or as legal highs, including the explicit warning that it is not for human consumption (92–97). The first evidence of synthetic cannabinoid use as a recreational drug appeared in 2004 (98). However, a wide spread use of synthetic cannabinoids did not emerge until 2008. In 2012, the lifetime prevalence for "Spice" consumption was already at 7% among the 15- to 18-year olds (99–101), thereby the coabuse of synthetic- and natural cannabinoids is common (102–109).

Research in the active ingredients of synthetic cannabinoids such as Spice and their neuropharmacological action has revealed several hundred compounds that are artificially added to a carrier medium of herbal origin (110). The synthetic compounds usually display a high affinity for cannabinoid receptors (CB-R), which reaches far beyond that of natural cannabinoids (100, 111). Compared to the partial agonist, Δ9-tetrahydrocannabinol (THC), synthetic cannabinoids can act as agonists, neutral antagonists, or inverse agonists at the CB-R1 (110–112). Synthetic cannabinoid preparations also lack the naturally occurring cannabidiol, which is present in cannabis preparations and which is supposed to antagonize some of the psychotogenic effects of THC (113, 114).

A gram of herbal preparation can contain up to 200 mg of a synthetic cannabinoid. However, the variability in substance composition and amount between one package and another is high and largely unpredictable. Additional ingredients have been found and may include, e.g., clenbuterol, which may be responsible for the frequently observed sympathomimetic manifestations of an intoxication with synthetic cannabinoids, or tocopherol. The latter is usually added to blur chemical detection (113–115). Occasionally, some investigated herbal preparations did not contain any pharmacologically active synthetic cannabinoids, but only psychoactive compounds from plant-derived carrier material, such as mitragynine (116–120).

Users report that synthetic cannabinoids can cause psychotropic effects that are qualitatively similar, but much more intense, than those of cannabis. As such, synthetic cannabinoids may cause THC-like effects including alterations of mood, sleep, perception/wakefulness, body temperature, and cardiovascular function (121–123). Additional diffuse effects, which are different from cannabis, include palpitations, tachycardia, and unspecific effects in the electrocardiogram (110, 124, 125). Harmful somatic effects comprise gastrointestinal and renal defects (91, 126–128). Neuropsychiatric symptoms were reported, such as psychosis, panic and anxiety attacks, agitation, and aggressive behavior (106, 107, 129, 130). A psychosis induced by synthetic cannabinoids manifests by delusions, acoustic and visual hallucinations, and paranoia. Neurological symptoms may include seizures, dystonia, and tremors. Other frequently reported side effects are nausea, vomiting, diaphoresis, and respiratory depression (131–141). Use of synthetic cannabinoids may have fatal consequences. Reported single cases mention coronary ischemic events and suicide caused by an extreme anxiety attack (138, 139).

The active compound of the preparation "Spice" was first described in 2009, following the detection of formerly non-declared, synthetic CB-R1 agonists (141, 142). Synthetic

cannabinoids were originally developed for research purposes in the 1970s with the goal of better understanding the endogenous cannabinoid pathways and to develop pharmacotherapies for conditions such as cancer-associated pain (108). Synthetic cannabinoids may contain aminoalkyl-indoles of the JWH series, which was first synthesized by the chemist J. W. Huffmann. Major ingredients of herbal preparations in the past included the aminoalkyl-indoles, JWH-018, JWH-073, JWH-019, JWH-250, and the cyclohexylphenols, CP-47,497-C6, CP-47,497, and CP-47,497-C8. These compounds are lipid-soluble, non-polar, and typically contain 20–26 carbon atoms. However, there are at least 100 chemically related compounds currently known (122, 143–146). While some of them have been legally controlled on individual level, recent legislation in Germany now considers the lead structures and attempts to control whole drug classes. It is expected that this will make it more difficult to simply replace single banned compounds by their substituted analogs in the synthetic cannabinoid preparations (122, 147–153).

At the current stage, one may conclude that synthetic cannabinoids constitute dangerous psychoactive drug preparations with a rather chimeric nature (154). It is not a single compound, but draws from a plethora of already available synthetic cannabinoids that are unsystematically mixed and brought on a plant carrier material, that may even by itself have psychoactive effects. This strategy of drug preparation paved the way into the perception as a natural and perfectly "legal high" by consumers. The natural claim is now clearly rejected by the understanding that most psychoactive effects are brought about by purely synthetic compounds added to a natural carrier. Given the strong cannabinoid-like effects of synthetic cannabinoids, which are now increasingly understood, single substances have been legally banned. But this has done little damage to the unique drug design of synthetic cannabinoid preparations in that single disallowed compounds were almost immediately replaced by substituted analogs that had not been banned yet. The now emerging control of whole substance classes will most likely put an end to this strategy and help to reduce harm that is clearly associated with synthetic cannabinoid consumption.

DIMETHYLTRYPTAMINE

N-*N*-dimethyltryptamine (DMT) is an indole alkaloid found in plants and animals. It has been proposed that the endogenous DMT may act as a neurotransmitter. DMT is a natural psychedelic substance and has similar effects as other serotonergic hallucinogens such as lysergic acid diethylamide (LSD), psilocybin, and mescaline. DMT is one of the ingredients used in various shamanic preparations, such as ayahuasca, hoasca, or yagé in South America and is used as a recreational drug in Europe and North America (155). DMT rich plants belong to genera such as *Phalaris*, *Delosperma*, *Acacia*, *Desmodium*, *Mimosa*, *Virola*, and *Psychotria*. When DMT is ingested at high concentrations, the user experiences episodic visual hallucinations (155, 156). The recreational use of DMT has been rising for its acclaimed self-perceived benefits. Capsules, known as pharmahuasca, became available containing DMT as a free base together with some monoamine oxidase inhibitors (MAOIs), such as synthetic harmaline, or plant-based MAOIs such as Harmala alkaloids (157, 158). The MAOIs inhibit the otherwise rapid metabolization of DMT and, thus, allow for the hallucinogenic effects when the drug is taken orally.

Endogenous DMT can be found in the human brain and other tissues of the body such as blood, urine, cerebral spinal fluid (155, 156, 159), and the pineal gland (156, 160). Synthesis of endogenous DMT begins with the decarboxylation of tryptophan to tryptamine. *N*-methyltryptamine (NMT) and DMT are the products of methyl group additions to tryptamine by the enzyme indolethylamine-*N*-methyltransferase (160). DMT levels were found to increase under stress in the rodent brain and adrenal gland (161). This can activate trace amine-associated receptors and serotonin receptors (5-HT-Rs), such as the 5-HT_{1A}-Rs, 5-HT_{2A}-Rs, and the 5-HT_{2C}-Rs (159, 162). It was suggested that endogenous DMT has a role in cellular protective mechanisms (155).

Exogenous DMT is metabolized by MAO and peroxidases leading to the metabolites NMT, 6-hydroxy-DMT, 6-OH-DMT-*N*-oxide, DMT-*N*-oxide, and indole-3-acetic acid (160). The pharmacokinetics of DMT shows a rapid onset of action within 5–30 min. This is followed by an intense modification of the mental state lasting for approximately 4 h (163). The routes of DMT administration are *via* smoking or snorting. For the hallucinogenic or psychedelic effects to occur, an oral formulation must contain MAOIs to prolong the half-life of DMT in the body. MAOIs block the enzyme in the stomach after which DMT is able to be absorbed through the stomach lining into the blood stream. An oral dosing of DMT, e.g., *via* ayahuasca, produces both behavioral and neuroendocrinological effects, such as a decrease in locomotor activity, cognitive impairments, sympathomimetic effects, increased prolactin, and cortisol levels (164, 165). DMT also interacts with various ionotropic and metabotropic receptors in the glutamate, DA, and acetylcholine systems. The subjective effects of exogenous DMT are primarily mediated by 5-HT_{2A}-Rs. 5-HT_{2C}-Rs play little or no role (166, 167). Glutamatergic mGluR2 receptors might have modulatory effects in DMT action (167). DMT does not affect DA receptors but may alter DA levels in the brain with subsequent neurochemical and behavioral effects.

Chronic DMT induces tolerance for some behavioral and subjective effects. However, it failed to elicit tolerance to the disruption of responding maintained on a fixed-ratio schedule of food reinforcement (168, 169). DMT yields similar discriminative stimulus effects as the serotonergic hallucinogens 2,5-dimethoxy-4-methylamphetamine (DOM) and LSD. Furthermore, DMT fully substituted in DOM-trained rats and for LSD in rats and pigeons (170, 171).

Beside its sought-after acute effects, DMT can cause considerable side effects. The ingestion of DMT may induce intense fear, paranoia, anxiety, grief, and depression, which may result in physical harm to the user or others (157). There have been no serious adverse events reported on long-term use of DMT apart from the acute cardiovascular effects. Single and repeated administrations of DMT produce marked changes in the cardiovascular system (172). In fact, DMT has been reported to act as neuroprotective agent, working *via* Sigma-1 receptor (Sig-1R) activation (173–177). Sig-1Rs activate the antioxidant response elements (176). Hence, DMT may function as an indirect antioxidant. Frecska et al. (177)

have suggested that peripheral synthesis of DMT, consumptions of DMT-containing plant material, or systemic administration of DMT can trigger endogenous central nervous system pathways that produce psychedelic experiences. At the same time, it may serve mechanisms such as neuroprotection and neuroregeneration. Interestingly, ayahuasca and DMT mixtures have been proposed as a treatment for psychiatric disorders. Symptoms of schizophrenia, such as delusions and hallucinations, have been assumed to involve activation of 5-HT_{2A}-Rs along with changes in the DA system (166, 178). Endogenous DMT has been reported to be increased in schizophrenic patients during psychotic episodes (179) indicating that the endogenous DMT signaling pathway might be a treatment target for schizophrenia. Based on animal models and on clinical studies in humans, DMT has potential antidepressant and anxiolytic effects (180), possibly mediated by a 5-HT_{1A}-R agonistic action (181). Further therapeutic applications include the treatment of cancer and inflammations. DMT has been shown to increase immune system activity (165, 182). Sig-1R activation can reduce pro-inflammatory cytokines and enhance the production of the anti-inflammatory cytokine IL-10 (183).

In conclusion, DMT is a naturally occurring psychoactive compound found in various plants. It is now understood that its main psychoactive effects are mediated by 5-HT_{2A}-R activation. Endogenous DMT may play a role in the immunoregulation in peripheral and brain tissues. Preliminary evidence now suggests a possible therapeutic use of DMT.

NOVEL SEROTONERGIC HALLUCINOGENS

Since thousands of years, indigene cultures in North and South America have used plants and mushrooms containing serotonergic hallucinogens for shamanic rituals and religious ceremonies (184). The most famous examples are (1) *Psilocybe* mushrooms containing psilocybin, which were used as Teonanacatl ("god's flesh") by the Aztecs, (2) the cactus *Lophophora williamsii* enclosing mescaline and applied as Peyote or Peyotl by Mexican and North American indigene cultures, and (3) a brew of *Banisteriopsis caapi* and *Psychotria viridis* called Ayahuasca utilized by Amazonian indigene cultures containing the psychedelic ingredient DMT together with harmala alkaloids acting as MAOIs inhibitors and preventing the metabolism of DMT (185).

Classical serotonergic hallucinogens usually have either a tryptamine or phenylethylamine basic structure (186). Typical tryptamines, such as psilocybin and its psychoactive metabolite psilocin, 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), and bufotenine, resemble in their structure the neurotransmitter 5-HT, while the phenylethylamine mescaline has a similar basic structure as the neurotransmitter DA and as amphetamines. In addition, ergoline alkaloids such as the naturally occurring D-lysergic acid amide, also called ergine—the psychoactive compound of *Turbina corymbosa*, *Argyreia nervosa*, and *Ipomea tricolor*—and the semi-synthetic LSD (Delysid®), have a tryptamine backbone as well (186).

It was suggested that the term "hallucinogens" may be a misnomer as these drugs not necessarily produce real hallucinations, at least when applied at typical doses, but many other emotional, perceptual, cognitive, and behavioral effects. It was suggested that "psychotomimetics" might be the more appropriate term for them (186). However, all 5-HT hallucinogens have in common that they induce altered states of consciousness (186, 187). According to Hollister (188), the psychoactive effects of classical serotonergic hallucinogens usually include (1) somatic symptoms: dizziness, weakness, tremors, nausea, drowsiness, paresthesia, and blurred vision; (2) perceptual symptoms: altered shapes and colors, difficulty in focusing on objects, sharpened sense of hearing, and rarely synesthesia; and (3) psychic symptoms: alterations in mood (happy, sad, or irritable at varying times), tension, distorted time sense, difficulty in expressing thoughts, depersonalization, dream-like feelings, and visual hallucinations.

All tryptamine- and phenylethylamine-based hallucinogens share the agonistic mechanism of action at postsynaptic 5-HT_{2A}-Rs and 5-HT_{2C}-Rs, where they act as partial, mixed-partial, or full agonists (186, 189). In animals and humans, 5-HT_{2A}-R antagonists such as ketanserin are able to block most of the behavioral and psychotropic effects of psilocybin, mescaline, DOI, and LSD, indicating that the 5-HT_{2A}-R agonism is necessary for the induction of psychedelic effects (189–194). However, some of these drugs show a strong affinity to 5-HT_{1A}-Rs and other 5-HT receptor subtypes as well as to DA D2-Rs. These additional mechanisms are likely to contribute to the specific psychotropic effects of each compound (189, 191, 195). A decade ago, it has been proposed that only 5-HT_{2A}-Rs coupled to metabotropic mGluR2 mediate the psychotogenic effects of 5-HT hallucinogens (196)—a position that has been questioned recently (197). At the neuronal level, 5-HT hallucinogens, such as psilocin, LSD, and DMT, directly activate 5-HT_{2A}-Rs located on cortical pyramidal neurons. In addition, they increase extracellular glutamate levels in the prefrontal cortex through stimulation of postsynaptic 5-HT_{2A}-Rs located on large glutamatergic pyramidal cells in deep cortical layers V and VI. This glutamate release leads to an activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors and *N*-methyl-D-aspartic acid (NMDA) receptors on cortical pyramidal neurons (187).

Historically, LSD was probably one of the first NPS of the hallucinogen class as it was a semi-synthetic compound whose psychedelic effects have only accidentally been discovered by its inventor Albert Hofmann in 1943 (198). The next, even though less accidental, producer of NPS hallucinogens was Alexander T. Shulgin, who synthesized hundreds of novel hallucinogenic tryptamines and phenylethylamines in his home laboratory. He described the synthesis of these compounds and also their psychotomimetic effects experienced in self-experiments in detail in his books PIHKAL and TIHKAL (199, 200). He created several dimethoxy-substituted phenylethylamines, such as DOM, 2,5-dimethoxy-4-bromoamphetamine (DOB), 2,5-dimethoxy-4-iodoamphetamine (DOI), and 2,5-dimethoxy-4-ethylamphetamine (DOET), which all display strong hallucinogenic properties. These drugs usually have much longer durations of action (12–30 h) and are much more potent agonists at 5-HT_{2A}-Rs (50- to 175-fold) compared to their related phenylethylamine derivative mescaline (duration of action: 4–8 h) (189, 199, 200). Also, another novel class of substituted

dimethoxyphenethylamines—the "2C psychedelics"—was invented by Shulgin, which mostly contains methoxy groups at positions 2 and 5 of a benzene ring together with lipophilic substituents (often halogens) at position 4. The most famous exponent of this class is 2,5-dimethoxy-4-bromophenethylamine (2C-B, "nexus," "bromo"), which was initially marketed as a legal surrogate of MDMA ("ecstasy") in the late 80s before it was finally scheduled by the UN Commission on Narcotic Drugs in March 2001 (201). Dozens of 2C-B analogs, such as 2C-I, 2C-C, 2C-F, 2C-E, and 2C-N, have later been sold as "research chemical" or "legal highs" *via* the Internet. Because their structure can be easily changed without losing their psychoactive properties, 2C drugs have, thus, often been referred as a typical class of designer drugs (201). 2C drugs commonly do not only act as 5-HT_{2A}-R and 5-HT_{1A}-R agonists but also as monoamine transporter inhibitors (195). Consequently, these compounds have not only hallucinogenic properties but also slight stimulating and empathogenic/entactogenic effects sometimes mimicking the effects of the prototypical empathogen MDMA (199). Shulgin also described novel ergolines such as *N*-allyl-nor-lysergic acid diethylamide (AL-LAD), *N*-ethyl-nor-lysergic acid diethylamide (ETH-LAD), and *N*-propyl-nor-lysergic acid diethylamide (PRO-LAD) (200). These LSD-analogs are as potent as LSD (potency relative to LSD in human: AL-LAD: 110%, ETH-LAD: 140%, PRO-LAD: 90%), but AL-LAD and PRO-LAD have shorter duration of action (6–8 h) as ETH-LAD and LSD (both: 8–12 h) (189, 200). Finally, Shulgin synthesized a large number of novel tryptamines, such as 4-hydroxy-*N*-methyl-*N*-ethyl-tryptamine (4-HO-MET), 5-methoxy-diisopropyltryptamine (5-MeO-DIPT), and alpha-ethyltryptamine (alpha-ET), which are mostly hallucinogenic, but with some exceptions (e.g., alpha-ET has pronounced empathogenic effects) (200). Shulgins books PIHKAL and TIHKAL served as cook books for a generation of illegal drug laboratories. His dimethoxyphenethylamines, 2C drugs, and novel ergolines and tryptamines are still circulating as NPS, although they have been created at least 20 years ago. However, their human toxicology and their consequences are still unknown as they are neither used frequently nor purely enough in order to systematically investigate their chronic effects in recreational users.

In the last decade, a substantial amount of new serotonergic hallucinogens appeared on the drug markets. As their number grows each day, it is simply not possible to list them exhaustively here. Thus, only some prototypical exponents of each class will be discussed. Again the main classes are either tryptamines and related ergolines or substituted phenethylamines but also some new classes such as benzodifurans and aminoindanes occurred (202–205). Novel tryptamines such as alpha-methyltryptamine (AMT), *N*,*N*-diallyl-5-methoxytryptamine (5-MeO-DALT) have multiple serotonergic actions including strong affinity for the 5-HT_{2A}-R, but can also act as monoamine transporter substrates. They combine hallucinogenic effects with stimulant and empathogenic features (203, 205). Novel ergolines such as 1-propionyl-lysergic acid diethylamide (1P-LSD) and lysergic acid 2,4-dimethylazetidide (LSZ) are LSD-analogs mainly interacting with 5-HT_{2A}-R and 5-HT_{1A}-R subtypes. They are slightly more potent as LSD and have a comparable duration of action. They are also mostly marketed as blotters (202, 205). *N*-2-methoxybenzyl derivatives of 2,5-dimethoxy-substituted phenethylamines also called NBOMe drugs, such as 25B-NBOMe, 25C-NBOMe, 25I-NBOMe, 25T2-NBOMe, and mescaline-NBOMe, are highly potent 5-HT_{2A}-R full agonists. In addition, they show a high-binding affinity to the 5-HT_{1A}-R, to adrenergic α1A and α2A, and histamine H1 receptors. Some derivatives also possess low-to-moderate affinity to DA D2- and D3-Rs. Several NBOMe drugs show higher affinity, higher activation potency, and higher activation efficacy at 5-HT_{2A}-Rs than LSD. Anecdotal user reports consider them as very strong hallucinogens (195, 205, 206). Benzodifurans, the so-called "fly drugs," such as 2C-B-FLY, 3C-Bromo-Dragonfly, and TFMFly, are a group of ring-substituted phenethylamines that are structurally related to MDMA. Unlike MDMA, benzodifurans commonly display a high affinity for 5-HT_{1A}-Rs, 5-HT_{2A}-Rs, 5-HT_{2B}-Rs, and 5-HT_{2C}-Rs, but show only little action at monoamine transporters (195, 205). Aminoindanes, such as 5-iodo-2-aminoindane (5-IAI), are usually 5-HT and noradrenaline (NA) releasers that have been sold as a legal surrogate for MDMA (203, 205). At least 5-IAI was recently demonstrated to show a strong affinity for 5-HT_{1A}-Rs and 5-HT_{2A}-Rs, thus, indicating that aminoindanes can not only be empathogens, but they can also display hallucinogenic properties (207).

At the moment, systematic investigations on the prevalence of novel serotonergic hallucinogens are rare. In the global drug survey of 2012, 11.3% of the respondents, mainly regular drug users, reported to have used a 2C drug at least once during their lifetime and that 2C-B was the most common one (8.4%). Moreover, 2.6% of respondents reported to have used 25B-NBOMe, 25C-NBOMe, or 25I-NBOMe at least once, while 25I-NBOMe (2.0%) was the most popular derivate. The most common drug source for NBOMes was the Internet (41.7%). For comparison, 39.4% of the respondents in this survey had used LSD and 43.1% "magic mushrooms" at least once during lifetime (206). A recent representative survey in the US ($N = 213.076$) revealed that the lifetime prevalence of novel hallucinogenic drugs was generally low: NBOMes, 0.015%; 2C drugs, 0.195%; dimethoxyphenethylamines, 0.019%; novel tryptamines, 1.060% (primarily DMT) (208). It should be noted that DMT was the only hallucinogenic NPS that was systematically asked for but that participants were given the opportunity to type in the names of NPS they used, indicating that these numbers are likely underestimated (208).

Data from the European Drug Emergencies Network have recently shown that, compared to all other investigated drugs, novel tryptamine users have the highest risk [odds ratio (OR) = 12.4] to be treated for psychosis-like symptoms in an emergency care unit, while also LSD use was significantly associated with an increased psychosis risk (OR = 3.1) (209). Overall frequencies for the development of acute psychosis following experimentally administered LSD range between 0.08 and 4.6%, while patients having a psychiatric disorder before LSD intake displayed the highest risk (185). However, if 5-HT hallucinogens can also induce long-lasting psychotic disorders is still controversially discussed (185). Beyond acute psychotic reactions including hallucinations, ego impairment, and

paranoia, also "bad trips," panic attacks, confusion, agitation, aggression, and disorientation are common acute psychiatric side effects of classical and novel serotonergic hallucinogens (185, 203, 205, 210). Moreover, also nausea and vomiting, serotonin syndrome including hyperthermia, liver and kidney failures, and cardiovascular complications have been reported for serotonergic hallucinogens. The acute toxicity of high potency dimethoxyphenylethylamines, NBOMEs, and 2C drugs seems to be considerably increased compared to classical hallucinogens. High potency compounds have been associated with a number of life-threatening conditions, such as rhabdomyolysis, seizures, vasoconstriction/hypertension, tachycardia, pulmonary edema, and serotonin syndrome with hyperthermia and organ failures, sometimes with fatal outcome (210–214).

Chronic side effects of hallucinogens can include panic disorder and a hallucinogen persisting perception disorder (HPPD, "flashback") (185). In fact, 60% of LSD users know "flashbacks" and 4% of users report sustained HPPD of putative clinical significance (215). Also, MDMA users are at risk to develop HPPD (216). It is highly likely that potent novel serotonergic hallucinogens bear a strong risk to induce HPPD too. Changes of 5-HT_{2A}-R function in the visual cortex were claimed to be responsible for HPPD (185, 216). In general, 5-HT-Rs show considerable plasticity after exposure to serotonergic drugs. Accordingly, due to post-transcriptional mechanisms, 5-HT_{2A}-Rs show a rapid and long-lasting downregulation in response to 5-HT agonists (217–219). Specifically, LSD, 2-bromo-LSD, and DOI selectively reduce 5-HT_{2A}-R density without affecting 5-HT_{2C}-Rs (220). Furthermore, hallucinogens acting at 5-HT_{2A}-Rs show strong behavioral tolerance coinciding with a robust decrease in 5-HT_{2A}-Rs. This might explain the strong tolerance effect of 5-HT hallucinogens (221). Recently, it was shown that 5-HT hallucinogens can also reduce either 5-HT_{2A}-R binding sites or glutamate-binding sites and that tolerance effects were correlated with changes in both binding sites (222).

High potency 5-HT hallucinogens—specifically if they have a long duration of action—are probably neurotoxic due to their sustained activation of 5-HT_{2A}-Rs that can induce apoptosis in neurons (223). Neurotoxic effects have been shown not only for DOI (224, 225) and 5-MeO-DIPT (226) but also for chronic low doses of LSD (227) and repeated high doses of MDMA (223–225). Thus, it is likely that all long-acting dimethoxyphenylethylamines, 2C drugs, NBOMes, tryptamines, and ergolines with strong agonistic actions at 5-HT_{2A}-Rs have a neurotoxic potential.

In conclusion, beyond LSD, mescaline, and psilocybin, a vast amount of new serotonergic hallucinogens appeared on the drug market during the last decades. Their distribution has strongly increased and will likely further increase in the future due to their easy availability on the Internet. Alarmingly, little is known about the acute and chronic effects of novel 5-HT hallucinogenic drugs in human users. The neuropsychiatric long-term consequences of regular intake of such compounds are completely unclear. However, it is becoming increasingly apparent that high potency drugs with very strong affinities to 5-HT_{2A}-Rs and long durations of action bear a considerable risk for negative health effects and fatalities.

MEPHEDRONE AND METHYLONE

Dozens of research chemicals with a cathinone basic structure appeared as "legal highs" on the drug marked. However, an exhaustive discussion of all of them is not possible here due to space restrictions (228). Thus, in this section, the two generic compounds, mephedrone and methylone, are discussed as important examples.

Mephedrone (4-methylmethcathinone) is a substituted cathinone homolog of ephedrine first described in 1929 (229, 230). Mephedrone has a ring-substituted cathinone structure which is related to the phenethylamine family, to which also drugs such as amphetamine, MDMA, and methamphetamine belong to (231). As a hydrochloride salt, mephedrone is a water soluble white, yellow, beige, or brown powder. In the European market, it is sold under different names such as Meow Meow, Bubbles, Mef, MMC Hammer, and many more (231). Mephedrone is available on the Internet, or from street dealers. On Internet sources, mephedrone is often marketed as bath salt, plant fertilizer, or research chemical (232, 233).

Mephedrone was first identified as an abused drug by European authorities in 2007 (234, 235). By 2010, mephedrone use spread, and the drug was found in many European countries (236). The use of mephedrone increased rapidly in the club scene and soon reached the level MDMA and cocaine use, reaching a life-time use in Europe among the 15- to 24-year olds of 6% by 2010 (236, 237). Mephedrone is frequently used together with other synthetic cathinones, such as methylone, butylone, or ethylcathinone (236). The predominant user populations are teenagers and young adults (238), thereby use of new psychoactive cathinones is highly correlated with binge-drinking habits in young adults (239).

Mephedrone can be consumed by different routes. In an oral preparation, mephedrone powder is rolled up in cigarette paper (bombing). Furthermore, intranasal, intramuscular, intravenous (slamming), and rectal routes of administration have been reported (240). Mephedrone is also mixed with other drugs, such as heroin, alcohol, cocaine, MDMA, or cannabis (235, 241). Consumption usually takes place in a social context at home, at rave parties, clubs, or music festivals. Mephedrone binge consumption has been reported to last for up to 9 h with a new dose all 0.5–2 h (231). Intranasal mephedrone elicits rapid effects within minutes. They reach a peak level in less than 30 min and last for up to 1 h. Orally applied mephedrone powder or tablets induce psychoactive effects in 45–120 min which may last for 2–4 h, thereby a sequence of first intranasal snorting followed by repeated oral ingestion has been reported, in order to achieve both, fast and long-lasting effects (231, 240, 242, 243). The sought-after psychoactive effects of mephedrone comprise an elevated mood, the feeling of an intense euphoria, a sense of well-being, increased self-esteem, motor excitation, reduced tiredness, increased alertness and concentration, talkativeness, empathy, disinhibition, and a mild sexual stimulation (231, 244, 245).

A high dose and/or chronic consumption of mephedrone have been associated with significant adverse effects. Those include cardiovascular, gastrointestinal, and neurological side effects

(233, 246). Well-described effects are also jaw clenching, reduced appetite, increased body temperature, increased sweating, abnormal vision, dilated pupils, headaches, tachycardia, palpitations, hypertension, arrhythmias, chest pain, nausea, bruxism, teeth grinding (bruxism), rhabdomyolysis, and renal failure (247). An important dangerous side effect is the significant hyponatremia. This is similar to that shown after acute MDMA consumption. It is supposed to be induced by a combination of sweating, electrolyte loss, and antidiuretic hormone secretion (247). The intranasal application of mephedrone is associated with a significant nasal irritation. Mephedrone addiction is often associated with intravenous drug use that is also found to be linked to an increased risk of using other addictive drugs (248). Intravenous mephedrone injections often result in vein blockages, leading to localized infections, blisters, abscesses, scabs, lumps, gangrenous tissue, blood clots, and large necroses at the injection site (249). Major adverse psychiatric effects associated with mephedrone use include agitation, anxiety, dysphoria, depression, insomnia, hallucinations, paranoia, delusions, aggressive behavior, as well as suicidal ideation and suicidal action. Cognitive impairments affect short-term memory and attention span (250). Psychotic effects predominantly occur after a high mephedrone dose, after binge consumption in one session, and in users with an individual vulnerability for psychiatric disorders (251–253). Fatalities resulting from mephedrone use have been reported worldwide now (254). They are related to hyponatremia and brain edema (255–257). However, the lethal dose (LD_{50}) is not known yet (258).

Accumulating evidence suggests that mephedrone has a clear addiction potential (246, 259, 260). The abuse potential for intranasally consumed mephedrone was suggested to be comparable with that of cocaine or methamphetamine (246). Among regular users, about 50% reported an addiction to the drug (261) and about 25% admitted mephedrone-related craving (262). Mephedrone withdrawal effects include tiredness, insomnia, impaired concentration, irritability, tremor, temperature dysregulation, palpitations, headaches, depression, anxiety, and paranoia (235, 244, 260).

Virtually all synthetic cathinones are considered to inhibit the monoamine uptake in the brain, thereby mephedrone acts as a substrate for the transporter proteins and evokes a reverse neurotransmitter transport and, thus, neurotransmitters release (231, 244, 263).

Synthetic cathinones including mephedrone are now classified as illicit substances in many countries (231). However, since the legal ban of single substances came in place, various second-generation analogs have appeared, including 4-methyl-*N*-ethylcathinone (4-MEC). The consumption may in the long term only effectively be limited when whole substance classes, i.e., with a cathinone lead structure, are legally controlled (231).

Methylone (3,4-methylenedioxymethcathinone) is a substituted cathinone methylated on the amine group of the ketophenethylamine backbone. It has a chemical structure similar to that of MDMA by a methylenedioxy ring attached to the aromatic ring (264). Methylone was first synthesized in 1996 as a potential antidepressant and anti-Parkinson agent (265), which, however, never made it into pharmacotherapy. Instead, it emerged on the street market under different names, such as Ease, Explosion, M1, MDMC, and bk-MDMA (231, 246). Methylone was marketed initially in a liquid solution as a vanilla-scented room odorizer. Following its introduction in 2004, methylone could be purchased in the Internet and in headshops (266), where it was sold in powder form and as tablets (267). Methylone use has been reported to be high in the club scene (261) and in addicts on substitution therapy (267).

Similar to other cathinones, methylone can be administered by different routes, such as orally, intranasally, intravenously, sublingually, or rectally. The most popular route is the oral administration. A common application pattern is to start with a large "boosting" dose and then maintain effects by smaller "bumping" doses (268, 269). The onset of the desired psychoactive effects of methylone is usually 15–60 min after oral administration. These effects last approximately 30–45 min (268). They have been described as an amphetamine-like stimulation with calm euphoria, happiness, thought acceleration, alertness, restlessness, reduced fatigue, and increased locomotor activity. They might also involve MDMA-like entactogenic effects with a strong sense of emotional openness, enhanced empathy, and reduced fear (270). A methylone high can be from moderate to extreme euphoria with tingling sensation (231, 268).

The adverse effects of methylone include anxiety and psychosis with derealization, depersonalization, hallucinations, and suicidal ideation. Cognitive impairments affect the short-term memory (258). Furthermore, methylone may induce seizures and hyponatremia, similar to that induced by MDMA. Methylone may also induce a hyperthermia (271). This is believed to be a major cause for the fatal consequences of a methylone overdose (272). Other factors in fatal overdose can be cardiac events, metabolic acidosis, rhabdomyolysis, acute renal failure, intravascular coagulation, and a serotonin syndrome (273–276).

Accumulating evidence suggests a considerable addictive potential of methylone (231, 277). Much like mephedrone, methylone acts as a monoamine reuptake blocker that leads to a profound hyperactivity of DA, 5-HT, and NA in the brain and periphery (263). In particular, dopaminergic and serotonergic adaptations in the brain may drive the addiction potential of psychostimulant drugs (278, 279). The use and abuse of the substance emerged with considerable side effects around the world (268). The legal ban of methylone started in 2007 with now an increasing number of countries controlling it (231).

KETAMINE AND NOVEL DISSOCIATIVE DRUGS

(±)Ketamine (±2-chlorophenyl-2-methylamino-cyclohexanone) is a non-competitive antagonist of the NMDA receptor (27). It has been widely used in clinical settings as an anesthetic agent and in veterinary medicine. However, ketamine is also recreationally consumed in entertainment settings for its hallucinogenic, mood enhancing, and reinforcing properties by young club goers (28, 280–282). Ketamine is a derivative of phencyclidine (PCP), which was discovered as anesthetic in 1956 and became a popular street drug during 1960s (280). Ketamine is regulated in many countries due to its abuse potential as a psychotropic substance

(282). A significant number of studies have demonstrated that ketamine has a short-acting antidepressant effect and is increasingly used to treat therapy-refractory major depression and pain (29, 283–285). Although ketamine is viewed as a safe substance in medical settings, its recreational use is reported to impose adverse effects on users by producing neurological and peripheral toxicity (286, 287).

Ketamine can be administered through intravenous, intramuscular, smoking, and snorting routes (288). Apparently, snorting or intranasal use is the main route of ketamine consumption among recreational users (289). Ketamine produces dose-dependent effects. Lower doses are associated with a feeling of relaxation. At higher doses, ketamine induces a dream-like state called a "*k-hole*." This experience is akin to dissociative anesthetic characteristics (290, 291). Chronic ketamine use is reported to induce schizophrenia-like positive and negative symptoms, including hallucinations, detachment, delusion, auditory, and verbal hallucinations (292). A major concern of ketamine use is that people drive under the influence of the drug (293). Ketamine can impair cognitive functioning, such as executive and memory function, as well as attentional control (294, 295). Ketamine users are also more vulnerable to HIV infections. The use of the drug is reported to enhance sexual experience and predispose users to engage in unprotected sex (296, 297). Ketamine-related mortality has increased 10-fold in the UK from 1999 to 2008 (287), while in Australia 40% of party drug users were tested positive for ketamine use (281).

Some of the most common complaints of ketamine use include chest pain, palpitations, and tachycardia (298). However, these symptoms are often transient (286). Abdominal pain and urinary tract symptoms, such as suprapubic pain, dysuria, and hematuria, are common symptoms of chronic regular ketamine use (299–301). Findings from clinical case studies have shown that ketamine use can decrease bladder volume, bladder wall thickening, mucosal enhancement, dilation of ureter, and cause perivesical inflammation (302, 303). The renal toxicity of ketamine is due to the direct toxic action of ketamine and its metabolites (288).

Fatigue, poor appetite, drowsiness, craving, anxiety, sleeping problems, and dysphoria are common physical and psychological side effects of ketamine use (304, 305). Currently, there is no specific treatment for ketamine users presenting with peripheral toxicity. However, it was reported that cessation from ketamine abuse may lead to a recovery from organ damage (28). Despite its abuse potential and reported side effects, ketamine has promising medicinal properties. Currently, it is used to treat therapy-refractory depression (306), although the antidepressant effect of a single infusion only last for some days. Despite that development, which moved the drug increasingly out of the drug abuse focus, proper prevention strategies for young club goers engaged in recreational ketamine use are still warranted. Moreover, addiction experts warned recently that psychiatrist should not underestimate the addictive potential of ketamine when treating depressive patients with the drug (307).

Dissociative anesthetics such as PCP and ketamine are non-medically used since more than 60 years (280). Importantly, "dissociative anesthetics" are originally defined as substances inducing a general form of anesthesia characterized by analgesia, amnesia, and cataplexy, but with minimal effect on respiratory function (308). Today, the term "dissociative drugs" includes the family of dissociative anesthetics but is not restricted to them. It more generally denotes hallucinogenic drugs inducing dissociative states, including sensory alterations and hallucinations as well as dream-like states or trance (280). More than 14 known derivatives of PCP have been marketed for non-medical but also illicit use already between the late 1960s and the 1990s. However, with the advent of online drug shops selling "legal highs," novel dissociative drugs appeared too. Starting with the first dissociative, 4-MeO-PCP in 2008, thenceforth at least 12 novel dissociative drugs appeared on the drug marked, which were unknown in the scientific literature prior to their introduction to the drug market (280). In the meantime, the most common agents, methoxetamine (MXE), diphenidine, methoxphenidine (MXP), 3-MeO-PCP, and 4-MeO-PCP, have reached widespread use in Europe and North America.

PCP, ketamine, and its novel derivatives belong to the chemical class of arylcyclohexylamines, which have in common that they act as non-competitive antagonists at the PCP-binding site of the NMDA receptor (280). Beyond their high affinity for NMDA receptors, some of the arylcyclohexylamines have shown agonistic actions at DA receptors (e.g., D2 receptors) and inhibitory effects at DA transporters, agonistic effects at μ-opioid and σ-1 receptors, as well as antagonistic actions at both nicotinic and muscarinic acetylcholine receptors. It is plausible that the specific receptor profile of each compound mediates its characteristic psychotropic effects (280). Beyond the desired dissociative acute effects, these drugs exert a number of severe and sometimes fatal side effects. Following MXE ingestion, users were confused, agitated, hallucinating, and unresponsive. The somatic and neurological adverse effects included tachycardia, hypertension, ataxia, mydriasis, nystagmus, seizures, leukocytosis, massive rhabdomyolysis, hepatic failure, onset of acute renal failure, sinus bradycardia, elevated creatinine kinase, and hyponatremia (210). Several fatalities have been reported each for MXE, MXP, 3-MeO-PCP, and 4-MeO-PCP (210, 240). According to anecdotal reports, MXE and MXP seem to have stronger empathogenic and euphorigenic properties than PCP and ketamine (210).

Novel dissociative drugs from the arylcyclohexylamine class, such as MXE, have been sold as a "legal" and "bladder friendly" alternative to ketamine. However, animal studies have shown that MXE and likely all arylcyclohexylamines are in fact equally toxic for the bladder and the kidneys as ketamine when applied chronically (240). Further chronic side effects of novel arylcyclohexylamines have not been investigated yet, but it is likely that the total class might have an addictive potential similar to that of ketamine and PCP (309, 310). This seems to be specifically high in adolescents and young adults (311). Moreover, like PCP and ketamine, all arylcyclohexylamines with a strong action at the NMDA receptor may impair memory function (310) and induce psychotic symptoms after acute and chronic consumption (312, 313).

γ-HYDROXYBUTYRATE, γ-BUTYROLACTONE, AND 1,4-BUTANEDIOL

γ-Hydroxybutyrate (GHB, or sodium oxybate), γ-butyrolactone (GBL), and 1,4-butanediol (1,4-BD) are potent central depressant agents with a broad spectrum of subjective, behavioral, and neuropharmacological effects in humans. These drugs are used clinically for the treatment of neuropsychiatric disorders such as narcolepsy, alcohol withdrawal, and fibromyalgia but also instrumentalized illicitly for hedonic purposes (314).

GBL and 1,4-BD are rapidly metabolized endogenously to GHB. The psychoactive effects of the drug result from this conversion (315, 316). GHB is an endogenous short-chain fatty acid. It is biosynthetically derived from γ-aminobutyric acid (GABA) which occurs naturally in the mammalian brain, mainly in the hypothalamus and the basal ganglia (317, 318). The molecule binds to GABA-B receptors (319) and to specific GHB receptors (320). Due to the presence of endogenous GHB in the brain, specific G-protein-coupled GHB receptors, and the specificity of the GHB antagonist NCS-382, GHB is considered to be a neurotransmitter (321). While physiological concentrations of GHB seem to be insufficient to stimulate GABA-B receptors, the subjective and behavioral effects of the exogenously applied drug, and thus GBL and 1,4-BD, result from direct stimulation of these receptors (322). Moreover, GHB has extensive downstream effects on DA, 5-HT, NA, glutamate, and acetylcholine transmission (323). GHB, GBL, and 1,4-BD are well absorbed orally in humans. Peak plasma concentrations are reached within 25–60 min, with a half-life of 20–60 min (324, 325). All compounds are metabolized to water and carbon dioxide through the citric acid cycle (326).

In humans, the spectrum of the subjective effects of these compounds ranges from euphoria, stimulation, and disinhibition in oral doses of 10–25 mg/kg (327–329), toward heavy sedation and loss of consciousness at oral doses of 35–70 mg/kg (324, 330). A seemingly paradoxical pattern of concomitant sedation and stimulation was described in several reports (327, 328).

GHB, GBL, and 1,4-BD strongly influence behaviors related to core autonomic functions, such as the control of food intake, sexual behavior, and sleep–wake regulation (314). GHB was reported to normalize dysfunctional food intake behavior and body weight in preclinical and in clinical studies (331–334). It was effective in the treatment of binge-eating disorder (335). Confirming subjective reports from illicit GHB users (336–338), the drug was experimentally shown to have prosocial (328), and prosexual effects in healthy male subjects (339). Moreover, GHB and its precursors have a unique effect on sleep–wake regulation (340). Since GHB improves sleep and daytime vigilance, it is used as standard treatment for disorders of the sleep–wake cycle, such as narcolepsy and fibromyalgia (341–343).

Neuropharmacological studies with GHB, GBL, and 1,4-BD are scarce and were until recently limited to early EEG investigations. Resting state EEG studies showed a paradoxical EEG-behavioral dissociation with the occurrence of increased delta and theta oscillations, during wake states, which usually occur during sleep (344, 345). Moreover, increased nocturnal slow wave sleep under the influence of GHB was demonstrated (346). A recent EEG study showed increased current source density of theta oscillations in the posterior cingulate cortex and alpha oscillations in the anterior cingulate cortex (ACC) under 20 and 35 mg/kg GHB in healthy male subjects (347). In the first functional neuroimaging study with GHB, 35 mg/kg of the drug increased regional cerebral blood perfusion in the ACC and the insula, both of which correlated with increased subjective ratings of emotion and body awareness (348). Moreover, the drug increased the susceptibility of the mesolimbic reward system, resulting in an increased sexual arousal after the presentation of erotic but also neutral pictures of persons. This effect correlated with an increased activity in the nucleus accumbens and the ACC (349).

The euphoric, prosocial, and prosexual effects of GHB, GBL, and 1,4-BD are instrumentalized illicitly, mostly by members of urban subcultures (314). Internationally, GHB, GBL, and 1,4-BD are mainly used as recreational drugs by young adults aged 20–29 years (349, 350). Reliable prevalence data are difficult to obtain (351). However, the prevalence of GHB, GBL, and 1,4-BD seem low compared to other drugs of abuse and are estimated at about 4.3% in Europe (349). After GHB was used in a deadly case of drug-facilitated sexual assault in the USA in the year 2000, the drug was internationally banned (352). However, a recent meta-analysis showed that GHB is very infrequently used as a date rape drug (353).

The development of addiction after illicit use of these drugs was estimated for about 4–21% of illicit users (351). Both addiction and withdrawal can be severe and in extreme cases lead to psychosis, delirium, and death (314). Interestingly, the development of addiction after medical use of GHB is at a very low rate with an estimated risk of about 0.015% (351).

Internationally, GHB is approved for the treatment of narcolepsy with cataplexy. In a recent meta-analysis, it was confirmed to be effective in treating major, clinically relevant narcolepsy symptoms and sleep architecture impairments in patients (354). Another clinical indication is the treatment of alcohol withdrawal, for which GHB is used since two decades in Italy and Austria (355). Moreover, several randomized controlled trials showed a therapeutic effect of GHB on clinical course and life quality in patients suffering from fibromyalgia (343, 356–358). Other neuropsychiatric disorders in which GHB showed therapeutic effects are binge-eating disorders (335), schizophrenia (359), Parkinson's disease (360), and cluster headache (361, 362), mostly by regulating homeostatic dysbalances, as well as improving sleep and pain symptoms. Because disrupted homeostatic processes including food intake, sexual behavior, and the sleep–wake cycle frequently occur in major depressive disorder, GHB was proposed as an experimental therapeutic in this condition (363, 364). However, therapeutic use of the drug is limited by side effects, such as nausea, vomiting, altered consciousness, and nocturnal O_2 desaturations (357, 365–367).

In conclusion, GHB and partially its precursors GBL and 1,4-BD have undeniable caveats such as limiting side effects and abuse liability. These, however, seem to be outweighed by a unique spectrum of clinically relevant psychopharmacological effects, which warrant further studies in neuropsychiatric conditions such as major depressive disorder following a personalized treatment paradigm (368).

CONCLUSION

The amount of evidence on the psychoactive drugs discussed shows that many of them are not really novel anymore. For most of them a classification in terms of their use and harm potential has been made. In fact, most of them are already legally controlled or banned in certain countries. An important feature of this process is that it appears socio-geographically biased. Even in a globalized world, new psychoactive drugs emerge and spread in a regionally bound way. This brings about that evidence on their use, instrumentalization, and abuse accumulates often only regionally. Also, the drug may for a long time not spread beyond the socio-geographic boundaries. However, this does not mean that it is not eventually "discovered" by other societies making use of the drug for a new and essentially different purpose. The scientific challenge is then to use locally gathered knowledge to be prepared for a drug that is novel in a certain culture and establish a judgment on its harm potential and/or medical use on a rather global scale. It also means to delineate future research needs for those drugs that are brand new as a psychoactive drug. This review shows that despite accumulating evidence, for many of those NPSs, a final classification is still in progress and gathering of more evidence is pivotal.

AUTHOR CONTRIBUTIONS

CM and ZH planned the review article and contributed to several chapters. CM prepared the final version of the manuscript. CM, ZH, OB, DS, SN, BK, ES, JK, and BQ wrote single chapters of the manuscript.

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