NEW AND LITTLE KNOWN DRUGS OF ABUSE

Objectives

When the reader has finished this module, they will be able to:

1. Identify a common designer opioid analogue
2. Identify 2 common tryptamines
3. Identify the toxic effects of tryptamines
4. Identify the toxic effects of piperazines
5. Identify the toxic effects of GHB
6. Compare khat to a common class of drug
7. Name a therapeutic use for ketamine
8. Describe the effects of intoxication with salvia divinorum
9. Compare the effects of dextromethorphan with a common class of drug

The urge to alter consciousness is almost universal, and very, very old; humans have been using psychoactive substances for thousands and thousands of years, and they still do so today. Almost every ancient society used psychoactive plants to some degree. The Greeks had the Eleusinian mysteries and hallucinogenic mushrooms, West Africans had ibogaine, South American Indians chewed coca leaf and smoked ayahuasca, the Aztecs had psychoactive mushrooms, and Native Americans had – and still have today – peyote. The substances were ingested as parts of mystical and healing rites and recreational use was minimal.

Most of these societies used these psychoactive substances infrequently and as part of religious rites or ceremonies. But *recreational* use of psychoactive drugs has become common, and there has always been a search for better, safer, or more powerful drugs, or drugs that produce a unique effect. This search continues today (Some travel agencies offer "enlightenment tours.' They organize trips to countries where the use of psychoactive drugs such as ibogaine, if not legal, is not actively prosecuted and arrange for the tourist to sample these drugs), and the result is that there are always new drugs of abuse.

What are these new drugs of abuse? It's impossible to make a complete list with any certainty. The presence of a new drug is not detected until someone presents for treatment or law enforcement officials capture a supply, and new ones are being discovered and marketed all the time. Many of them appear, have a brief period of popularity and then disappear, some times forever, some times until a new generation discovers them. Some only have regional popularity, eg, they will be used in the Midwest but nowhere else, or they are popular in Europe but not in the United States. Some are too difficult and expensive to synthesize. Others, eg, a-methyltryptamine, known as AMT, are quickly found to be unpleasant and/or dangerous; this information is circulated in the drug subculture and their use is abandoned.

And calling them new is also not quite accurate. Almost all are derivatives of existing drugs, legal and illegal. A molecule is changed, a side group is substituted, a synthesis process is altered a bit and you have a new drug (It's interesting to note that the action

of a derived drug – to a lesser degree – and the strength of a derived drug – more so – often cannot be predicted from its chemical similarity to the parent drug). This has given rise to the popular term *designer drugs*. This was originally coined to describe powerful heroin-like substances that were based on the fentanyl molecule. The first of these appeared in California in the late 1970s, a fentanyl derivative called *China White* that is still around today. Early in 2006, there was a series of more than 70 fatal heroin overdoes on the East Coast, and they were caused by heroin laced with China White. Also during the 70s and 80s, a meperdine derivative called MPPP appeared on the scene that caused a handful of cases of irreversible Parkinson's

How popular are designer drugs? What do they do? It's impossible to know the extent of use for many of them. Ecstasy (3,4-methylenedioxymethamphetamine, MDMA), a phenylethylamine commonly called a hallucinogenic amphetamine, is the only designer drug about which much is known of the use patterns. It appears to have considerable popularity in Europe (where most of it is manufactured) and there is a small but steady demand for the drug in the United States. It is also the only designer drug that has been subjected to scientific study in humans. For all the rest, there is no, or very little, information on their effects in humans (and much of that is comes from post-mortem exams or personal accounts of the users) and small amounts of animal research for a few.

Are the designer drugs dangerous? There have been reports of fatalities and significant morbidity associated with ingestion of designer drugs. The issue can be put into perspective when the standard industry practice of designing a drug is examined. In that process, hundreds of compounds are synthesized and their pharmacological profile carefully investigated, outlined and reported, and scrutinized in the scientific literature. If the drug looks promising, the drug company must then get massive amounts of data, toxicological and pharmacological, before the drug can be given to human subjects. Given this information, the risk of designer drugs is obvious. In some case, the designer drug is an analogue of a substance that is well-known, eg, amphetamine. In other cases, the designer drug is an analogue of a compound about which little is known. In either case, the drug goes directly from the laboratory to the user. To that information add the fact that there is no quality control of illicit designer drugs and the dangers of these substances are clear.

So with all the designer drugs available and with new ones being regularly synthesized and abused, how is it possible to understand these drugs? If you are taking care of a patient who has ingested an unknown designer drug – and the only thing the patient knows about it is that it is called Foxy – how do you know what to expect, how do you know what toxic effects to look for? How do you know what care this patient needs? Given that fact that there are dozens of new drugs of abuse, aka designer drugs, this can seem to be an impossible task. You can't possibly memorize and remember all of the designer drugs and their nicknames. There are over 50 different synthesized tryptamines with hallucinogenic properties, there are over 170 different phenylethylamines and psychedelic amphetamines, there are more 1200 naturally occurring indole alkaloids (these terms, tryptamines, phenylethylamines and indole alkaloids will be discussed later), and psychoactive alkaloids have been found in plants, animals and fungi.

Fortunately, as mentioned before, the many of the "new" drugs of abuse are, in one sense, not new. *They are often derivatives of existing drugs* and although they have different names and occasionally their pharmacological action can differ from the parent

compound (usually not by too much), they have *essentially the same effects*. So if you understand the parent compound, and you realize that the parent compounds of these designer drugs can be divided into specific categories based on their structure and their pharmacological effects, you can understand these drugs. Example: DMT (*N*,*N*-dimethyltryptamine, aka the businessman's special) has a different structure and a somewhat different effect than 5-MeO-DIPT (5-methoxy-N,N-diidopropyltryptamine, aka Foxy), *but they are both tryptamines*. The structure and effect will differ somewhat but will *essentially* be the same. If you understand the tryptamines, you can take care of someone who has taken DMT, Foxy, psilocybin, or bufotenine. Most nurses won't be familiar with several of these new drugs of abuse, but there are several that would be familiar to any experienced nurse. All of them work by mechanisms that are familiar to every nurse. Also, although there are many designer drugs/new drugs of abuse, they can be divided into several easily remembered categories.

Opioids

Opioids have been abused for hundreds of years and heroin addiction is still a significant public health problem in the United States. Although the purity of heroin has been increasing in recent years, heroin dealers have always diluted or *cut* their product with a variety of substances: some are benign, eg, powdered milk, and some not so benign, eg, scopolamine, clenbuterol, and fentanyl. There have also been attempts to produce opioid analogs/opioid designer drugs and this led to the manufacture of *alpha-methylfentanyl*, aka *China White.*

China White first surfaced in California in late December 1979. There were two fatal overdoses in Orange County. The victims were known heroin users, they were found with drug paraphernalia and autopsy findings – pulmonary edema and needle marks – that indicated an opioid overdose, but the post-mortem toxicology tests were not positive for heroin. More overdoses followed until it was revealed that the addicts had been injecting a fentanyl analog, alpha-methylfentanyl, known on the streets as China White, and that China White has the same effects as heroin. And China White continues to surface. In the latter part of 2005 and the early part of 2006, over 70 deaths were reported on the East Coast that were attributed to China White. It may be surprising that after a few deaths, heroin users would continue to seek out and abuse China White, but apparently its legendary strength and the danger of the drug are part of the allure.

Alpha-methylfentanyl is a simple analogue of fentanyl, a synthetic opioid first synthesized in the 1950s and available for medical use in the early 60s as an anesthetic under the trade name of Sublimaze®. China White continued to make sporadic appearances in the following years, and there were other analogues that surfaced as well. In 1984, alpha-methyl acetylfentanyl appeared. It was found to be less potent than fentanyl but had a longer duration of action; other fentanyl analogs were not so harmless. In early 1984, 3-methylfentanyl was involved in several overdoses and depending on the form, was 400 to 6000 times as strong as morphine. At least 10 fentanyl analogs have been have been identified.

Fentanyl itself is a synthetic opioid that is in common use as a potent analgesic; figures vary but one source notes that fentanyl is 80 times more potent than morphine.[1] It is available for parenteral use and it is commonly found in the form of a transdermal

patch. In the transdermal patch, the drug is contained in reservoir and a special membrane controls the diffusion of the drug from the reservoir to the skin. It is very popular for the control of chronic pain or for controlling pain in cancer patients.

As fentanyl is such a powerful narcotic and is in such common use, not surprisingly, abuse is common. Fentanyl from transdermal patches can be abused in several ways. The drug can be removed from the reservoir, placed on aluminum foil and heated and the fumes inhaled. The drug can also be removed from the reservoir and ingested or injected. As the amount of fentanyl in a patch can be very large and it is impossible to titrate the dose when using the patches in these ways, fatal overdoses have been seen.[2]

Other opioid analogues have also been synthesized, at times with tragic results. A meperdine analogue was sold on two separate occasions in the late 1970s and the early 1980s. The chemist, trying to make the meperidine analogue 1-methyl 4-phenyl 4-propionoxypiperidine (MPPP), mistakenly produced a drug that contained 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). This is metabolized to MPP. MPP is directly toxic to the nigrostriatal neurons and a handful of users developed irreversible Parkinson's.[3]

The toxic effects of these drugs is identical in nature, if not intensity, to that of the other opioids, eg, heroin, morphine, etc. Central nervous system depression and respiratory depression are common and hypothermia and hypotension are possible. Treatment of the opioid analogs/derivatives should focus on maintaining a patent airway and ensuring adequate oxygenation. Occasionally blood pressure support or re-warming measures may be needed. Naloxone is the antidote; it acts as a competitive antagonist at the μ receptors. It should be stressed that the goal of naloxone therapy is *not* the restoration of full consciousness. It is restoring adequate respiratory drive to ensure oxygenation. Restoration of full consciousness in a patient who is addicted to opioids is *very* unpleasant for the patient and can be dangerous for the staff.

Instant feedback: If a patient is exhibiting the classic triad of signs of opioid overdose – coma, respiratory depression and miosis – but does not respond well to high dose of naloxone, they may be intoxicated with a fentanyl analogue.

Tryptamines

Tryptamine (3-(2-aminoethyl)indole) is a monoamine compound, a naturally occurring alkaloid that is widespread in nature and found in animals, plants and fungi. Tryptamines can also be produced semisynthetically or synthetically. The basic structural component and functional group of tryptamine is the *indole* molecule. A short carbon chain is added to the indole molecule to make tryptamine, and substitutions to the tryptamine molecule produce the various functional tryptamines, eg, serotonin, melatonin, the hallucinogenic tryptamines, and drugs such as sumatriptan.

Indole + carbon chain = tryptamine.

Tryptamine + ethylamine substitutions = functional tryptamines

Note: Occasionally the tryptamines will be called *indolealkylamines.* This is the term for

psychoactive drugs that contain the indole molecule and includes beta-carbolines such as harmaline, coryantheine-related indoles such as yohimbine, ergolines such as LSD and ibogaines. All have hallucinogenic properties, all have the indole molecule, and all have unique substitutions that give them their specific properties.

Tryptamines have been used by humans for centuries for their psychotropic effects, and they are an endogenous compound (their exact function is not known). Natives of the Amazon area have long smoked *ayahuasca,* a plant that contains the psychoactive substance tryptamine *N,N*-dimethyltrptamine (DMT). Natives in ancient Mexico used psilocybin-containing (psilocybin is a tryptamine) mushrooms and called them teonancatl (flesh of the gods), they were used by shamans in Siberia, in religious rituals in ancient India, and a psychoactive fungus is though to be the source of the mysterious potion, kykeon, that was used by ancient Greeks in the religious rite the Eleusinian mysteries.

Tryptamines as recreational drugs have gone in and out of favor through the years. They enjoyed a brief popularity in the 1960s (especially DMT). The ones in current use are synthetic and over 50 psychoactive tryptamines have been synthesized (Most of these have been synthesized but for various reasons have not been used). Tryptamines are also found in the genus of mushrooms known as *Psilocybe* (magic mushrooms) and 5-OH dimethyletryptamine is found in secretions of toads of the *Bufo* species. Until 2004, the tryptamines were not scheduled drugs (scheduled drugs are drugs that have their use and distribution tightly controlled because they have abuse potential) except for DMT. There is some evidence that the tryptamines are enjoying a resurgence in popularity.[4]

How do the tryptamines work, and what do they do? The exact mechanism by which the drugs work has not be clearly outlined, although given their similarity to serotonin it has been suggested that they are serotonin agonists. They may also acts as agonists at the norepinephrine and dopamine receptors.[5] The lack of information is not surprising. As the tryptamines are Schedule I drugs (these are drugs with high abuse potential and no recognized medical use), there is obviously a dearth of controlled, scientific investigation, and receiving permission and funding for studying Schedule I drugs is an almost impossible task. In one of the few published papers, Strassman administered IV DMT to experienced hallucinogen users.[6] He noted that the effects began within 2 minutes and were essentially gone in 30 minutes and that *heart rate, blood pressure and pupil size* all increased. *Visual hallucinations* (kaleidoscopic displays of intense abstract images) and auditory hallucinations were common, as were elevations in body temperature. Subjects described perceptual and cognitive changes and feelings of dissociation. The effects last approximately 30 minutes. A later study (1996) confirmed these findings.[7] Given the structural similarity of all tryptamines, it's reasonable to expect all tryptamines would produce similar effects.

But although there is a dearth of information about how tryptamines work and how they affect physiology, there is no shortage of information about the *subjective* experience of a tryptamine high. Websites such as Erowid, MAPS and many others offer long, detailed, first-hand accounts of the highs experienced from DMT, Foxy and other tryptamines. These drugs, the users say, are like being shot out of a cannon. The onset of effects is almost immediate and the maximum effect is experienced in minutes. Users all describe intense changes in the sense of self and reality. The sense of time is particularly disrupted. The hallucinations are intense, vivid and occur even when the eyes are closed.

Some people experience feelings of calm and peace, but acute anxiety and paranoia are also possible. With some tryptamines, the user is essentially incapacitated.

What tryptamines are in popular use right now? It appears the most common is 5-methoxy-N,N-diisopropylttryptamine (5-MeO-DIPT), aka *Foxy* or *Foxy methoxy.* This drug has been in use since the late 1990s and its use seems to be increasing.[8] The drug can be taken orally, injected or smoked, and the effect of a Foxy high includes euphoria, loss of inhibition and visual and auditory hallucinations. Adverse effects include nausea, vomiting, restless and mydriasis. The effects usually have an onset of 20-30 minutes and last for approximately 3-6 hours. Little is known about serious adverse effects, although one case of rhabdomyolysis associated with Foxy has been reported, (and one associated with DMT), [9] patients may seek medical attention because of a acute anxiety and fear of the drug's effects[10] and several fatalities related to Foxy and alpha-methyltryptamine have been recorded.[11]

Treatement of an overdose of a tryptamine is symptomatic and supportive. Most users simply require a quiet, supportive, non-judgmental atmosphere and occasional use of benzodiazepines if anxiety is incapacitating.

Instant feedback: Tryptamines probably work by stimulating serotonin receptors, neurotransmitter receptors that are located in parts of the brain that influence, mood, sleep, arousal, and sexuality.

Instant feedback: The duration and intensity of effects vary, but all tryptamines produce hallucinations, disorientation, an out of body experience, and slight elevations of heart rate, blood pressure, and temperature.

Instant feedback: The common tryptamines all have nicknames:

N,N-dimethyltryptamine – DMT, businessman's special, Dimitri
N,N diisopropyltryptamine: Foxy, foxy-methoxy, fake ecstasy
Alpha methyltryptamine – AMT, spirals, Amtrak

Piperazines

Piperazines are a class of synthetic drug that includes the antihelmintics used in veterinary medicine for eliminating parasites, the antihistamine meclizine, a drug used to treat erectile dysfunction (sildenafil), and in recent years, drugs of abuse. Many of the piperazines that are currently abused are not new drugs, and they were synthesized years ago (BZP was first synthesized in 1944); some were abandoned, some are still in use today. Collectively the piperazine drugs of abuse have been called *Legal E* or *Legal X* and they can be divided into two categories:

- Benzylpiperazines: **BZP, A2** (N-benzylpiperazine) and **MDBP**(1-(3,4-methylenedioxybenzyl)piperazine.
- Phenylpiperazines: **mCPP** (1-(3-chlorophenyl)piperazine), **MeOPP** 1-(4-methoxyphenyl)piperazine, **TFMPP/ Molly** (1-(3-trifluoromethylphenyl)piperazine).

As with the tryptamines, the basic mechanism by which these drugs produce a desirable high is not entirely clear. There is little pharmacological data and the majority of this has been in vitro experiments or experiments with animals, However, BZP has effects similar to amphetamine – it causes increased heart rate and blood pressure – and there is evidence that BZP and TFMPP increase serotonin and dopamine levels (BZP more so). [12, 13] There have been several clinical experiments with mCPP (this drug has been used in the past as a serotonin agonist for research into the serotonergic system and it is a metabolite of several psychotropic drugs). mCPP did not increase heart rate or blood pressure in patients who had some experience with MDMA (ecstasy)[14] and this appears to be supported by a study by Johanson.[15] Users report euphoria, agitation, and increased energy levels. The piperazines can also occasionally cause hallucinations.[16] These compounds may exacerbate the symptoms of people with obsessive-compulsive disorder.

But again, although there is little information about how these drugs work, there is a lot of subjective information about what these drugs do. Piperazine users most commonly report symptoms similar to that of amphetamines: racing heart, a *rush* (this the word is used to describe the onset of the effects of a drug. It is usually used if the effects happen rapidly and intensely), and euphoria. Sounds and visual field may be altered. There are no spiritual or deep emotional effects. One user reported a headache, the sensation that his lungs were filling with liquid and a hangover sensation of headache, muscle aches, and fatigue that lasted 2 days. He also noted that the experience was somewhat like MDMA (ecstasy) but the physical sensations were very uncomfortable and frightening. One fatality due to BZP has been reported and tolerance has been reported.[17]

Treatment would be symptomatic and supportive. As these drugs have an amphetamine-like effect, it would be prudent to monitor for tachycardia, hypertension, seizures and rhabdomyolysis.

Gamma Hydroxybutyrate - GHB

GHB (gamma hydroxybutyrate), is not a new drug of abuse – it has been around since the 1960s – and the frequency of use rises and falls, but few nurses are familiar with GHB and what it does.

GHB was first synthesized in the 1960s for use as an anesthetic. It was also used to help with the study of the neurotransmitter GABA (gamma aminobutyric acid). It has been used as a general anesthetic, as a hypnotic, for the treatment of insomnia, as a treatment for clinical depression, and as an athletic performance enhancer. It could be bought legally in health food stores until 1990. However, later that year, after a series of poisonings [18] an increase in use, and concern for the use of GHB as a date rape drug, it was banned by the FDA for OTC sales. Today it is used under the trade name Xyrem® as a treatment for reducing the incidence of cataplexy attacks in patients who suffer from insomnia. Currently it is both a Schedule I drug (due to its potential as a date rape drug) and a Schedule III drug.

GHB occurs naturally in the central nervous system but its exact role in human physiology as a neurotransmitter is not known. It is a precursor to GABA and GABA regulates wakefulness and sleep. GABA cannot cross the blood brain barrier, so GHB

may provide the converting compound. GHB binds with GHB receptors and very weakly with $GABA_B$ receptors. When the drug is used in high amounts, there may be enough GHB to bind with the $GABA_B$ receptors. The GHB receptors are found in dense clusters in many parts of the brain, and only in the CNS, not in the periphery. The absorption of GHB is rapid, the onset of effects is within 15 minutes, and the duration of effects is approximately 6-10 hours. The toxic effects of GHB include [19]

- Central nervous system depression,
- Respiratory depression,
- Bradycardia, and
- Hypothermia

These effects can be quite profound and deaths have been reported from GHB use.[20] The drug is easily available through street purchase and there are many sites on the internet that provide instructions for GHB synthesis – a simple process that does not require exotic and/or illegal chemicals or specialized knowledge of chemistry (Note: Although GHB synthesis is simple, it is not without its dangers. Sodium hydroxide, a strong alkaline compound, is part of the process and used incorrectly, the resulting GHB can cause serious burns to the mouth and esophagus). There are also two other substances – gamma butyrolactone (GBL) and 1,4-butanediol (aka *1 comma 4*, or *1 4 bee*)that are precursors of GHB, they are converted in vivo to GHB and have the same effects. There is some evidence that GHB can be habit forming, and a withdrawal syndrome that can produce agitation, severe delirium, prolonged psychotic symptoms, hallucinations, hypertension, and tachycardia.[21]

Treatment for GHB intoxication is symptomatic and supportive, with special attention to maintaining a patent airway, ensuring adequate oxygenation, and preventing hypothermia.

Instant feedback: There are too many nicknames for GHB to remember them all, but the most common seem to be *grievous bodily harm* and *liquid ecstasy*.

Khat

Khat (pronounced *cot*) is a psychoactive compound and a stimulant that is derived from the *Catha edulis Forssk* plant. This plant is widely cultivated in East and Central Africa and the Arabian peninsula and is also known as *qat, chat, jaad and miraa*. Khat use is a tradition in many countries in those areas, it has long been used by immigrant populations in other countries [22] and there is evidence that its use is growing in the United States : 800 kilograms of khat were seized in 1992, but in 2002, 37 metric tons was intercepted.[23] Some of this increased use may be due to returning military personnel who were exposed to khat while on duty in the Gulf and brought the habit back with them. At the present time, the active ingredients of khat are scheduled substances.

The active components of Khat are contained in the leaves, especially young leaves near the top of the plant. The active components are *cathine* and the more powerful *canthione*. Canthione and cathine are *phenylethylamine* type substances (phenylethylamine is the central molecule in amphetamine) and are similar to the

phenylethylamine phenylpropanolamine (this was used for many years as an OTC decongestant, but it has been taken off the market). Cathine is found in the dried leaves while canthione is found in fresh khat leaves and converts to cathine within 48 hours, so young, fresh khat leaves are much more desirable to the users.

Khat has traditionally been used as a euphoric and stimulant and is also valued for its effect as an anorectic; some Muslims use khat during Ramadan, the month of the year in which Muslims must fast from sunrise to sunset. Use is widespread (it has been estimated that over 20 million people chew khat daily), khat ingestion is often convivial in nature, and in most parts of thwe world in which use is common, it is not considered a social problem, although it is outlawed in Saudi Arabia. Traditionally, small amounts of the leaf are placed in the mouth and chewed and then held next to the oral mucosa (khat may also be smoked or brewed as a tea.[24]

The drug works by stimulating release of catecholamines from presynaptic nerves.[25] The users typically report feeling of stimulation, euphoria and mental alertness.[26] although anxiety and restlessness have been reported. Physically, the effects are indistinguishable from those of amphetamine. Heart rate and blood pressure are increased and it is a positive inotrope.[27] Oxygen consumption and respiratory rate are increased. These effects are generally perceived as mild and enjoyable and part of the khat experience.

Information about the toxicity of khat is limited. Chronic khat users may have an increased risk for oral malignancies, similar to that of users of chewing tobacco.[28] and chronic khat users may develop tolerance to the effects. Constipation is possible and it is also genotoxic and teratogenic.

Some of the effects are not so benign. Al-motarreb noted that khat chewing was a significant risk factor – as high as 39-fold – for developing acute myocardial infarction, most likely due to catecholamine surge or possibly coronary vasoconstriction. [29,30] Chest pain, hypertension and tachycardia have been noted. One report noted leukoencephalopathy in a chronic user of khat. The patient has been chewing excessive amounts of khat for five weeks. He became confused and agitated and an MRI showed diffuse abnormality in deep cerebral white matter. This patient had also previously had a khat-induced psychosis and there have been other cases of severe mental disability related to khat use.[31]

Treatment for khat intoxication would be symptomatic and supportive and should focus on observing for, and treating, tachycardia, agitation and hypertension.

Instant feedback: Khat intoxication is identical to amphetamine intoxication: increased heart rate and blood pressure, increased respiratory rate and hyperexcitability.

Instant feedback: Given the fact that khat is in widespread use, and given the conditions in which it is normally taken – used in moderation in social settings – serious overdoses with khat are unlikely.

In addition, there have been reports of khat derivatives manufactured and abused. Methcathinone is a methyl derivative of cathinone known as ephedrone and it has amphetamine-like effects similar to ephedrine.

Salvia divinorum

Salvia divinorum is a member of the sage genus and the mint family. It is also known as diviner's sage, magic mint, or María Pastora, and the name salvia divinorum is Latin for *sage of the seers;* the genus name is derived from the Latin word *salvare* which means to heal or to save. It grown by indigenous people in the Oaxaca mountains of southern Mexico. Wild populations are reported, although deliberate cultivation is relatively common. At the present time, salvia divinorum is not a scheduled substance in the United States.

Although it is not known with certainty, salvia divinorum may have been used by ancient people in Mexico; certainly its use dates back 100s of years and it was traditionally used for religious practices or sacred rituals and also used to treat anemia, headache and rheumatism. It is valued for its psychoactive properties, and the psychoactive component is *salvinorin A*. This diterpenoid is the most powerful naturally occurring hallucinogen, and it is unique its actions. It has been speculated that most hallucinogens produce their effects by stimulation of the serotonin receptors. However, salvia divinorum is a very potent and selective kappa opioid receptor agonist – the only known naturally occurring compound that has this action.[32,33]

Salvia divinorum is ingested by chewing the fresh leaves and swallowing them or by drinking the juice from crushed leaves. It can also be smoked by the same method that cocaine and heroin are smoked: the purified crystals are heated on a piece of aluminum foil and the vapors are inhaled through a straw. The effects are short-lived: approximately 15 minutes when smoked and 1 hour when ingested. Users generally describe out of body experiences, body and object distortion, time distortion and lack of motor control.[34] A feeling of oneness with the universe and nature is common. Visual hallucinations are infrequent: at times the effects of salvia divinorum may be barely perceptible. It appears as if the effects are unpredictable: users may experience a high when using it one day but not the next. Most reports indicate that the high experienced with salvia divinorum, compared to the high experienced with LSD or mescaline, is very mild.

There have no definitive toxicological tests on humans or animals, [35] there are no case reports of overdose or toxic exposures, and so the safety of salvia divinorum is still in question. There is also no estimate of the extent of use. There has been speculation that salvia divinorum may have some use as an antidepressant.

Overdoses of salvia divinorum have not been reported. It is expected that the toxic effects would be similar to those of the tryptamines, albeit less intense, and treatment would be symptomatic and supportive.

Ketamine

As with many of the "new" drugs of abuse, ketamine is not new. It was developed in the 1960s for use as a dissociative anesthetic as an analogue to phenycyclidine (PCP), which was too toxic for use. Ketamine works by inhibiting the uptake of neurotransmitters, dopamine, norepinephrine, serotonin and inhibiting glutamate activation in the *N*-methyl-*D*-aspartate receptor. It is in relatively common use by veterinarians and in pediatric medicine. It has analgesic and anesthetic properties without cardiac or respiratory depression. Patients receiving ketamine appear to be awake but are unaware of, and unable to respond to, their surroundings.[36]

Ketamine produces a wide spectrum of effects. It can be smoked, ingested or injected. Users usually report an intense mind-body separation, a dream-like state and visual hallucinations. Less pleasurable effects include tachycardia, palpitations, hypertension, chest pain, nystagmus, rhabdomyolysis, respiratory depression, and apnea. Fortunately, the effects are short-lived: in one small cases series, the median time of observation in the emergency department for resolution of symptoms was 3 hours.[37]

Treatment would be symptomatic and supportive. Benzodiazepines can be used for agitation and tachycardia and the patient should be monitored for rhabdomyolysis. If the patient is initially suspected of using ketamine, but does not improve within several hours of observation, there is a good chance that ketamine is not involved.

Dextromethorphan

Dextromethorphan is a cough suppressant that is widely available in OTC cough and cold preparations. It works centrally as an antitussive by stimulating the sigma opioid receptors. Unlike opioids, dextromethorphan does not produce analgesia, respiratory depression or miosis. However, it does produce sedation and for that reason – and along with its easy accessibility – has gained popularity as a drug of abuse.[38] It is commonly known as "dex," "red devil," "robo," or "robocop (the last because it is available in a common cough suppressant, Robitussin®). It is also known as "CCC," or "triple C," again because of its OTC availability (Coricidin HBP®).

Effects of dextromethorphan intoxication naturally depend on the amount ingested, and it is interesting to note that the therapeutic dose is 15 to 30 mg three to four times a day, but users may take as much as 1500 mg at one time. Users experience drowsiness, euphoria, disorientation and occasionally hallucinations. In overdose, CNS depression of varying degrees, ataxia, slurred speech tachycardia, hyperreflexia, and acute psychosis are possible. As dextromethorphan increases the release and blocks the reuptake of serotonin, there is the possibility of serotonin syndrome if it is taken in combination with another drug that affects serotonin meatbolism. Also, may of the OTC preparations that contain dextromethorphan also contain decongestants such as pseudoephedrine and antihistamines such as chlorpheniramine, putting the abuser at risk for sympathomimetic toxicity (hypertension and tachycardia) and anticholinergic toxicity (agitation, urinary retention, tachycardia, fever).

Treatment for detromethoprphan toxicity is symptomatic and supportive. As it is an isomer of levorphanol, a codeine analogue, naloxone may be used, but success with naloxone in these situations has been mixed.

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