Drugs of Abuse and the Nervous System

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REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: This article discusses the neurologic complications of traditional, nontraditional, and emerging drugs of abuse.

RECENT FINDINGS: The manufacture, distribution, and use of so-called designer drugs are increasing. These agents can induce dramatic neurologic manifestations and can evade identification on conventional drug-screening assays. Additionally, gabapentinoids, drug agents that are very familiar to neurologists, are being abused in the general population at increasing rates to achieve euphoric highs and potentiate the effects of opiates. Furthermore, even well-known illicit narcotics such as heroin are posing dangers above their baseline because of "lacing" with additives or substitutes such as fentanyl and related compounds. These clandestine agents increase the potency of what are thought to be typical dosages to lethal levels, thus leading to more unintentional overdose deaths.

SUMMARY: The potential for short- and long-term nervous system injury from drug abuse is well established. However, it is important for the practicing neurologist to possess awareness of the features and observed sequelae of the toxidromes of both traditional and nontraditional drugs of abuse. This is because the use of both is widespread in our society and conventional drug screening can miss detection of some powerful agents, thus forcing us to maintain a high index of suspicion based on recognition of the clinical features.

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INTRODUCTION

The landscape of drug abuse worldwide is more complex than ever. With both the number of different classes of agents available and the number of individual agents within these classes continuing to expand, drug abuse must be considered in the differential diagnosis not just for acute and subacute alterations in neurologic functions but for chronic changes as well. This article provides a broad survey of the wide array of illicit drugs that have proven to be associated with neurologic injury and dysfunction. TABLE 11-1 lists the common classes of drugs of abuse that are discussed.

From the neurologist's perspective, it is of utmost importance to know the clinical manifestations of intoxication, potential neurologic complications, and management of these adverse effects; however, before proceeding, it would be helpful to define what constitutes a true substance abuse disorder. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), the salient features of a substance abuse disorder include tolerance of higher and

higher doses of the medication to achieve the same effect, withdrawal effects after cessation, and maladaptive behaviors to satisfy cravings.[1] Drug dependence manifests both psychologically, with intense cravings and drug-seeking actions, and physically, with somatic symptoms and examination findings during states of withdrawal.[2]

OPIOIDS

Both opioid receptor agonists and partial agonists have abuse potential. Prescription opiates and illegally manufactured street drug formulations, such as heroin, have been widely abused and have caused well-known complications in great numbers for over 2 decades (the so-called opioid epidemic). The origin of the opioid epidemic, in part, likely traces back to a five-sentence letter published in the *New England Journal of Medicine* in 1980 by a group from Boston University that challenged the thought that long-term opioid use led to a high risk of addiction. According to a subsequent report in 2017,[3] this brief 1980 letter has been since cited more than 600 times to claim the low risk of long-term prescription opioid therapy for chronic pain, despite the original 1980 letter providing no supportive evidence of that interpretation. These citations increased dramatically in the literature after the industry introduced long-acting formulations of opioids (such as extended-release oxycodone in 1995). In this setting, from 1999 to 2014, drug overdose deaths tripled in the United States, with the spike largely attributable to the opioid epidemic.[4] However, a paradigm shift has begun, and promotion and implementation of nonpharmacologic measures or nonopioid agents to manage chronic pain are increasing. TABLE 11-2 lists opioids that are commonly abused.

Opiate intoxication yields, unsurprisingly, significant analgesia. However, people who use opiates also experience a euphoric high. In addition to different degrees of sedation, examination features include miosis and cough suppression (or decreased air hunger in those with active respiratory insufficiency). The latter is caused by central depression of the respiratory drive. It is this effect that makes overdose so high risk for mortality or significant morbidity. With heroin

TABLE 11-1 Classes of Common Drugs of Abuse

- Anticholinergics
- Cannabis and synthetic analogues
- Ethanol
- Gabapentinoids
- Hallucinogens
- Inhalants
- Opioids
- Phencyclidine (PCP)
- Psychostimulants
- Sedative/hypnotic agents
- Tobacco/e-cigarettes

and other parenterally injected or inhaled opioids, people get a near-immediate "rush" sensation that is interpreted as a false, but intense, feeling of warmth, well-being, and heaviness in the body. Similar rush effects can be seen with cocaine and crack cocaine.[5] In addition to the pleasurable effects, those intoxicated with opiates may experience pruritus, sweating, and decreased libido. Slowed intestinal motility leads to constipation.

Opioid overdose is characterized by the hallmark triad of respiratory depression, coma, and miosis. To avoid irreversible anoxic-ischemic injury, treatment is centered on rapid airway and ventilation support as well as prompt administration of naloxone (an opioid antagonist). Naloxone's duration of effect is short, so close monitoring of the respiratory rate for recurrent hypopnea is essential, as subsequent dosing or even a continuous infusion may be required. Recent trends show heroin, cocaine, and other street drug overdoses are now increasingly deadly because of "lacing" with synthetic opioids such as nonpharmaceutical fentanyl, fentanyl analogues, and "designer" novel opioid compounds such as U-47700.[6] These greatly increase the potency (although unknown to the person using), leading to extremely high numbers of fatalities due to unintentional overdose. These synthetic compounds are not detected on conventional drug-screening assays and require either so-called targeted opioid screens (in the case of fentanyl), which are available at many hospitals, or even liquid chromatography high-resolution mass spectrometry in the case of these novel compounds. Because the rate at which these new synthetic opioids appear on the market is much faster than the arduous process it takes for them to be regulated/criminalized, these deadly compounds can often be easily obtained on the internet as "legal highs."

Opioid withdrawal is often described as like having a very severe case of the flu. It is characterized by significant myalgia, hyperthermia, rigors, piloerection, rhinorrhea, vomiting, diarrhea, and irritability. Although the symptoms can be dramatic, they are very rarely life-threatening and are not associated with increased risk of seizures, as is the case with withdrawal from some sedatives/hypnotics. Some health care institutions have opioid maintenance/tapering

Commonly Abused Opioids

TABLE 11-2

Agonists

- Codeine
- Fentanyl
- Heroin
- Hydrocodone
- Meperidine
- Methadone
- Morphine sulfate (injection)
- Oxycodone
- Tramadol

Mixed Agonist/Antagonist

- Buprenorphine

programs for pregnant patients with opioid dependence, as withdrawal can be a severe stress on infants born to mothers who are addicted (known as neonatal abstinence syndrome).[7]

In addition to the potentially fatal or devastating conventional hypoxic-ischemic injury that can occur with opioid overdose, other severe, and more novel, neurologic complications can result from opioid intoxication. For example, heroin is often abused not just through IV administration but also through insufflation. A popular insufflation technique, called *chasing the dragon*, involves heating black tar heroin on a sheet of aluminum foil and inhaling the vapor. This results in a quick and intense high that avoids the use of needles. Heroin insufflation has been associated with multiple severe neurologic sequelae. One of the most widely reported is a progressive, toxic spongiform leukoencephalopathy.[8] A typical presentation is progressive abulia, bradykinesia, ataxia, and, eventually, spasticity over the course of 1 to 2 weeks after months of heroin vapor exposure. MRI often reveals significant symmetric white matter hyperintensity on T2-weighted images, sparing the subcortical U fibers and preferentially affecting the white matter of the posterior cerebrum, splenium, internal capsule, and

CASE 11-1

A 24-year-old man with a history of polysubstance abuse took a large dose of liquid methadone at a New Year's Eve party, after which he collapsed and became unconscious. He quickly became cyanotic. Resuscitation was initiated; he received naloxone for reversal and was intubated.

In the emergency department, he was found to have severe lactic and respiratory acidosis with severe rhabdomyolysis. He was comatose but withdrew to pain, and his brainstem reflexes were intact. MRI performed on day 3 showed diffuse leukoencephalopathy of the cerebral white matter tracts with sparing of the cerebellum, brainstem, and subcortical U fibers (FIGURE 11-1A). He was monitored for 2 weeks for any signs of improvement, but his examination remained unchanged. In accordance with the patient's previously expressed wishes should he experience a catastrophic brain injury, he was transitioned to hospice care and died 6 days later. An autopsy was performed, and pathology showed widespread spongiform changes in the cerebral white matter (FIGURES 11-1B AND 11-1C).

COMMENT

This is a case of a toxic opioid-associated spongiform encephalopathy. It can be acute, as in this case, or chronic, as in those originally described as being related to *chasing the dragon* (heating black tar heroin on a sheet of aluminum foil and inhaling the vapor). The chronic form tends to preferentially affect the posterior cerebral and cerebellar white matter.

cerebellum.[9] More acute fatal leukoencephalopathies have also been the result of opioid overdose, including with prescription forms (CASE 11-1).[10] Also, in addition to a leukoencephalopathy, opioid overdose has been observed to yield an acute cerebellar edema causing herniation and hydrocephalus.[11]

Acute myelopathy has also been associated with heroin overdose, both with injection and inhalation. The typical presentation is fast-onset flaccid paraplegia and urinary retention, often in the setting of the first-time use of heroin or subsequent use after a period of abstinence; rhabdomyolysis can be an accompanying feature.[12,13] Often these acute heroin-related myelopathies can possess clinical and imaging features consistent with spinal cord infarct, according to recently proposed diagnostic criteria.[14] FIGURE 11-2A shows the thoracic spinal cord MRI of a patient with acute heroin-associated myelopathy, in which a long segment of anterior predominant pencil-like enhancement is seen; this feature is sometimes observed in spinal cord infarct.[15] FIGURE 11-2B shows the spinal cord MRI of a patient with acute myelopathy after heroin and 3,4-methylenedioxymethamphetamine (MDMA) insufflation, showing anterior horn cell changes (a finding also commonly observed in spinal cord infarct).[16]

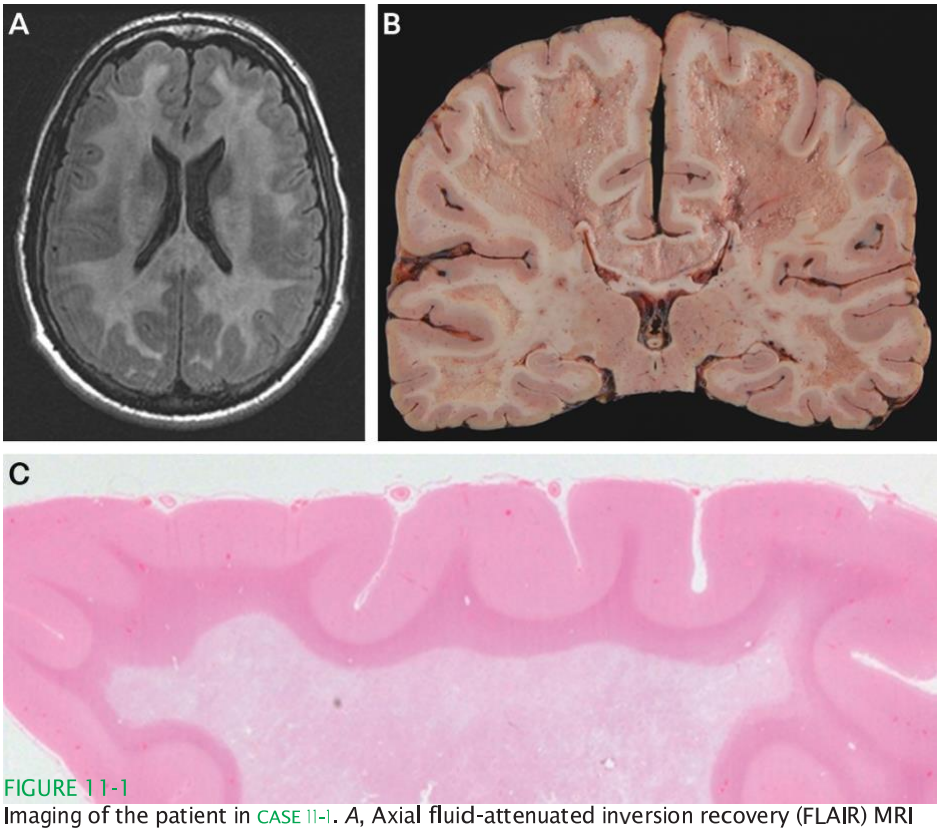

FIGURE 11-1
Imaging of the patient in CASE 11-1. *A*, Axial fluid-attenuated inversion recovery (FLAIR) MRI shows diffuse and dramatic hyperintensity in the cerebral white matter sparing the subcortical U fibers. *B*, Coronal brain section at autopsy showing subtotal hemispheric white matter damage. *C*, Hematoxylin and eosin (H&E) stain showing diffuse spongiform changes in the white matter with subcortical U fiber sparing.

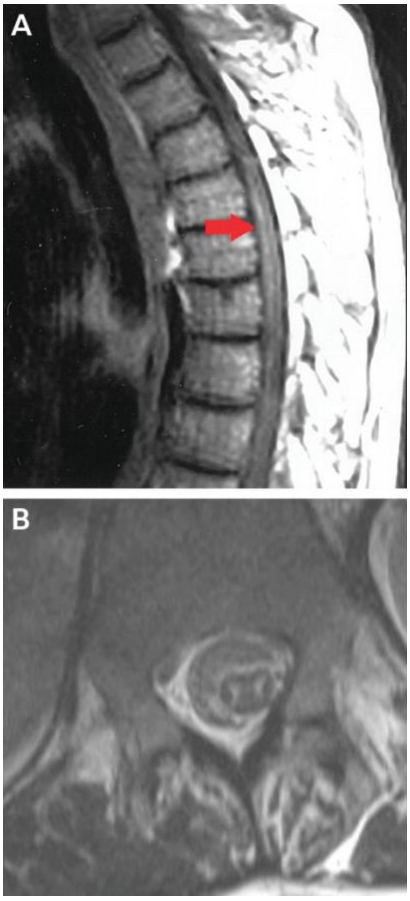

FIGURE 11-2
Myelopathy related to heroin abuse. *A*, Sagittal postcontrast T1-weighted thoracic spinal cord MRI showing anterior-predominant, linear, pencil-like enhancement in a case of heroin-associated acute myelopathy, similar to some observations in spinal cord infarct. *B*, Axial thoracic spinal cord MRI in a patient with acute myelopathy after heroin and 3,4-methylenedioxymethamphetamine (MDMA) intoxication showing anterior horn cell T2 hyperintensity, which is also a common imaging feature in spinal cord infarction.
Panel A reprinted with permission from McCreary M, et al, Neurology.[15] © 2000 American Academy of Neurology.
Panel B reprinted with permission from Riva N, et al, J Neurol Neurosurg Psychiatry.[16] © 2007 Journal of Neurology, Neurosurgery & Psychiatry.

Overall, this seems supportive of the hypothesis of an ischemic/vasculopathic mechanism of injury in these cases. However, significant pleocytosis in the CSF has been discovered in some cases of acute heroin-associated myelopathy.[13] This may reflect an inflammatory component to the process, possibly on the basis of a hypersensitivity reaction, given the onset after subsequent exposure preceded by abstinence. Interestingly, ongoing inhalational heroin use has been reported to be associated with a chronic, progressive myelopathy with selectivity for the posterior and lateral columns.[17]

GABAPENTINOIDS

Gabapentin and pregabalin are drugs that are very familiar to neurologists, used mostly for the treatment of neuropathic pain. They work by modulating neurotransmission at the presynaptic calcium channel.[18] However, they have more recently also become drugs of abuse. Known on the street as *gabbies*, gabapentin and pregabalin are described to cause a significant feeling of euphoria with illicit consumption; most concerning is their potentiation of the effects of opioids, as coabuse of gabapentinoids and opioids is on the rise.[19] However, gabapentin alone, even at excessively high doses, is generally nonlethal.

SEDATIVES/HYPNOTICS

This class of drugs includes benzodiazepines, barbiturates, and some other miscellaneous substances. Some of the more commonly prescribed and abused benzodiazepines include lorazepam, diazepam, clonazepam, temazepam, and alprazolam. Notable barbiturates include phenobarbital, pentobarbital, and butalbital. Both benzodiazepines and barbiturates lead to intense sedation by being γ-aminobutyric acid–mediated (GABA-ergic). By being modulators of γ-aminobutyric acid A ($GABA_A$) receptors, these two classes of drugs promote an effect of robust inhibitory neurotransmission. This explains their conventional use as anticonvulsant medications, anxiolytics, and procedural sedatives.

Intoxication with benzodiazepines or barbiturates commonly produces a euphoric, drowsy state. Amnesia of recent events is very frequent with higher doses. However, occasional paradoxical reactions are noted in some who have taken benzodiazepines, which can mimic a hyperactive delirium. Both benzodiazepines and barbiturates cause respiratory depression, and overdose can lead to life-threating hypopnea/apnea and coma. The use of barbiturates in health care, especially in the outpatient setting, has become less prevalent compared to benzodiazepines in recent decades because of their higher risk of respiratory depression and their potential for abuse and withdrawal. Both barbiturates and benzodiazepines share properties with ethanol, so their withdrawal syndromes can be similar: hallucinations, diaphoresis, agitation, and the most feared consequence, seizures. Long-term use of benzodiazepines and barbiturates is recognized to contribute to cognitive impairment and also leads to tolerance and physical dependence. Thus, any patient discontinuing long-term use of these agents should be tapered gradually under physician guidance. This includes patients who have been on long-term daily butalbital for headaches.

Notable miscellaneous agents in the hypnotic class include gamma-hydroxybutyric acid (GHB) and zolpidem. GHB gained popularity in the 1990s as a club drug and also for the unscrupulous use of its sedative and amnestic powers as a "date rape" drug that would not be detected on standard drug screens. It is typically administered concurrently with alcohol. Intoxication is initially marked by inebriation from the potentiated effects of alcohol, followed by coma, which can rapidly resolve back to the fully alert state.[20]

Zolpidem is a nonbenzodiazepine hypnotic that binds to the $GABA_A$ receptor. Although as a sleep aid it has less dependence potential than actual benzodiazepines, it is still a notable risk. Its ability to cause euphoria, eventual tolerance, and observed withdrawal symptoms in people who use the drug more heavily produce its known abuse potential.[21] Although anecdotal reports of strange adverse events, including hallucinations, amnesias, and peculiar movement-based parasomnias (such as sleep driving), have been linked with zolpidem use, on formal analysis these events were found to be quite rare, their risk likely falsely inflated by rigorous media coverage.[22]

PSYCHOSTIMULANTS

Psychostimulants are possibly the most complex class of drugs to review, given the seemingly innumerable compounds within the class and the fact that new compounds are continually being developed to evade regulation and detection. TABLE 11-3 lists notable psychostimulant compounds. The primary backbone chemical compound from which many of these drugs are derived is phenylethylamine. All the thousands of compounds available for abuse have a similar pharmacologic effect of increasing dopaminergic, serotonergic, and noradrenergic neurotransmission in the central nervous system, but they do this to different degrees. It is this mechanism of action that leads to an intense, rewarding, euphoric high that creates a high risk of addiction. Conversely, this leads to an undesirable withdrawal, or "comedown," which, for psychostimulants in general, yields a state of increased hunger (opposite of the anorexia that comes with intoxication), depression, and fatigue that is due to the relative drops in these monoamine neurotransmitters. Withdrawal is a nuisance and can lead to intense cravings but is not life-threatening. In general, psychostimulant overdoses lead to a delirious state with significant risk of cardiac arrhythmia,

KEY POINTS

- Severe opioid overdose is characterized by the triad of coma, miosis, and respiratory depression. Treatment is rapid respiratory support and administration of an opioid antagonist (naloxone).
- New synthetic opioid compounds are being used to lace common street drugs, such as heroin, to increase their potency, which leads to more unintentional overdoses.
- Heroin abuse carries the risk of both acute and chronic central nervous system complications, including a toxic spongiform leukoencephalopathy and myelopathy.
- Gabapentin and pregabalin are increasingly becoming abused substances. Their effects serve to potentiate the already dangerous effects of opioids.
- Barbiturates have higher abuse, dependence, and withdrawal potential than benzodiazepines.
- The manifestations of benzodiazepine and barbiturate withdrawal are similar to that of alcohol, with seizures being of highest concern.
- The risk of bizarre behavioral adverse events from zolpidem use is quite low. Its abuse/dependence potential is also low but should not be ignored.
- All psychostimulants have a similar pharmacologic effect of increasing dopaminergic, serotonergic, and noradrenergic neurotransmission.

seizures, marked hyperthermia, hypertensive emergency, rhabdomyolysis, and psychotic features.

One typical example of this class is cocaine, refined from the *Erythroxylum coca* plant native to South America. Its hydrochloride form is most popularly consumed by nasal insufflation. The processing of the drug into an alkaloidal form yields the solid crack cocaine; its "rocks" are smoked to achieve an intense, rapid high leading to significant abuse potential.

Methamphetamine, also known as *meth* or *speed*, can be synthesized from the decongestant pseudoephedrine. The abuse of methamphetamine has ballooned in recent decades, given the ability to synthesize it in makeshift laboratories by unskilled individuals with little or no chemistry training.[23] Its final synthesized form is a solid called *ice* because of its translucent appearance. Methamphetamine is often smoked or put into solution and injected intravenously.

MDMA, popularly known as *molly* or *ecstasy*, is a widely used club drug around the world. It is often used with the goal of enhancing the party experience by creating a feeling of warmth, increased alertness, a sense of interpersonal connectedness, enhanced sexual experience, and disinhibition. Its effects overlap with the hallucinogen lysergic acid diethylamide (LSD). It is also somewhat novel compared to other drugs in this class because it structurally resembles serotonin, which likely explains its potentiation of serotonergic activity by further increasing its release and inhibiting its reuptake.[24]

Cathinone is a psychostimulant that is found in the khat plant (*Catha edulis*), which is native to parts of Africa and the Arabian Peninsula. Its twigs and leaves can be placed in the mouth and chewed to release the cathinone compound for absorption that then leads to a euphoric effect similar to that of amphetamine. Methcathinone is another designer drug that is derived from cathinone. It can

TABLE 11-3 Commonly Abused Psychostimulants

- Cathinone
- Cocaine
- Dextroamphetamine
- Ephedrine
- Methamphetamine (*speed*)
- Methcathinone
- Methylenedioxymethamphetamine (MDMA, *ecstasy*)
- Methylphenidate
- Pemoline
- Phenmetrazine[a]
- Phentermine
- Phenylpropanolamine[a]
- Pseudoephedrine
- Synthetic cathinones (*bath salts*)

[a] No longer available in the United States.

also be synthesized from ingredients in over-the-counter cough medicines. A host of other synthetic cathinones have made their way onto the scene in the past decade in the form of so-called bath salts. As with other designer drugs, some are marketed as legal highs that are not detected on conventional drug-screening assays, and their active ingredients are novel enough that their chemical structure has yet to be formally designated as a controlled substance. Although some of the earliest synthetic cathinones have become regulated as schedule I narcotics (such as mephedrone, methylone, and 3,4-methylenedioxypyrovalerone), newer compounds with the same toxicity continue to be produced and have yet to be regulated. Manufacturers can circumvent blanket regulations against these drug analogues by labeling them as "not for human consumption." Routes of bath salt administration are diverse but are primarily through ingestion, inhalation, or injection, and core clinical signs of intoxication are agitation, hallucinations, and tachycardia.[25] This syndrome of excited delirium can lead to violence, self-harm, and adverse cardiac events. One newer and notorious synthetic cathinone known as *flakka* was tied to 80 deaths in Florida from September 2014 to December 2015.[26]

In addition to their clinical features of intoxication, overdose, and withdrawal, the various subsets of psychostimulants can have several other potential neurologic complications. People who use cocaine are at increased risk of provoked seizure, even in the absence of fulminant overdose or other evidence of intoxication. Seizures attributed to cocaine use have been known to produce the phenomenon of *kindling*, in which the likelihood of recurrent seizures continues to increase over time despite taking nonescalating doses of the drug.[27] MDMA can induce features of serotonergic excess in addition to the classic stimulant toxidrome. This can manifest with seizures, hyperthermia, hyperkinesis (including exaggerated or sustained clonus on examination), and diarrhea. Bruxism and acute dystonic reactions have been described with MDMA abuse.[28] An acute toxic leukoencephalopathy has been anecdotally reported with MDMA use; MRI has been shown to reveal the white matter adjacent to the basal ganglia and midbrain to be preferentially affected.[29] As it is toxic to serotonergic nerve terminals, residual cognitive-behavioral disruption is a known sequela, especially in people who chronically use MDMA.[24] Hyponatremia (from the syndrome of inappropriate secretion of antidiuretic hormone [SIADH] and polydipsia) and hepatotoxicity are also common features with MDMA overdose (CASE 11-2).

Considering the unregulated, illicit production of many drugs of abuse, the impurities of the manufacturing process or reagents used in drug synthesis can sometimes have neurotoxic effects. One example in the psychostimulant category is the symmetric, irreversible, levodopa-unresponsive extrapyramidal syndrome from manganese toxicity that has been observed as a potential consequence of IV methcathinone abuse that is synthesized using the reagent potassium permanganate.[30] FIGURE 11-3 shows a representative brain MRI from a patient who developed parkinsonism after home-produced methcathinone abuse, with hyperintensity on T1-WEIGHTED imaging in the basal ganglia bilaterally.[31] Given the vasoactive nature of monoamines, it is no surprise that cerebrovascular events, including both ischemic and hemorrhagic stroke, have been observed time and time again in the setting of abuse of these psychostimulants. The use of cocaine, amphetamines, synthetic cathinones, and MDMA potentially contributes to induction of severe hypertension and cerebral vasoconstriction that can lead to intraparenchymal hemorrhage, ischemic stroke, and reversible cerebral

KEY POINTS

- Acute intoxication with most psychostimulants carries the risk of serious cardiovascular and cerebrovascular complications, as well as seizures.
- "Bath salts" are synthetic cathinone derivatives and are often marketed as "legal highs." They are not detected on standard drug-screening assays.
- Cerebrovascular complications of stimulant abuse, such as abuse of methamphetamine and cocaine, are well known to include hemorrhagic and ischemic stroke as well as reversible cerebral vasoconstriction syndrome.

vasoconstriction syndrome. The vasoconstriction and stroke syndrome may not occur immediately in the setting of acute intoxication but may be delayed by a few days, as has been observed with inhalation of synthetic cathinones.[32]

With regard to concerns about long-term cognitive and behavioral effects of chronic psychostimulant abuse, research studies have shown mixed results. Long-term methamphetamine use has been associated with impairment in learning, memory, and executive function in some studies. People who are addicted to methamphetamines can develop a persistent psychotic disorder that is more likely with longer duration of chronic use.[33] Conversely, a 2018 review of the literature did not show chronic cocaine abuse to be definitely associated with multidomain cognitive impairment.[34] Neurologic effects of chronic synthetic cathinone exposure have yet to be well delineated.[35]

MARIJUANA

Marijuana is developed from the cannabis plant. Tetrahydrocannabinol is the compound that is most responsible for producing the desired high. The marijuana high is commonly described as a carefree feeling, an altered sense of

CASE 11-2

A 22-year-old man was transported to the emergency department via ambulance after having a witnessed generalized seizure after coming out of the bathroom of a dance club. Friends reported that earlier that evening he had taken roughly 10 tablets of 3,4-methylenedioxymethamphetamine (MDMA) over the course of about 3 hours. In the hour leading up to the seizure, he was seen leaving the dance floor to drink multiple bottles of water and energy drinks, while sweating profusely. He informed his closest friends that he had a sudden urge to defecate and went to the bathroom. Upon exiting, he collapsed and experienced a 2-minute generalized tonic-clonic seizure.

On arrival at the emergency department, he was agitated and exhibited visual hallucinosis. His temperature was 40.2°C (104.4°F), heart rate 125 beats/min, and blood pressure 205/108 mm Hg. Neurologic examination was notable for significant agitation, perseverant speech, and responding to visual hallucinations but no compliance with examiner questions or commands. He also had diffuse hyperreflexia with sustained clonus at the knees and ankles bilaterally. Laboratory testing revealed severe hyponatremia, with a sodium level of 117 mmol/L and elevated liver enzymes with an aspartate aminotransferase (AST) level of 324 U/L and an alanine aminotransferase (ALT) level of 286 U/L.

COMMENT

This is a case of acute MDMA intoxication. Hallucinations and seizures can be seen in states of significant intoxication or overdose. This patient also showed signs of serotonergic excess (lower extremity clonus, diarrhea), which is more likely to occur with MDMA than with other psychostimulants. Management is essentially supportive and includes cooling the patient, administering benzodiazepines for seizures and agitation, and consideration of cyproheptadine given the serotonergic excess.

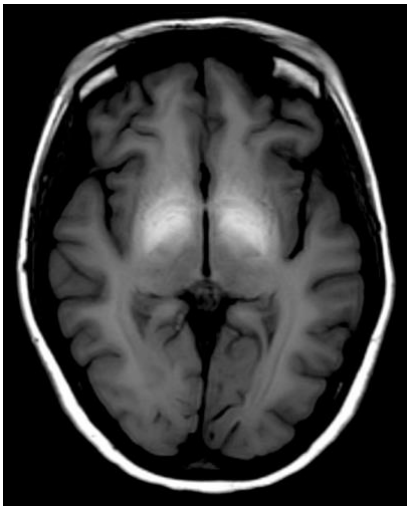

FIGURE 11-3
Brain MRI in a patient with parkinsonism due to manganese toxicity as a result of abuse of methcathinone synthesized using potassium permanganate. Axial noncontrast T1-weighted image shows hyperintensity of the globus pallidus bilaterally.
Reprinted with permission from Poniatowska R, et al, Pol J Radiol.[31] © 2014 Polish Journal of Radiology.

the passage and perception of time, depersonalization, jocularity, and increased appetite. However, the toxidrome has a spectrum of symptoms, with some people getting undesirable paranoia, dysphoria, or psychotic intrusions. Although significant physical withdrawal symptoms are uncommon, a psychiatric dependence forms with repeated use and can lead to strong cravings in the setting of new abstinence. Marijuana has traditionally been consumed by inhalation, but ingestion has become increasingly popular, especially as more and more parts of the world have legalized marijuana for recreational use. Several US states have also legalized the recreational use of marijuana, although it remains illegal under US federal law. So-called edibles are now a popular way to ingest the drug via tetrahydrocannabinol-infused foods such as candies, brownies, and cookies.

Additionally, a less predictable threat has emerged in the past 15 years in the form of synthetic marijuana or synthetic cannabinoids. These compounds are not marijuana but are actually synthetic cannabinoid receptor agonists. The endocannabinoid network is widely distributed in the central nervous system. Because of their increased potency compared to conventional cannabis, synthetic cannabinoids have greater potential for neurologic manifestations and complications from their toxicity. These synthetic compounds bind with more affinity to the cannabinoid receptors, producing a greater stimulant effect than marijuana.[36] Similar to synthetic cathinones and synthetic opioids, synthetic cannabinoids are designer drugs that are viewed as legal highs and are not detected on conventional hospital drug-screening assays. *K2* and *spice* are two of the more common street names for these agents, but the list is extensive and ever-growing. They are typically consumed by dissolving their solid form into solution and then spraying the solution onto plant or herbal materials of the person's choice for smoking.

The neuropsychiatric effects of synthetic cannabinoid use include anxiety, agitation, paranoia, delusions, and psychosis. Clinical signs may include tachycardia, diaphoresis, hypokalemia, and a notable risk of seizures.[37,38] Contaminants are another potential hazard with synthetic cannabinoids. Outbreaks of spontaneous coagulopathies have been linked with synthetic cannabinoid use (including intracranial hemorrhage) due to adulteration with the potent warfarinlike compound brodifacoum.[39]

Both marijuana and synthetic cannabinoids have been tied to stroke in the young. Marijuana use has been associated with stroke from multifocal intracranial vasoconstriction and is a risk factor for reversible cerebral vasoconstriction syndrome.[40,41] Synthetic cannabinoids have been reported to be

KEY POINTS

- Synthetic cannabinoids are more potent than conventional cannabis and can induce greater stimulantlike effects, including severe agitation and psychosis.
- Seizures are a known and concerning risk with the use of synthetic cannabinoids.

temporally associated with hemorrhagic and ischemic stroke with embolic-appearing infarcts.[42,43] Interestingly, a syndrome of recurrent vomiting and nausea has been well known to potentially occur with chronic cannabis use (both conventional and synthetic); it is characterized by the novel feature of the patient reporting getting exquisite relief with hot baths or sustained hot showers. This syndrome is known as cannabinoid hyperemesis syndrome.[44,45] The risk of cognitive impairment from chronic cannabis use is not well defined.

HALLUCINOGENS

Hallucinations are a potential manifestation of intoxication with many illicit substances. However, the class of drugs known as hallucinogens have the primary effect of yielding an altered sensory perception and frank hallucinations. For this reason, their effects are referred to as being "psychedelic." Specifically, the altered perception felt includes a heightened sensation of various modes of stimuli (eg, sound, smell, color). The common mechanism by which these agents produce the psychedelic toxidrome is agonist activity or potentiation of central serotonergic activity. TABLE 11-4 lists popular hallucinogenics. The most common route of consumption for these agents is oral. Somatic symptoms such as nausea, vomiting, and paresthesia can precede the psychedelic effects. People who use hallucinogens often refer to their high as a *trip*. *Bad trips* occur when the resulting perceptual alterations are unpleasant or induce paranoia and panic. Severe intoxications and overdose are managed supportively with calming and medications to reduce harmful agitation, if needed. A physical withdrawal syndrome is not a feature of hallucinogens.

LSD is a synthetic hallucinogen that is still abused today, but to a lesser degree than at the height of its popularity in the 1960s and 1970s. Many hallucinogens have the capability to cause flashbacks, but LSD is well known for this potential. As the name implies, a flashback occurs when the person using LSD experiences a completely unprovoked recrudescence of the symptoms or effects of intoxication, even long after the last use. This can occur days to months after last taking the drug. Although flashbacks tend to be experienced by people who chronically use LSD, they are possible after just one exposure. When those who have abused LSD or similar substances have recrudescence of the sensory disturbances that are persistent and distressing enough to cause impairment of their functionality, it is termed *hallucinogenic*

TABLE 11-4 Popularly Abused Hallucinogenic Agents

- Ibotenic acid/muscimol
- Kratom
- Lysergic acid diethylamide (LSD)
- Mescaline
- Psilocin
- Psilocybin
- *Salvia divinorum*

persisting perception disorder.[46] LSD is an ergot derivative, so it should be considered to have cardiovascular and stroke risk similar to other conventional ergot agents because of its vasoactive properties.

Many other hallucinogens are naturally found compounds. Psilocybin and psilocin are indolealkylamine compounds found in multiple mushroom species. These agents are consumed orally for a variable psychedelic experience. Mescaline is another agent in this class that occurs naturally in the peyote cactus or can be synthesized.

Some atypical agents in this category include *Salvia divinorum* and kratom. Salvia is a sage plant; its toxic properties come from the compound salvinorin A, which is a kappa opioid receptor agonist but, interestingly, produces a short-duration psychoactive high.[47] It is another drug that gets labeled as a legal high and is available by internet acquisition. It is often sold as seeds or leaves and is consumed by smoking or chewing. People who use *S. divinorum* can feel significantly altered sensory perception, including visual phenomena of elaborate geometric figures or body distortions.[48] Kratom (*Mitragyna speciosa*) is a tropical tree; its leaves can yield psychoactive effects because of the active chemicals mitragynine and 7-hydroxymitragynine. These compounds have opioidlike properties; thus kratom is one of the exceptions in this category in that it is known to produce withdrawal symptoms.[49] It is still legal is most of the United States and is often consumed as an adjunct to other illicit drugs, such as amphetamine or benzodiazepines.[48] It, too, is often sold as a bath salt and can often be purchased online. Kratom is consumed orally. It is often brewed into a tea, taken directly in powder form with a beverage to wash it down, or in capsules. It does appear on conventional drug-screening assays.

PHENCYCLIDINE

Often referred to as *PCP* or *angel dust*, phencyclidine is a dissociative agent that is chemically similar to ketamine. Its use has declined compared to prior decades such as the 1970s. Its potentially dramatic effects are due to strong *N*-methyl-D-aspartate (NMDA) receptor antagonism[50] and monoaminergic reuptake inhibition. This likely explains why people who are intoxicated with PCP can present with profound acute psychotic manifestations and significantly elevated blood pressures. Consciousness during severe acute intoxication can range from aggressively combative agitation to marked psychomotor retardation or even coma, given its anesthetic properties. Features such as hallucinations, delusions, or a catatonic state are so likely with phencyclidine intoxication that it should be considered in the differential of any acute schizophrenialike presentation. Seizures and myoclonus are other observable acute effects. At lower levels of intoxication, a mild euphoric feeling or widespread tactile sensory alterations may be the only effect.

Treatment for severe overdose includes benzodiazepines for seizures and agitation as well as cardiopulmonary support for severe hypertension, labile heart rate, and respiratory depression.[51] The patient should be assessed for possible rhabdomyolysis and treated accordingly. Phencyclidine is often assessable by conventional drug-screening assays. Strong physical withdrawal is not usually significant, but cravings can occur.

Those recovering from phencyclidine intoxication can experience an emergence reaction after cessation of exposure while drug elimination is still ongoing, manifesting with recurrence of psychosis, behavioral change, and mood

KEY POINTS

- Marijuana use is not totally benign. Increased risk for neurologic injury exists due to acute cerebral vascular disease; people who use marijuana chronically are at risk for cannabinoid hyperemesis syndrome.
- Hallucinogens cause psychedelic highs marked by distorted sensory perception.
- Hallucinogen overdose is managed supportively. Pharmacologic agitation control may be indicated.
- Withdrawal is a not a standard feature of even repeated psychedelic drug use.
- Lysergic acid diethylamide and other hallucinogens can cause flashbacks of their effects even long after the last usage. Long-term use has been associated with a chronic hallucinogenic persisting perception disorder.
- Phencyclidine is a dissociative drug that produces a syndrome similar to a marked schizophrenic episode.

disturbance. People who use phencyclidine regularly and in the long term can develop a persistent psychotic syndrome.[52]

INHALANTS

Many household or industrial agents contain volatile liquids, the fumes of which can be inhaled intentionally or unintentionally, creating an intoxicated state similar to that of conventional drunkenness from ethyl alcohol. Acute effects are usually short-lived, often on the order of a few hours. The typical chemical structure of inhalants is an aromatic, halogenated, or aliphatic hydrocarbon. The drunken euphoria can be followed by a letdown feeling of depression. More intense levels of exposure can precipitate seizures and hallucinations. A strong physical withdrawal syndrome is not recognized, but people who use inhalants can acquire strong cravings, leading to maladaptive behavior to obtain the drug. TABLE 11-5 lists commonly abused inhalants.[53]

Both central nervous system and peripheral nervous system complications are possible with agents in this category. Toluene is a widely used solvent that is one of the commonly implicated toxins in the abuse of "huffing" paint thinner or spray paint. Its chronic exposure is known to lead to a white matter dementia with leukoencephalopathy on MRI involving not only the cerebral white matter but also the brainstem. *n*-Hexane is another solvent widely used in many products. Glue sniffing is one known means of voluntary exposure. Repeated exposure has been known to lead to a potentially significant axonal sensorimotor peripheral neuropathy that can leave significant residual deficits or even progress after discontinuing exposure (called *coasting*).[54]

TABLE 11-5 Common Sources for Inhalant Abuse[a]

- Aerosols
- Anesthetics (eg, dental surgical supply, whipped cream dispensers or chargers)
- Cleaning fluids, spot removers
- Fire-extinguishing agents
- Furniture polish
- Glues, cements, rubber patching
- Lighter fluid
- Marker pens
- Mothballs (p-dichlorobenzene)
- Nail polish remover
- Natural gas
- Paints, enamels, paint thinners
- Petroleum (eg, gasoline, naphtha gas, benzene)
- Room deodorizers (eg, amyl nitrite, butyl nitrite, isobutyl nitrite)

[a] Modified with permission from Brust JC, Continuum (Minneap Minn).[53] © 2014 American Academy of Neurology.

Nitrous oxide is an inhalant used for sedation for procedures such as those performed by dentists. It is also found in canned aerosol food products such as whipped cream dispensers. Inhaling nitrous oxide from these pressurized canisters is often referred to as doing *whip-its*. Repeated exposure essentially creates a functional vitamin B_{12} deficiency due to the oxidation of cobalamin by nitrous oxide, leading to subacute combined degeneration of the spinal cord (CASE 11-3). In addition to stopping the inhalant abuse, patients with nitrous oxide–related myeloneuropathy should also receive vitamin B_{12} supplementation via injections.

ANTICHOLINERGICS

Anticholinergic toxicity manifests with encephalopathy, dilated pupils, tachycardia, dry mouth, constipation, anhidrosis, and urinary retention. Seizures, myoclonus, and coma are risks in severe cases. People using anticholinergics wish to gain a euphoric sedation. Sources of abuse in the population are diverse and include plant products such as *Datura stramonium* (jimsonweed, which contains atropine and scopolamine), but most relevant are conventional pharmaceuticals such as diphenhydramine, tricyclic antidepressants, and certain antiemetics.

One notable trend in anticholinergic abuse in the 21st century is that of promethazine as a common component of the concoction known as *sizzurp*, which is also known by many other names, including *lean* and *purple drank*. Although several variations exist, codeine cough syrup is the base, frequently combined with the prescription antiemetic promethazine. Sweet artificial flavorings and lemon-lime sodas are added to improve taste. Its prevalence is notable in young adults and likely is influenced by its use by professional athletes and notable recording artists.[55] The sedative effect of promethazine potentiates that of the codeine, making for a potentially deadly combination in cases of overdose because of respiratory drive depression. People who regularly use anticholinergics can experience cravings, but strong physical withdrawal is not common, other than irritability.

Physostigmine, a parasympathomimetic agent via its action as an acetylcholinesterase inhibitor, is an antidote for anticholinergic toxicity. It is used in IV form for treatment of acute anticholinergic toxicity because of its central nervous system penetrance.[56]

TOBACCO/E-CIGARETTES

Although negative neurologic sequelae from tobacco abuse are well known and rampant, predominantly stemming from the provocation of cerebrovascular disease, emerging trends are showing another potential effect of which neurologists should be aware. In April 2019, the US Food and Drug Administration (FDA) released a report about a possible link between use of e-cigarettes (known as *vaping*) and subsequent seizures, mostly in younger patients.[57] The liquid used in the vaping apparatus is also reported to cause seizures and cardiac death when consumed by direct ingestion.[58]

Vaping has also been found to be a newer route of administration for fentanyl analogues, as compounds such as furanyl fentanyl have been detected in the vaping liquids discovered at the scene of presumed overdose fatalities.[59] These neurotoxic effects are in addition to the outbreak of e-cigarette and vaping

KEY POINTS

- Inhalant agents of abuse are volatile hydrocarbons with short euphoric highs lasting a few hours.
- Toluene abuse can cause a chronic white matter dementia from toxic leukoencephalopathy.
- *n*-Hexane is associated with a potentially severe axonal sensorimotor peripheral neuropathy that can persist after discontinuation.
- Nitrous oxide abuse (often in the form of *whip-its*) can lead to a functional vitamin B_{12} deficiency.
- Anticholinergic toxicity manifests with encephalopathy, dilated pupils, tachycardia, dry mouth, constipation, anhidrosis, and urinary retention. Seizures, myoclonus, and coma are risks in severe cases.
- Recreational use of *purple drank* is a means of opioid and anticholinergic toxicity due to the combination of codeine-containing antitussive agents mixed with promethazine.
- IV physostigmine is used as a reversal agent for anticholinergic toxicity because of its central nervous system penetrance.
- A possible link exists between e-cigarette use (*vaping*) and risk of seizures.

CASE 11-3

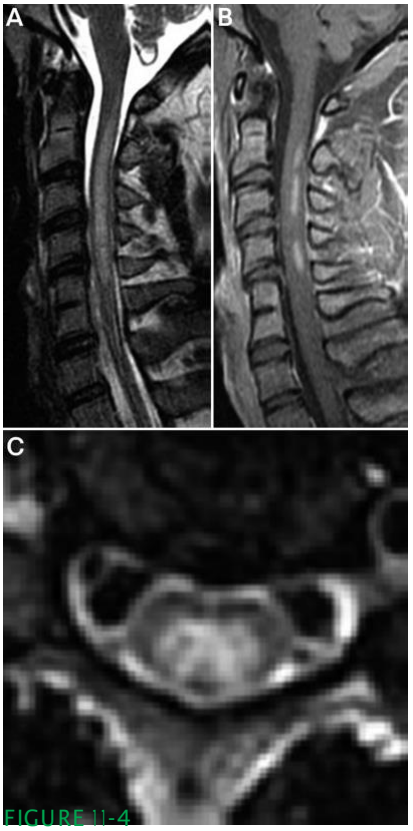

FIGURE 11-4

Imaging of the patient in CASE 11-3. *A*, Sagittal T2-weighted cervical spinal cord MRI showing a hyperintense longitudinally extensive cord lesion. *B*, Sagittal postcontrast T1-weighted MRI showing active, noncontiguous contrast enhancement in the posterior cord. *C*, Axial T2-weighted MRI shows the lesion in the posterior columns and, to a lesser extent, the lateral cord.

A 21-year-old man presented to neurology clinic with 6 months of gradually progressive foot paresthesia. He reported that he could no longer run. He also reported that his roommates had similar symptoms.

Neurologic examination revealed mild toe extensor weakness and decreased vibratory sensation and proprioception in the distal lower extremities greater than the upper extremities. Reflexes were slightly reduced in the upper extremities and absent in the lower extremities. He had a positive Romberg sign.

MRI of his brain and his CSF profile were normal. His cervical spine MRI showed a T2-hyperintense, longitudinally extensive cord lesion (FIGURE 11-4). Vitamin B_{12} level was normal at 354 ng/L, but homocysteine level was elevated at 42 µmol/L.

COMMENT

This is a case of myeloneuropathy resulting from functional vitamin B_{12} deficiency created by repeated exposure to nitrous oxide. The imaging and clinical syndrome are essentially identical to that of the prototypical subacute combined degeneration of the spinal cord. This patient later admitted to regularly inhaling *whip-its* with his roommates to get high. He improved in the ensuing weeks after both cessation of the abuse and supplementation with vitamin B_{12} via IM injections.

product–associated lung injury (EVALI) that led to over 2500 reported cases and garnered significant public attention in the latter half of 2019. Most victims were younger males who had used e-cigarette products containing tetrahydrocannabinol.[60]

ETHANOL

Ethanol is a legal drug that has been consumed by billions of people around the world. Its acute intoxication syndrome is well known to medical professionals but also easily recognized by the general public. Jocularity, ataxic dysarthria, limb ataxia, gait ataxia, disinhibition, and sleepiness are common symptoms and signs of mild to moderate intoxication. Severe intoxication can cause coma and potentially fatal respiratory depression. People who sporadically use ethanol may experience residual effects of intoxication, such as a hangover. In people who chronically abuse alcohol, the withdrawal state is called *delirium tremens* and is marked by agitated delirium, tachycardia, hyperthermia, hallucinations, and generalized seizures. The syndrome often begins 48 to 72 hours after the last consumption. Judicious use of benzodiazepines is the staple of treatment in severe cases to supplant the GABA-ergic effects of ethanol with a controlled taper. Alcoholic hallucinosis is not the same condition as delirium tremens. The former refers to hallucinations that begin 12 to 24 hours after cessation and resolve by day 2.[61]

Chronic abuse of alcohol is toxic to the nervous system in many ways, including cerebellar toxicity, peripheral neuropathy (small fiber predominant), and chronic cognitive impairment that may not resolve after cessation. Hepatic encephalopathy is a cardinal feature of alcoholic cirrhosis. People who chronically abuse alcohol are at risk for developing nutritional deficiencies that lead to neurologic injury (thiamine, vitamin B_{12}, and vitamin B_6 deficiencies). Wernicke encephalopathy is a well-known acute or subacute presentation of thiamine deficiency in people who chronically abuse alcohol. Common manifestations are ataxia, eye movement abnormalities (such as vertical nystagmus or ophthalmoparesis), and encephalopathy. All three components of this triad are rarely observed simultaneously, so diagnostic suspicion needs to be high in confused patients who are at risk. If not treated with aggressive thiamine repletion, a high proportion of patients with Wernicke encephalopathy will go on to develop the chronic amnestic cognitive disorder known as

Common Recreational Drugs Not Detected on Conventional Toxicology Screens

TABLE 11-6

Inhalants (eg, nitrous oxide, spray paint)
Kratom
Psilocybin mushroom
Salvia divinorum
Synthetic cannabinoids (*K2, spice*)
Synthetic cathinones (*bath salts*)
Synthetic opioids[a]

[a] Many hospital laboratories offer "targeted opioid screens" that can detect fentanyl.

KEY POINTS

- Chronic abuse of alcohol is toxic to the nervous system in many ways, including cerebellar toxicity, peripheral neuropathy (small fiber predominant), and chronic cognitive impairment that may not resolve after cessation.
- People who chronically abuse alcohol are at risk for developing nutritional deficiencies that lead to neurologic injury (thiamine, vitamin B_{12}, and vitamin B_6 deficiency).

Korsakoff syndrome, in which patients often display confabulation during the encounter.[62] Marchiafava-Bignami disease is an idiopathic sequela of malnutrition in chronic alcohol use disorder characterized by selective necrotic lesions of the corpus callosum and adjacent white matter. Presenting symptoms are often stupor, ataxia, and upper motor neuron signs. Thiamine deficiency is a known mimic and has the same risk factors, so it is recommended that patients with features of Marchiafava-Bignami disease receive aggressive thiamine repletion.[63] Disulfiram is an agent prescribed for alcohol addiction that is associated with a peripheral neuropathy.[64]

CONCLUSION

The landscape of illicit drugs of abuse around the world is ever-changing. The prevalence of the abuse of one agent compared to another is in constant flux. Because of the wide array of profound potential effects on the nervous system these agents can have, diligent awareness is required to make the diagnosis. The category "toxic" should be included in any differential diagnosis in which it is remotely reasonable. Unfortunately, the increasing use of designer drugs that evade detection on conventional testing makes the diagnostic challenge even more difficult. TABLE 11-6 reviews commonly used recreational drugs that are not found on standard toxicology laboratory studies. Finally, with regard to imaging, any bilateral, symmetric abnormality on MRI should also prompt the practitioner to consider a toxic (or metabolic) process.

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