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Neurotoxicology Syndromes associated with Drugs of Abuse

Jonah P. Zuflacht, MD*,

Beth Israel Deaconess Medical Center, Boston Children's Hospital, Harvard Medical School, Boston, MA

Rachel A. Caplan, MD*,

Massachusetts General Hospital, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Jed A. Barash, MD, MHS,

Soldiers' Home, Chelsea, MA

Corey R. Fehnel, MD, MPH**

Beth Israel Deaconess Medical Center, Hinda and Arthur Marcus Institute for Aging Research, Harvard Medical School, Boston, MA

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Opioids

Epidemiology and Pharmacology

Oxycodone, fentanyl, and other related agents belong to a class of synthetic and semi-synthetic prescription analgesics that have been at the center of an epidemic of misuse in the United States (U.S.) since the early 2000's. This public health crisis has been further complicated by rising rates of abuse of illegal opioids, including both heroin and illicitly manufactured fentanyl. In 2017, over 47,000 Americans died as a result of an overdose on prescription and illicit opioids, or about 130 people per day. That year, approximately 1.7 million U.S. residents lived with a diagnosis of a substance use disorder associated with prescription opioids.²

** Indicates corresponding author. Corey R. Fehnel: 330 Brookline Avenue, Boston, MA 02215, cfehnel@bidmc.harvard.edu.

* Indicates co-first author

Mailing Addresses:

Jonah P. Zuflacht: 330 Brookline Avenue, Boston, MA 02215

Rachel A. Caplan: 25 Shattuck Street, Boston, MA 02115

Jed A. Barash: 91 Crest Avenue, Chelsea, MA 02150

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Opioids promote analgesia primarily at mu opioid receptors with full agonist effects, although buprenorphine, a medication prescribed for opioid abuse, has partial agonist properties.³ Mu receptors are distributed throughout the central and peripheral nervous system. Shorter- and longer-acting opioid preparations, including morphine (duration of effect, 3-6 hours) and transdermal fentanyl (duration of effect, 72 hours), are available.⁴

Acute and Chronic Complications

Opioid intoxication may have a varied presentation. From a neurologic perspective, opioids can cause euphoria, agitation, drowsiness, delirium, and miotic (“pinpoint”) pupils.^{5,6} In recent years, a sudden-onset amnestic syndrome in association with bilateral hippocampal damage on magnetic resonance imaging has been reported in patients with a history of opioid abuse.^{7,8} Other acute signs and symptoms from heroin use may include nausea, vomiting, constipation, xerostomia, pruritis, diaphoresis, and urinary retention.⁹ Overdose may lead to respiratory depression and stupor. Treatment of overdose includes use of the opioid antagonist, naloxone, which can be administered repeatedly as needed by intranasal, parenteral, and pulmonary routes. For respiratory depression, ventilatory support is necessary and orotracheal intubation may also provide protection against a major complication of opioid overdose, aspiration.¹⁰

Signs and symptoms of opioid withdrawal are often described as flu-like and may include myalgias and rhinorrhea; however, together with other features such as drug craving, pupillary dilation, diarrhea, and yawning, the picture may be more suggestive.¹¹ For heroin, withdrawal symptoms typically peak between 1-3 days, but may last a week or longer. While the syndrome is unpleasant, it is rarely fatal.⁹ Treatment of withdrawal typically involves the administration of methadone or buprenorphine with tapering of dosing guided by stabilization of the patient’s condition. Clonidine has also been used effectively as another option for autonomically-mediated symptoms of withdrawal.¹²

Opioid abuse use is associated with longer-term complications. For example, infections with potentially enduring implications, including epidural abscess, have represented a growing complication of the opioid epidemic.¹³ There is also evidence to suggest that opioid-dependent patients experience memory dysfunction across multiple domains in comparison to healthy counterparts.¹⁴ Whether chronic opioid-associated memory deficits lie on a spectrum with the aforementioned acute opioid-associated amnestic syndrome is unknown and will require further study for clarification.

Alcohol (Ethanol)

Epidemiology and Pharmacology

In 2015, over 15 million American adults aged 18 and older lived with an alcohol use disorder. Nearly 2/3 of these adults were men.¹⁵ Moreover, excessive alcohol use — defined by underage, pregnant, binge, or heavy drinking — accounts for 88,000 deaths in the U.S. annually. Approximately 10% of deaths in working age adults are attributable to excessive alcohol consumption; in those who die, lifespan is shortened by an average of 30 years.¹⁶

Alcohol is primarily metabolized in the liver, where it is converted by alcohol dehydrogenase to acetaldehyde. With acute exposure, ethanol exerts inhibitory or enhancing effects at a variety of receptors in the brain, including NMDA and GABAergic systems.¹⁷ Factors that can influence the extent of acute intoxication include the volume and percentage of alcohol ingested, the interval over which it was ingested, and the size and tolerance of the person ingesting it.¹⁸

Acute and Chronic Complications

Alcohol generally has a depressant effect on the central nervous system, but presentation with intoxication is varied. At lower blood alcohol levels, ethanol is associated with changes in personality, impairments in judgment, and inattention. At moderate levels, dysarthria, ataxia, and nystagmus may become apparent. Finally, at higher levels, stupor, coma, or even death due to respiratory depression may occur. As such, use of other drugs, including those with sedative effects, should be considered with caution.⁹ Appropriate ventilatory support, including intubation, may be initiated in cases of respiratory depression.¹⁹ To prevent potential complications associated with alcohol abuse, including hypotension, hypoglycemia, electrolyte disturbances, and Wernicke-Korsakoff syndrome (see below), patients are often treated with intravenous fluids that include dextrose, thiamine, and multivitamins.^{9,18,19}

Patients in early withdrawal from excessive alcohol use (beginning 6 hours after stoppage or reduced intake) can present with a variety of signs and symptoms, including tremulousness and autonomic disturbances, both of which may last for 48 hours. Seizures may emerge during this window as well. Hallucinations reflect moderate withdrawal and can last 6 days. In contrast, delirium tremens — an encephalopathic state of late withdrawal that typically involves psychomotor agitation — may begin 2 days after cessation of chronic alcohol abuse and may persist for 2 weeks past the time of the last drink.²⁰ Before initiating treatment for withdrawal, it is critical to consider potential mimics or co-morbid diagnoses, including meningitis and traumatic brain injury.²¹ Symptom-driven treatment with benzodiazepines, as determined by a validated instrument [such as the Clinical Institute for Withdrawal Assessment (CIWA) Scale], is often the preferred strategy for withdrawal management.²²

Ethanol abuse may be associated with acute or, more commonly, chronic myopathy.²³ Peripheral nerve damage in the form of a mixed sensorimotor polyneuropathy is another neuromuscular complication; patients typically report sensory changes and later, weakness, beginning in the distal lower extremities.²⁴ Whether alcohol-related neuropathy and dementia result from direct ethanol neurotoxicity or indirect effects mediated by other factors, such as nutritional deficiency, has been a source of debate.^{25,26} A known complication of thiamine deficiency classically observed in patients with chronic alcoholism, Wernicke-Korsakoff syndrome, is characterized by ataxia, ophthalmoplegia, and a confusional state involving amnesia and confabulation.²⁷ Heavy alcohol use is also associated with an increased risk of ischemic and hemorrhagic stroke.²⁸ Lastly, Marchiafava-Bignami disease, a rare degenerative disorder of the corpus callosum, is a striking complication of chronic alcohol abuse with a poor outcome, often involving rapidly impaired consciousness and resulting in death within months of onset.²⁹

Marijuana

Epidemiology and Pharmacology

While alcohol and tobacco account for the greatest burden of disease, trends towards legalization of marijuana are expected to increase its use, and drive a greater burden of marijuana-related disorders. Tetrahydrocannabinol (THC), will be the focus of this discussion as the compound offers the euphoric effects associated with recreational use. Conversely, cannabidiol has few psychotropic effects, and has been associated with therapeutic properties of reduction in nausea, CB1 and CB2 receptor modulated pain reduction, and potential anti-inflammatory effects. The Food and Drug Administration (FDA) recently approved cannabidiol for treatment of the Dravet epilepsy syndrome.³⁰

Rates of marijuana use have steadily risen among select segments of the U.S. population. The implications of these trends for the neurological practitioner are two-fold: 1) a likely increase marijuana-use related neurological disorders; and 2) a window of opportunity for improving the scientific understanding of both potential benefits and harms of marijuana use.

Evidence suggests a clear trend of increasing THC potency.³¹ States with legalized recreational marijuana have experienced a rise in emergency department visits.³² While the effects of acute intoxication are generally transient, a proportion of individuals with known or unknown pre-disposition to psychiatric disorders may experience a *forme fruste* of psychosis associated with marijuana use. The neurological and other health effects of habitual use of marijuana remains understudied. This remains particularly true for long-term health consequences, which are based on the older generation of less potent THC products.³³

The wide distribution of cannabinoid receptors (CB1 throughout the central and peripheral nervous system) account for the myriad neurological effects of the drug. Delta-9-THC is the main psychotropic compound derived from cannabis plants, which have endogenously produced analogues in anandamide and noladin, among others.³⁴ When smoked, effects occur within 10-20 minutes, with a rapid decline in serum concentration within 1 hour owing to rapid distribution to other tissues, accounting for the excretion of THC components detectable in toxicology screening for prolonged periods of time (59-hours in non-habitual users).³⁵ Heavy users have detectable THC metabolites in urine for up to 2 months.³⁶

Acute and Chronic Complications

Acute marijuana intoxication has the detrimental effects of impaired short-term memory, incoordination, and impaired judgement. Other effects include initial anxiety, followed by euphoria, disinhibition, and depersonalization with subjective perception of the slowing of time. Higher doses induce paranoia and psychosis. Systemic effects include scleral injection, tachycardia, hypertension, urinary retention and decreased intraocular pressure.

Resting electroencephalogram recordings during intoxication may reveal slower alpha range frequencies while subtle changes in event related potentials (ERPs) are seen with higher order cognitive tasks.³⁷ Positron emission tomography (PET) recordings reveal increased

cerebral blood flow to the temporal lobes, including insular regions, parietal and occipital cortex and the cerebellum.³⁸

The mainstay of managing acute THC intoxication is time and reassurance. Severe symptoms are managed with benzodiazepines counteracting CB1-mediated blockade of GABA receptors. While naloxone appears to block some effects of THC in animals, this has not carried over to humans.

Habitual users of marijuana are observed to experience emotional lability, anxiety, insomnia, hyperreflexia, diaphoresis, and salivation. The symptoms are not experienced by all, and tend to resolve over 36 hours, while psychological need/dependence (craving) can persist much longer. Cardiovascular and neurovascular effects have drawn considerable attention in recent years, with reports of associated paroxysmal atrial fibrillation and transcranial Doppler evidence of increased cerebrovascular resistance.³⁹

There is high quality evidence suggesting that marijuana is addictive. Addiction is more strongly associated with use beginning in adolescence, where it has also been associated with abnormal brain development. Neurological complications appear to be dose dependent. Marijuana is associated with diminished lifetime achievement, motor vehicle accidents, and chronic bronchitis. Among adolescents it has been associated with abnormal neural development and impairments of executive function, memory and processing speed.¹ Cannabinoids readily cross the placenta and are associated with low birth weight and executive dysfunction. Lesser quality evidence supports its association with schizophrenia, and depression or anxiety disorders.⁴⁰

Cocaine, Methamphetamine and other Psychostimulants

Epidemiology and Pharmacology

While cocaine emerged as an anesthetic in the late 1800s and, soon after, as a drug of abuse, the coca plant from which it is derived has been used by indigenous populations in South America for thousands of years.⁴¹ The leaves of the coca plant have long been chewed by the Aymara people for social and medicinal purposes, including mitigation of altitude sickness in the Andes mountains. Cocaine has been isolated from mummified human remains in Northern Chile dating back 3000 years.⁴² Cocaine, an alkaloid, was first isolated from the coca plant in around 1860, but did not generate much attention until Sigmund Freud praised it as a cure for mental illness in “Uber Coca” in 1884; that same year Karl Koller described it as an excellent local anesthetic.⁴³ Soon, it was being used widely in medicine, including for treatment of opium addiction; abuse became common, especially among medical professionals like the pioneering surgeon and famous addict William Halsted.

Abuse of cocaine and other psychostimulants has remained prevalent and has even increased in the past several years. Cocaine and psychostimulants account for a high percentage of drug deaths and emergency room (ER) visits. In 2011, cocaine related illness accounted for around 40% of 1.3 million drug-related ER visits reported in the 2011 Drug Abuse Warning Network (DAWN) report.⁴⁴ Out of over 70,000 deaths from drug overdose in the United

States in 2017, nearly 14,000 involved cocaine.⁴⁵ Additionally, the opioid epidemic and the appearance of fentanyl-laced cocaine has driven a recent increase in the number of cocaine-related deaths; while non-opioid related cocaine deaths fell from 1.59 to 0.78 per 100,000 from 2006 to 2015, the rate of death from cocaine-related overdose involving heroin or synthetic opioids such as fentanyl has gone from 0.24 to 1.11 per 100,000 from 2010 to 2015.⁴⁶

Cocaine and other psychostimulants, which include amphetamine, methamphetamine, MDMA, cathinones, khat and others, are peripheral sympathomimetics that inhibit catecholamine reuptake at nerve endings, raising the blood pressure, heart rate, and body temperature, sometimes to a life-threatening degree.⁴⁷ They also work in the brain, increasing the availability of norepinephrine, dopamine, and serotonin at the level of the synapse.⁹ As a result, users experience a “rush,” accompanied by euphoria, alertness, and increased confidence; agitation and hyperactivity also result. Psychostimulants, therefore, have a wide variety of effects on the nervous system.

Acute and Chronic Complications

Changes in behavior are one of the most well-known side effects of cocaine and stimulant abuse. Cocaine can cause paranoia, psychosis, and hallucinations. Discerning between acute intoxication and schizophrenia can be made more challenging by the large portion of people with mental illness who have comorbid substance abuse. Attempts to distinguish the two presentations have found that cocaine users have more unformed visual hallucinations (such as shadows and lights) while those with schizophrenia have more complex and bizarre delusions. Substance abusers are also more likely to have tactile hallucinations and complain of bugs crawling on the skin.⁴⁸ Cocaine use increases the frequency of hallucinations in people with schizophrenia.

Synthetic cathinones, the class of stimulants known as “bath salts” have become feared for producing psychosis as well as violent, even homicidal behavior; intoxicated patients frequently need to be physically restrained.⁴⁹ Whether chronic cocaine users suffer from cognitive impairment even after sustained abstinence is not certain; some studies do show long-term memory and attention deficits while others indicate that these may become less severe after months of sobriety.⁵⁰

Psychostimulant use, which can cause acute blood pressure elevation, vasospasm and a prothrombotic state, raises the risk of acute ischemic and hemorrhagic stroke. A case-control study in over 2000 young adults, age 15-49, found a 5.7-fold risk of ischemic stroke found in those who used cocaine in the preceding 24 hours.⁵¹ Recent cocaine use has been associated with an increased risk of aneurysmal subarachnoid hemorrhage as well as higher rates of aneurysm re-rupture, delayed cerebral ischemia, and in-hospital mortality.⁵² Methamphetamine is an increasingly recognized risk factor for intracerebral hemorrhage in the young, both with and without aneurysm or arteriovenous malformation rupture.⁵³ Chronic cocaine abuse is known to lead to accelerated atherosclerosis through repeated endothelial damage, raising stroke risk.⁵⁴ Beyond stroke, cocaine has been implicated in a number of cases of leukoencephalopathy, both in patients who had supposed toxic white matter damage resembling heroin-induced leukoencephalopathy, as well as in patients with

likely demyelinating lesions thought to be an immune response to levamisole, a frequent cocaine adulterant.⁵⁵

Seizure is another common manifestation of acute psychostimulant intoxication. Out of a group of 47 patients who presented to San Francisco General Hospital for seizure after recreational drug use, 32 had used cocaine and 11, amphetamine.⁵⁶ Nearly 10 percent of 474 patients presenting to a hospital in Minneapolis with cocaine intoxication experienced seizures, usually of generalized tonic-clonic semiology.⁵⁷ Status epilepticus has been seen; partial status may mimic psychosis from intoxication.

Acute rhabdomyolysis is known to result from cocaine abuse, as documented in a study of 39 patients presenting to the University of Miami Medical Center with an average CK above 12,000; six of these patients died due to complications including renal and liver failure as well as disseminated intravascular coagulation.⁵⁸ In the acute setting, users of stimulants are subject to developing a variety of movement disorders, including tremor, dyskinesias and choreiform movements (in cocaine users, this is known as “crack dancing”).⁵⁹ Chronic users of amphetamine and methamphetamine often exhibit “punding,” purposeless, stereotyped and repetitive motor behaviors such as compulsively sorting household objects.⁶⁰

Acute management of stimulant intoxication involves treating tachycardia, hypertension, hyperthermia, and behavioral changes that result from sympathetic overactivation in the central nervous system. Benzodiazepines are a mainstay of therapy and address increases in heart rate and blood pressure as well as cocaine-associated chest pain and agitation.⁶¹ Blood pressure should be lowered with antihypertensive medications. While beta blockers are to be avoided in the setting of acute cocaine use due to a theoretical risk of coronary vasospasm from unopposed alpha-adrenergic activity, firm evidence on this risk is unclear,⁶² and non-beta blocking vasodilators like nitroglycerin or nitroprusside are preferred. Withdrawal from stimulants, which is characterized by anhedonia, lethargy, restlessness, cravings, and irritability, can be alleviated by beta blockers such as propranolol; GABA-ergic drugs are also being explored as a treatment for cocaine dependence.⁶³

Hallucinogens

Epidemiology and Pharmacology

Hallucinogens are “mind altering” drugs that, in botanical forms, have been used by humans for millennia.^{64,65} From Aristotle to the Aztecs, psychoactive plants - such as ayahuasca, psilocybe, and Peyote - have had sacred roles in shamanistic practices and religious ceremonies.^{9,66–69} Synthetic versions with similarly mystical properties, namely d-lysergic acid diethylamide (LSD), were first developed in the early 1940s by the Swiss pharmacologist Albert Hofmann.⁷⁰ Long banned by the federal government, LSD and other “classic” (i.e. serotonergic) hallucinogens are now re-emerging as both potent psychotherapeutic agents as well as novel research compounds.⁷¹

In 2010, more than 30 million people in the United States reported LSD, psilocybin, mescaline, or peyote ingestion at some point in their life.⁷² According to the UN World Drug Report (2017), 16% of all new psychoactive drugs - defined as uncontrolled substances

that have recently become available - fall under the category of classic hallucinogens.⁷³ LSD, by far the most potent, is also the most popular, with more than 10% of US adults in the most recent National Survey on Drug Use and Health endorsing lifetime use.^{74,75}

Classic hallucinogens - with either a phenylalkylamine group like amphetamine or an indolealkylamine ring like serotonin - act primarily by binding 5-HT₂ serotonin receptors.^{9,76} Though activation of the 5-HT_{2A} receptor, in particular, is necessary for the psychedelic effects, other serotonin, dopamine, and adrenergic receptors are also involved.^{9,77,78} LSD reaches peak plasma concentrations within 1 - 2 hours of oral ingestion and has an elimination half-life of roughly 3 hours.⁷⁹ The pharmacodynamics are similar for psilocybin, *N,N*-dimethyltryptamine (DMT - the active psychoactive compound in ayahuasca), and mescaline (the active psychoactive compound in Peyote); all of which produce peak physiologic effects within 1 to 4 hours.⁸⁰⁻⁸³

Acute and Chronic Complications

Within minutes of ingestion, users may develop signs of autonomic hyperactivity such as fever, tachycardia, mydriasis, and hypertension.^{9,81} Serotonin syndrome, characterized by the triad of dysautonomia, altered mental status, and neuromuscular abnormalities (especially hyperreflexia) is possible in more severe cases.⁸⁴ The intended psychedelic effects typically begin later, though last longer, on the order of 6 to 12 hours.⁹ They include perceptual distortions such as depersonalization, derealization, and hallucinations^{85,86} as well as subjective experiences involving the transcendence of time and space, dissolution of the ego, and encounters with God.⁸⁷⁻⁸⁹ The neuroanatomical basis of these bizarre effects is thought to result from opening of the so-called “thalamic filter” - allowing otherwise isolated brain regions to interact with one another.⁹⁰ Recent neuroimaging studies support this idea; LSD has been shown to increase blood flow to the visual cortex⁸⁷ and increase effective connectivity between the thalamus and posterior cingulate cortex.⁹¹

Management of acute hallucinogen intoxication is largely supportive since the somatic and neuropsychiatric effects are both self-limited and usually mild.⁹² Verbal reassurance and a calm environment are often sufficient. Cardiac monitoring is useful in patients with autonomic instability. In more severe cases, such as those with persistent agitation, antipsychotics and benzodiazepines may be used.⁹³ Similar strategies have been used in the management of patients who have ingested new, synthetic hallucinogens such as 25C-NBOMe (also known as “Boom” or “Pandora”).⁹⁴ Schizophrenia and other psychotic disorders can mimic acute hallucinogen intoxication.

Data on the long-term effects of hallucinogen use are limited. “Flashbacks,” characterized by the spontaneous occurrence of hallucinogen-like symptoms, have been reported in anywhere from 15% to 77% of users.⁹ Prolonged, recurrent symptoms reminiscent of acute hallucinogen intoxication, known as the hallucinogen-persisting perception disorder (HPPD), are less common.⁹⁵ Though there are numerous case reports to the contrary, the long-term use of hallucinogenic drugs does not - in general - appear to be associated with lasting neuropsychological⁹⁶ or mental health⁹⁷ problems. Ayahuasca users, compared to control groups, perform similarly or better on most measures of psychiatric morbidity, wellbeing, and cognitive function.⁹⁸

Other Drugs of Abuse

Anesthetics, inhalants, and other drugs have also been associated with a variety of effects of the nervous system. MDMA, or ecstasy, used by around 1% of the US population in 2018,⁹⁹ is a synthetic drug structurally similar to amphetamine that also promotes hallucinations and feelings of intimacy with others. Like stimulants, it is a sympathomimetic, causing increases in body temperature and heart rate, and it can produce agitation, tremors, and seizure; abusers at prolonged “raves” can be subject to rhabdomyolysis.⁹

Phencyclidine (PCP, also called “angel dust”) is a dissociative anesthetic with NMDA blocking activity that was used widely in the 1970s but has since become less popular. Users experience euphoria and sensory distortion as well as agitation and psychosis, depending on the amount of drug used; a muted feeling of pain and body awareness heightens the risk of serious injury.¹⁰⁰ Physical examination may show nystagmus, miosis, or ataxia; at higher doses myoclonus, posturing, rhabdomyolysis, and vital sign instability may be seen.⁹

Ketamine, which became popular in 1980s rave culture, is another NMDA antagonizing dissociative anesthetic that has similar effects to PCP, but is less toxic and shorter acting. The drug promotes feelings of expanded awareness and changes in perception that are seen in other psychedelics, and while death from overdose itself is very rare, users have suffered serious injury from accidents while intoxicated due to derealization and decreased pain perception.¹⁰¹

Nitrous oxide is an inhalant anesthetic that has become increasingly popular in the 2010s as a drug of abuse at clubs and music festivals, where it is inhaled from balloons. Infrequent use for a dissociative high has few side effects, but habitual users can develop myelopathy or even an acute demyelinating neuropathy as a result of functional B12 inactivation.¹⁰²

Other inhaled drugs of abuse include household products such as solvents, gasoline, and glues, which due to their accessibility are often used by school aged children and young teenagers; 58 percent of users in one survey had their first experience before starting high school. Acutely, inhalants are depressants and cause symptoms such as lethargy and ataxia, as well as systemic effects such as chemical airway burns and cardiac arrhythmias that can be fatal. Chronic users are subject to problems with cognition and coordination.¹⁰³

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Key Points

- The broad spectrum of signs and symptoms associated with opioid intoxication requires early recognition to provide proper treatment for patients presenting with this syndrome.
- Alcohol withdrawal can begin two days after cessation of chronic ethanol abuse and may lead to critical or even fatal illness.
- Habitual marijuana use is increasing, and is associated with diminished lifetime achievement and motor vehicle accidents. Among adolescents, it has been associated with abnormal neural development and impairments of executive function, memory and processing speed.¹ Cannabinoids cross the placenta and are associated with low birth weight and executive dysfunction.
- Cocaine and other psychostimulants, which include amphetamine, methamphetamine, MDMA, cathinones, and khat, are peripheral sympathomimetics that inhibit catecholamine reuptake at nerve endings, leading to dramatic elevations in heart rate, blood pressure, and body temperature. CNS effects are mediated through elevations in norepinephrine, dopamine, and serotonin leading to euphoria and increased alertness.
- Classic hallucinogens are serotonin agonists that result in both somatic and neuropsychiatric effects. In the acute setting, monitoring for autonomic instability may be warranted though the management is largely supportive. Anesthetics, inhalants, and other drugs of abuse can lead to non-specific neurological syndromes such as sympathetic hyperactivity, psychomotor agitation, and impaired awareness as well as more distinct complications such as decreased pain perception (PCP, ketamine) and myelopathy (nitrous oxide).

Synopsis

Substance use disorders – and their associated neurological complications – are frequently encountered by neurologists as well as emergency room physicians, internists, psychiatrists, and medical intensivists. Prominent neurological sequelae of drug abuse, such as seizure and stroke, are common, and often result in patients receiving medical attention. However, less overt neurologic manifestations, such as dysautonomia and perceptual disturbances, may be initially misattributed to primary medical or psychiatric illness, respectively. This chapter focuses on the epidemiology, pharmacology, and complications associated with commonly-used recreational drugs including opioids, alcohol, marijuana, cocaine, and hallucinogens. PCP, ketamine, and nitrous oxide are also briefly discussed. The neurological aspects of acute intoxication as well as associated withdrawal syndromes are reviewed alongside management strategies.

Clinics Care Points

- Diagnosing the opioid-associated amnesic syndrome requires timely toxicological screening and brain imaging; the window of detection for fentanyl and other opioids may last for several days, while that for the detection of characteristic hippocampal damage on MRI may last for approximately one week.
- Naltrexone is indicated for both opioid addiction and alcohol dependence.
- Tetrahydracannabinol (THC) has psychological effects that are sought with recreational use. Cannabidiol (CBD) has few psychological effects, and has been associated with reductions in nausea, pain, and as a potential anti-inflammatory.
- Cocaine and other psychostimulants account for roughly 40% of drug-related ER visits.
- Neurovascular complications of cocaine intoxication include ischemic stroke, aneurysmal subarachnoid hemorrhage, and intracerebral hemorrhage. Chronic cocaine use leads to accelerated atherosclerosis through repeated endothelial damage, chronically raising stroke risk.
- Acute management of cocaine and other psychostimulant intoxication involves treating tachycardia, hypertension, hyperthermia, and behavioral changes that result from sympathetic hyperactivity. Antihypertensive agents and benzodiazepines are both mainstays of therapy.
- Hallucinogens, in both organic and synthetic formulations, act primarily by binding 5-HT₂ serotonin receptors, but also act on other serotonin, dopamine, and adrenergic receptors.
- Antipsychotics and benzodiazepines can be used in the acute setting to help address autonomic instability and mitigate neuropsychiatric symptoms associated with classic hallucinogens.