In the name of god

Drugs of Abuse and the Nervous System

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- This article discusses the neurologic complications of traditional, nontraditional, and emerging drugs of abuse.
- 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.

- 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 article provides a broad survey of the wide array of illicit drugs that have proven to be associated with neurologic injury and dysfunction.

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

- 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

- 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.

Commonly Abused Opioids

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

- Agonists
- Mixed Agonist/Antagonist

- 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.
- 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 cerebellum .

- More acute fatal leukoencephalopathies have also been the result of opioid overdose, including with prescription forms .
- Also, in addition to a leukoencephalopathy, opioid overdose has been observed to yield an acute cerebellar edema causing herniation and hydrocephalus.

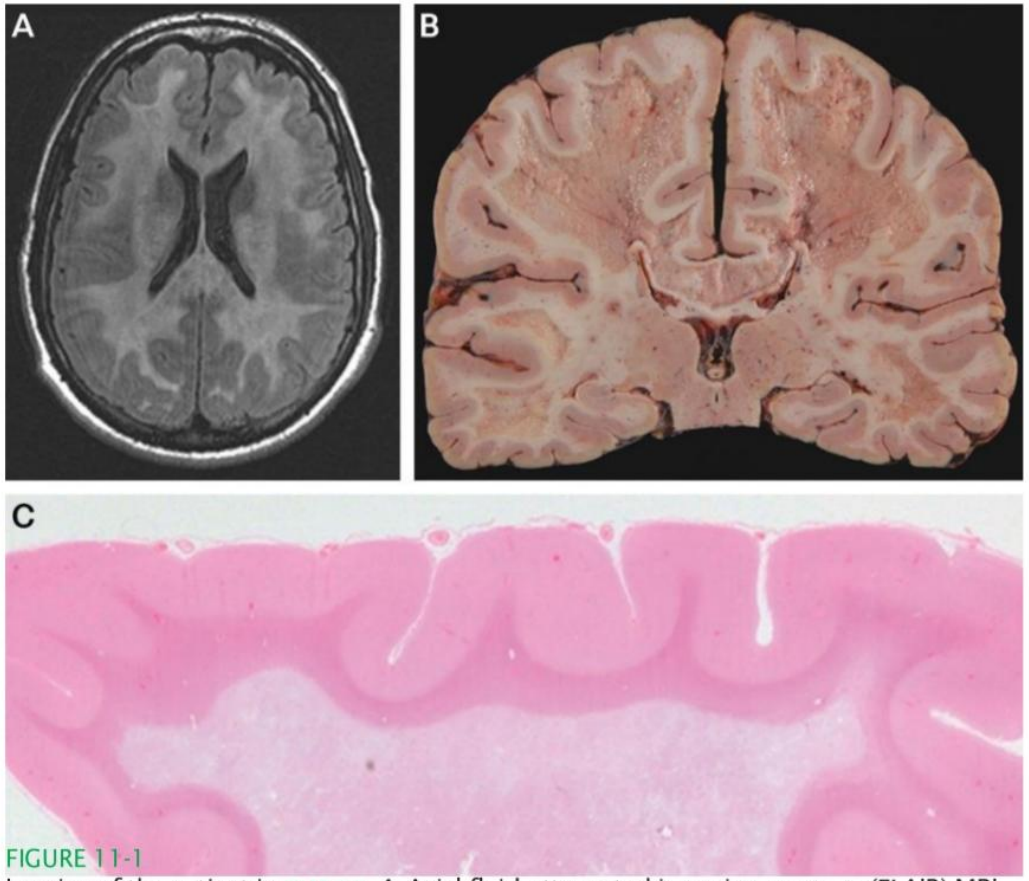

FIGURE 11-1
Imaging of the patient in CASE 11-1. *A*, Axial fluid-attenuated inversion recovery (FLAIR) MRI shows diffuse and dramatic hyperintensity in the cerebral white matter sparing the subcortical U fibers. *B*, Coronal brain section at autopsy showing subtotal hemispheric white matter damage.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

- 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.

- Often these acute heroin-related myelopathies can possess clinical and imaging features consistent with spinal cord infarct, according to recently proposed diagnostic criteria

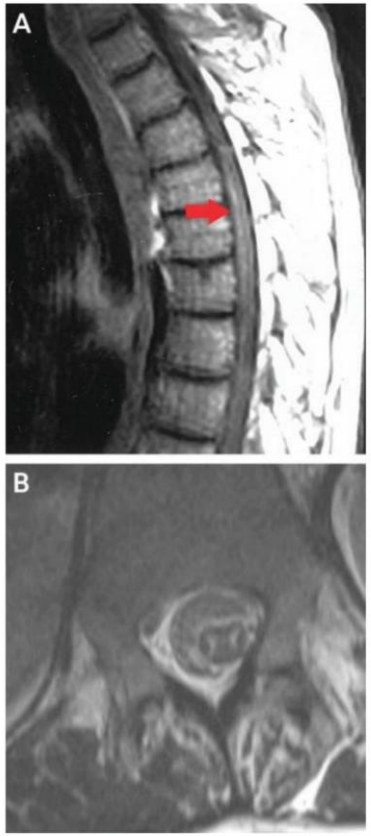

FIGURE 11-2

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.

- 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 .
- Interestingly, ongoing inhalational heroin use has been reported to be associated with a chronic, progressive myelopathy with selectivity for the posterior and lateral columns.

GABAPENTINOIDS

- Gabapentin and pregabalin are increasingly becoming abused substances. Their effects serve to potentiate the already dangerous effects of opioids.

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.

- Intoxication with benzodiazepines or barbiturates commonly produces a euphoric, drowsy state. Amnesia of recent events is very frequent with higher doses.
- Both benzodiazepines and barbiturates cause respiratory depression, and overdose can lead to life-threating hypopnea/apnea and coma.
- Both barbiturates and benzodiazepines share properties with ethanol, so their withdrawal syndromes can be similar: hallucinations, diaphoresis, agitation, and the most feared consequence, seizures.

- 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.

PSYCHOSTIMULANTS

- 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.

- In general, psychostimulant overdoses lead to a delirious state with significant risk of cardiac arrhythmia, seizures, marked hyperthermia, hypertensive emergency, rhabdomyolysis, and psychotic features.

Commonly Abused Psychostimulants

- ◆ Cathinone
- ◆ Cocaine
- ◆ Dextroamphetamine
- ◆ Ephedrine
- ◆ Methamphetamine (speed)
- ◆ Methcathinone
- ◆ Methylenedioxymethamphetamine (MDMA, ecstasy)
- ◆ Methylphenidate
- ◆ Pemoline
- ◆ Phenmetrazinea
- ◆ Phentermine
- ◆ Phenylpropanolaminea
- ◆ Pseudoephedrine
- ◆ Synthetic cathinones (bath salts)

- 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

- 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

- 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.

- 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 .

- 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.

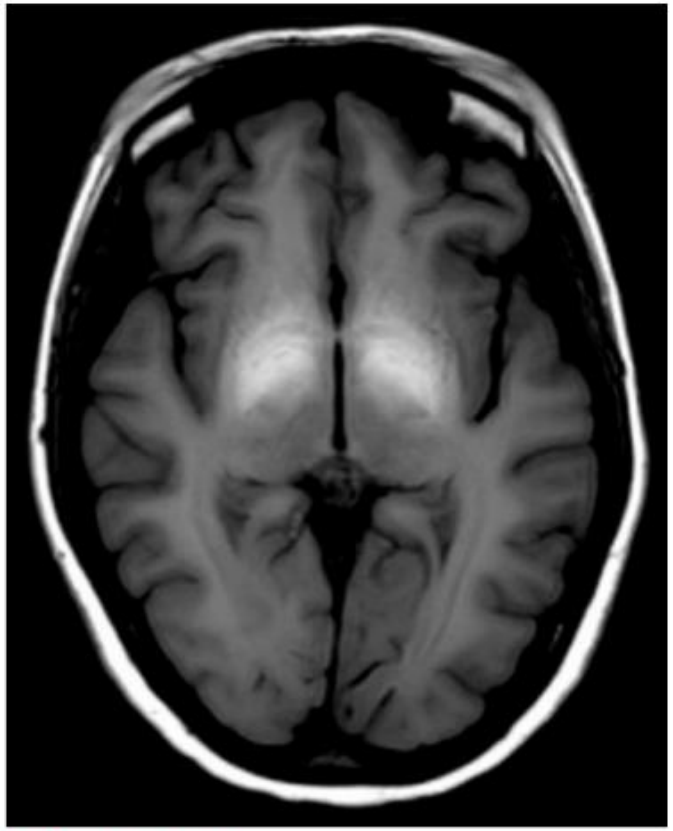

FIGURE 11-3

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.

MARIJUANA

- Marijuana is developed from the cannabis plant. Tetrahydrocannabinol is the compound that is most responsible for producing the desired high.
- 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

- 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. Contaminants are another potential hazard with synthetic cannabinoids.
- 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 .

- 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.

PHENCYCLIDINE

- Often referred to as *PCP* or *angel dust*, phencyclidine is a dissociative agent that is chemically similar to ketamine.
- Its potentially dramatic effects are due to strong *N*-methyl-D-aspartate (NMDA) receptor antagonism and monoaminergic reuptake inhibition .

- Phencyclidine is a dissociative drug that produces a syndrome similar to a marked schizophrenic episode.
- 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.

- Treatment for severe overdose includes benzodiazepines for seizure and agitation as well as cardiopulmonary support for severe hypertension, labile heart rate, and respiratory depression.

INHALANTS

- 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 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 B12 deficiency.
- Repeated exposure essentially creates a functional vitamin B12 deficiency due to the oxidation of cobalamin by nitrous oxide, leading to subacute combined degeneration of the spinal cord . In addition to stopping the inhalant abuse, patients with nitrous oxide–related myeloneuropathy should also receive vitamin B12 via injections.

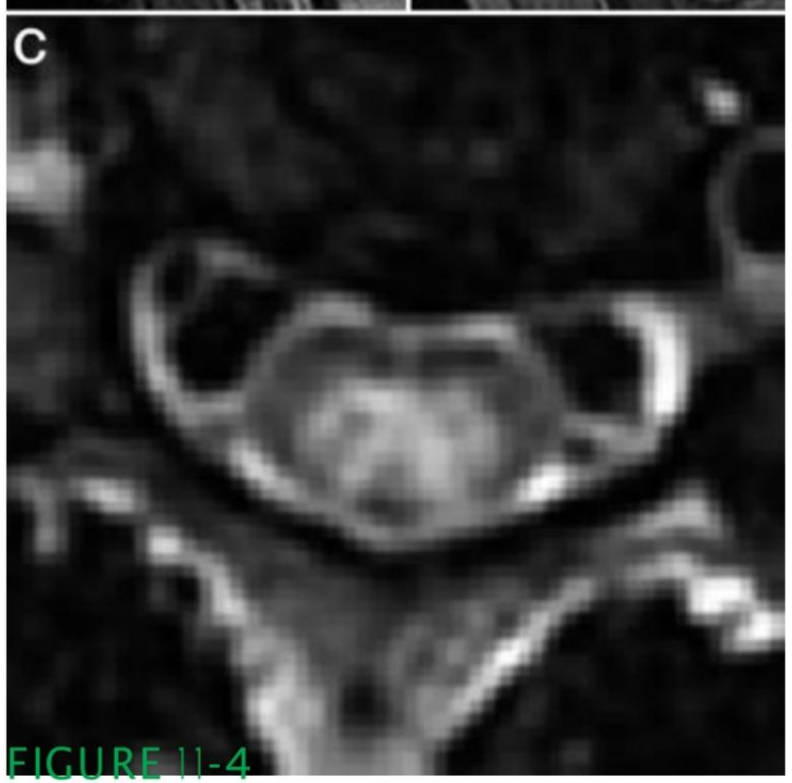

FIGURE 11-4

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.

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.

- 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 .

ETHANOL

- 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 B12, and vitamin B6 deficiency).

- 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

- 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 Korsakoff syndrome, in which patients often display confabulation during the encounter.

CONCLUSION

- Finally, with regard to imaging, any bilateral, symmetric abnormality on MRI should also prompt the practitioner to consider a toxic (or metabolic) process.

Thank you!

FOR YOUR ATTENTION