Neurologic Complications of Medical Disease
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CNS Toxicities: Drugs of Abuse
4/24/2017, 7.30 am – 8.00 am
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Recreational Drugs [1]

- Opioids[2]
  - Heroin[3]
  - Oxycodone and hydrocodone[4]
  - Desomorphine (designer opioid, Eastern Europe, "crocodile)
- Psychostimulants
  - Cocaine, cathinone, methcathinone
  - Methamphetamine ("speed"), dextroamphetamine
  - Methylenedioxymethamphetamine (MDMA, "ecstasy")[5, 6]
  - "Bath salts"[7]
  - Ephedrine, pseudoephedrine, methylphenidate
  - Pemoline, phenmetrazine, phentermine, phenylpropanolamine
- Cannabis/ marijuana, K2/ spice[8]
- Sedatives/ hypnotics
- Hallucinogens
  - Psilocybin and psilocin (in several mushroom species)
  - The phenylalkylamine mescaline (in peyote cactus)
  - LSD (synthetic ergot)
  - *Salvia divinorum*
  - Designer hallucinogens: FLY, DragonFLY, Bromo-DragonFLY
- Inhalants
  - Solvents
  - Nitrous oxide
- Dissociative Anesthetics
  - PCP, angel dust
  - Dextromethorphan
  - Ketamine, methoxetamine
- Anticholinergics
  - Datura stramonium (atropine and scopolamine)
  - Antiparkinsonian drugs, diphenhydramine, amitriptyline
- Ethanol
- Tobacco

Methcathinone Abuse and Manganese Neurotoxicity

- ***Methcathinone***
  - Cathinone, originally derived from the khat plant (*Catha edulis*), is a well known psychostimulant. The leaves and twigs of the khat plant are chewed for their amphetamine-like euphoric effects that result from release of catecholamines from presynaptic storage sites.
  - The designer drug methcathinone is a *N*-methyl analog of cathinone. Methcathinone was originally developed in the 1930s as an antidepressant but was never used clinically because of its strong addictive potential. Methcathinone (also called "Jeff", "Mulka", "Murtsovka", "Cat", "M-Cat", "Ephedrone") is manufactured by the oxidation of substances like ephedrine, pseudoephedrine, and phenylpropanolamine: constituents of various over-the-counter cough remedies. In Russia and Eastern Europe the preferred oxidizing agent is potassium permanganate. An intravenous preparation (referred

to by some as "Russian cocktail") is produced by oxidation (in the presence of acetic acid). In North America, a powder for inhalation or nasal insufflation is produced by chromate oxidation (in the presence of sulfuric acid).
    - Initial reports of methcathinone abuse and related manganese toxicity were from Russia and Eastern Europe. Global travel and online availability of information on methcathinone preparation have the potential of making it a more widespread problem.[9]
- ***Clinical features of manganese toxicity due to methcathinone abuse***
    - A distinctive extrapyramidal syndrome, likely due to manganese toxicity, has been reported in intravenous methcathinone users.[9-13] The duration of drug abuse does not correlate with severity of the extrapyramidal manifestations. Ephedrone use is often not accompanied by neurologic disease. A parkinsonian syndrome does not develop when users prepare the drug using potassium or sodium dichromate as the oxidation agent instead of potassium permanganate.
    - Reported comorbidities include hepatitis C and HIV positivity.[11] Key features of this symmetrical, levodopa unresponsive, akinetic-rigid syndrome include a gait disturbance (particularly a difficulty walking backwards) and hypophonic dysarthria. A "cock walk" gait (walking on the balls of feet), similar to than seen in ferromanganese mine workers with manganese toxicity has been reported.[11, 12] Mild executive dysfunction or emotional lability may be present.[12] Rest tremors are not common. Dystonia is commonly seen.[12, 13]
    - Cessation of methcathinone use may be accompanied by improvement or resolution of the MRI abnormalities.[11] Objective clinical improvement is generally not seen.
    - Delayed progression despite cessation of use has been reported.[12]

Investigations

- Blood manganese may be elevated but does not correlate with clinical severity or MRI findings.
- MRI may show a symmetric T1-hyperintensity involving the globus pallidus, striatum, and substantia nigra. Fluorodopa PET suggests relative sparing of the nigrostriatal dopaminergic system.[9] SPECT imaging in some former ephedrone users has shown a normal pattern of tracer uptake.[12] Diffusion tensor imaging in some of these patients has shown widespread white matter damage with greatest severity of damage in executive motor areas.[14]

<u>Synthetic Cathinones: The New "Amphetamines" ("Bath Salts")</u>

- Newer synthetic cathinones, such as mephedrone, methylone, and 3,4-methylenedioxypyrovalerone (MDPV), are now available in the US and are commonly called "bath salts." These three cathinones, have been temporarily listed by the US Drug Enforcement Agency (DEA) as schedule I substances as of October 2011. However, many other synthetic cathinones (e.g. butylone, methedrone, 3- and 4-fluoromethcathinone) remain legal. While the packaging may imply that they are to be used in a bath and the powdered contents appear similar to traditional bath salts, they are well known to contain drugs of abuse.[7, 15-17]
- ***Mechanism of action***
    - The synthetic cathinones are ketophenethylamines and are structurally similar to amphetamines. They increase presynaptic release of serotonin, dopamine, and norepinephrine and decrease reuptake of these same neurotransmitters.[18]
    - These substances are commonly ingested or nasally insufflated, although rectal administration, inhalation, and injection (IV or IM) have been described.
- ***Clinical manifestations***
    - Onset of effects is typically around 30 minutes with duration of a few hours. Initial effects of these substances include euphoria and agitation.[17] User reported neurologic symptoms include aggressiveness, bruxism, dizziness, headache, memory loss, and tremor. Medical providers additionally report dystonia, hyperreflexia, mydriasis, myoclonus, and seizures.
    - A recent report described hemiplegia after inhalation of the bath salt "ivory wave" that contains MDPV.[19]
    - The constellation of findings is typical of the sympathomimetic syndrome: tachycardia, hypertension, hyperthermia, and agitation. Serotonin syndrome[20] and myocarditis[21] have been reported as well.
- ***Investigations***
    - The synthetic cathinones are not detected by usual immunoassays for amphetamines, although some may be detected as a false positive methamphetamine screen.[18] Some commercial laboratories have developed assays for quantitative testing of mephedrone, methylone, and MDPV.

- ***Management***
    - There is no specific antidote for cathinone toxicity. Benzodiazepines may be used for agitation, seizures, tachycardia, and hypertension. Cyproheptadine may be helpful if concern for serotonin syndrome exists. Cooling measures may be required for severe hyperthermia.

Synthetic Cannabinoids: The New "Marijuana"

- *Spice* and *K2* are the most common brand names for the herbal marijuana alternatives that have been known drugs of abuse in Europe since the early 2000s. In March 2011, the DEA temporarily listed five of the synthetic cannabinoids as schedule I drugs (JWH-018, JWH-073, JWH-200, CP 47-497, and CP 47-497 C8 homologue).
- ***Mechanism of action***
    - A wide variety of herbals have been used as a substrate to which the synthetic cannabinoid is applied. The neuropsychiatric effects may be due to a combination of effects of the synthetic cannabinoid (eg JWH-018) itself, in addition to the herbal ingredients. Users may also purchase the synthetic cannabinoid in powder form, dissolve it in a solvent, and spray it onto the plant or herbal material of their choice.
    - The synthetic cannabinoids are molecules designed for research on cannabinoid receptors in attempt to harness the potentially therapeutic benefits of tetrahydrocannabinol (Δ9-THC) and avoid the neuropsychiatric adverse effects. As a consequence of this research, many synthetic substances have been described. In general, synthetic cannabinoids appear to bind more effectively at cannabinoid receptors (CB1 and CB2) than does Δ9-THC, resulting in more of a stimulant effect.[22]
- ***Clinical manifestations***
    - Neuropsychiatric effects of use include anxiety, agitation, paranoia and delusions, as well as psychosis. Clinical signs may include tachycardia, diaphoresis, hypokalemia and seizures.[8, 23, 24] Myocardial infarction has been reported in teenagers after stated use of *K2*.[25] The possibility of serotonin syndrome has been postulated due to the indole ring structure of many synthetic cannabinoids, but serotonin syndrome has not been reported.
- ***Investigations***
    - They are structurally dissimilar to Δ9-THC, so will not react with the standard marijuana screen on a urine drug test. Some commercial laboratories have developed assays for testing of specific cannabinoids in blood and/or urine.
- ***Management***
    - Management is symptomatic, as there is no antidote. Benzodiazepines should be administered for agitation, anxiety, or seizure.

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