Substance abuse in school aged children: Recent trends and drug of abuse review

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Review poisoning scenarios associated with some classic drugs of abuse
- Opioids
- Inhalants
- Anticholinergics
- Amphetamines and other sympathomimetics

Describe clinical effects seen with emerging drugs of abuse
- Designer stimulants
- Marijuana substitutes
- Dissociatives
- Misuse of prescription medications
A brief history of Poison Centers

- In early 1950s pediatricians recognized unintentional poisoning as a major source of morbidity/mortality in young children
- Chicago 1953: 1st US Poison Center
- Initially provided information to physicians to help manage poisonings
- Role expanded to include research, public/professional education, poison prevention, real time surveillance
Poison Center Basics

- Currently 57 US PCs
- Take calls from general public & HCFs
- Staffed by specially trained nurses and pharmacists with physician toxicologist available
- Data from each case entered into National Poison Data System (NPDS)
  - Substances involved, route of exposure, reason for exposure, clinical effects, treatment provided, outcome
Poisoning epidemiology

Poisonings in children age < 6 typically unintentional (dosing error, exploratory ingestion)
  ◦ After age 12 abuse/misuse and intentional self-harm
  ◦ Age 7–11 too old for exploratory ingestion, too young for abuse (?)

Following Poison Prevention Packaging Act (1970) pediatric poisoning mortality has declined

But poisoning death rates in 15–19 year age group nearly doubled from 2000 to 2009 (1)
  ◦ Proportion of deaths involving prescription drugs also nearly doubled (increased from 30% to 57%)

2011: Some fatalities reported in 7–11 age group that were suspicious for intentional misuse (2)

1. CDC 2012
2. Fine, Clin Toxicol 2012
Case 1

- 9 year old boy took 10 of his brother’s ADHD pills around 7:30 PM
  - He just wanted to see what they would do
- Parents did not find out until next morning
- Seemed hyper, seeing animals that weren’t there
- Child brought to ED
- In ED child initially tachycardic (HR 150), had dilated pupils, couldn’t sit still
15 yo F vomited after dinner & seemed confused
Told Mom she was kidnapped at school, then went riding in a Cadillac
In ED sleepy but agitated with stimulation
HR 108, BP 127/85, RR 18, T 37.2
Pupils 6 mm reactive
Horizontal nystagmus
Skin & mucous membranes moist
Heart, lung, abd exams normal
Confused, no tremor or rigidity, reflexes normal
Routine blood work unremarkable

Osterhoudt, Pediatr Emerg Care 2005
Opiates/Opioids

- **Opiate**: Derived from the opium poppy
  - Codeine, morphine

- **Opioid**: Broader class includes semi-synthetic & synthetic agents that bind to opioid receptors
  - Heroin (3,6-diacetyl morphine)
  - Oxycodone, hydrocodone
  - Meperidine
  - Propoxyphene
  - Fentanyl
  - Methadone

- **Urine opiate screens typically detect**
  - Codeine
  - Morphine
  - Heroin
  - +/- Oxycodone & HC

*Papaver somniferum*
Diacetylmorphine synthesized by Bayer company in late 19th century
Seeking less addictive alternative to morphine
Marketed as antitussive and analgesic in early 20th century until Harrison Narcotics Act (1914)
Opioids: Mechanism of action

- Primarily bind to the mu, kappa or delta opioid receptor
  - Mu receptor: responsible for analgesia, miosis, euphoria, respiratory depression, and decreased GI motility

- Clinical effects (opioid toxidrome)
  - CNS depression
  - Pinpoint pupils (miosis)
  - Respiratory depression
    - Also: Peripheral vasodilation with lowish heart rate and BP
Heroin: 3,6-diacetylmorphine

- Easily synthesized from morphine and acetic anhydride
- The "rush" related to enhanced blood-brain barrier penetration
- Lower affinity for mu receptor than morphine
- But rapidly metabolized to 6-monoacetylmorphine (MAM)*
  - More potent mu agonist than morphine

*Detection of MAM confirms heroin exposure
The antidote: Naloxone

- Competitive antagonist at mu receptor
- Oral naloxone poorly bioavailable
- Well absorbed IM, SQ, via inhalation
  - Onset (IV) 1–2 min, duration of action 30–90 min
  - Elimination half-life 60–90 min
- Indication: reversal of opioid–induced CNS depression with airway/respiratory compromise
  - Can be used diagnostically

Available as 0.4 mg/mL or 1 mg/mL solution
Fentanyl abuse

- Highly lipophilic $\Rightarrow$ rapid CNS penetration
- Fentanyl–related deaths in Philadelphia increased more than 10–fold from 2004 to 2006
- Patch can be eaten (after cutting membrane), used as teabag, smoked, or contents of reservoir extracted and injected
  - Used patches still have significant amount of drug
- Fentanyl analogs have been manufactured in clandestine labs

Wong, J Med Toxicol 2010
Abusers often crush pills and snort or inject for more rapid CNS effect

Risk of opioid overdose, microemboli, infections, vascular injury

Drug manufacturers reformulated some products making them more difficult to shoot or snort

Injection of reformulated Opana ER (oxymorphone) associated with thrombotic thrombocytopenic purpura* (TTP)
  - Not seen with oral abuse (1)

*Microhemangiopathic hemolytic anemia with low platelets

1. CDC, MMWR Morb Mortal Wkly Rep 2013
US death rates from unintentional overdose tripled in decade from 1997 to 2007

Data from CDC National Vital Statistics System

Inhalants

- Glues, spray paints (toluene, xylene, n-hexane)
- Solvents (toluene, xylene, methylene chloride)
- Correction fluid, spot remover (1,1,1-trichloroethane, trichloroethylene)
- Aerosol propellants (chlorofluorocarbons)
- Fuels (butane, propane); markers (acetone)
- Whipped cream propellant (nitrous oxide)
- Products easily accessible and legal
  - Commonly abused by pre-teens/younger adolescents
- Abuse by sniffing, huffing, bagging
Inhalants (cont’d)

- Acute CNS depression, asphyxia, pneumonitis, dysrhythmia (“sudden sniffing death”)
- Chronic exposure
  - Dependence and withdrawal syndrome
  - Encephalopathy, cerebellar dysfunction, peripheral neuropathy
  - Potential for impaired CNS development in early adolescence
  - Renal and hepatic injury, bone marrow depression
- Treatment: supportive care, avoid excessive stimulation (risk of ↑ catecholamine release → VFib)
- Recognition
  - Paint/oil stains on face/hands, chemical odor, nystagmus, injected sclerae, unsteady gait, dazed appearance, sleep disturbance, irritability, anorexia
  - Excessive hydrocarbon product or containers around home
Anti-cholinergic abuse

*Datura stramonium* aka Jimsonweed

Antihistamines, TCAs, some neuroleptics, many other drugs
*Datura* species (e.g. Jimsonweed) & many other plants
Antagonize effects of acetylcholine (ACh) by blocking receptors

- ACh receptors are either nicotinic or muscarinic
- The “anti-cholinergic” drugs only block muscarinic receptors
- We should call them “anti-muscarinic” because you don’t see anti-nicotinic effects such as muscle weakness
Anticholinergics: Clinical effects

- Hot as Hades – Fever (mild)
- Fast as a Hare – Tachycardia
- Dry as a Bone – Dry skin, MMs, armpits
- Red as a Beet – Flushed skin
- Mad as a Hatter – Delirium
- Full as a Tick – Urinary retention
- Blind as a Bat – Mydriasis
- Characteristic rapid mumbling speech
- Picking at sheets and clothing
- Public disrobing
What are potential major complications?
- Seizures, aspiration, co-ingestion
- Rare dysrhythmia and even rarer hyperpyrexia

How do we treat anticholinergic toxicity?
- Sedation, airway protection, fluids
- Rule out co-ingestants and other diseases
- Benzodiazepines: 1st (sedation & seizure prophylaxis)
- Physostigmine (2 mg IV over 4–5 min in adult or adolescent) for delirium with patient on monitor – typically given in consultation with medical toxicologist
  - Reversible AChE inhibitor with short duration of action
  - Contraindicated in TCA toxicity with Na channel blockade (wide QRS) or bradycardia
Sympathomimetics

- Cocaine
- Amphetamines/Methamphetamine
- Ecstasy (MDMA)
- ADHD meds like methylphenidate (Ritalin®, etc) & amphetamine/dextroamphetamine (Adderall®)
- “Designer” stimulants (mephedrone, MDPV, 2C–B, many others)

Structurally similar to endogenous neurotransmitters DA & NE
Nonmedical use of ADHD drugs

- Nonmedical use of prescription medications has surpassed illicit drug use except marijuana (1)
  - Calls to Poison Centers about ADHD med abuse rose 76% from 1998 to 2005, higher than ↑ in other calls (2)
- Abused recreationally and used as “study drugs” to enhance academic performance (3, 4)
- Students may give, trade, or sell to friends
- Others may describe ADHD symptoms to obtain prescription from health care provider

1. Fortuna, Pediatrics 2010
2. Setlik, Pediatrics, 2009
3. Schwarz A. The Good-grade pill. NY Times 6/9/12
Sympathomimetics: MOA

- Excessive stimulation of alpha and beta adrenergic receptors
- ↑ sympathetic activity through increased norepinephrine, epinephrine, and dopamine release & reuptake inhibition
The sympathomimetic toxidrome

- Tachycardia
- Hypertension
- Confusion
- Agitation
- Diaphoresis
- Mydriasis
- Seizures
- Rhabdomyolysis
- Hyperthermia ($T \geq 104^\circ F$ or $40^\circ C$)
  - Poor prognostic sign
  - Treat with aggressive external cooling
What are potential major complications?
- Seizures, dysrhythmias, rhabdomyolysis, hyperthermia and multi-system organ failure

Treatment of sympathomimetic toxicity

Supportive care (no specific antidote)
- Airway
- IVF, monitor
- Diagnostic tests

Liberal use of benzodiazepines

BP elevation: If severe HTN not improved with benzos short acting vasodilators occasionally used
Sympathomimetics: What to avoid

- This class of drugs increases alpha and beta adrenergic stimulation
  - Giving a beta blocker only blocks beta activity
  - Can lead unopposed alpha stimulation
    - Results in vasoconstriction
    - Labetolol is mainly a beta blocker with weak alpha antagonism
- We recommend against using β-blockers to treat sympathomimetic toxicity
- If ↑↑ BP not improved with benzos use vasodilators such as nitrates
Amphetamines

- Amphetamine and methamphetamine developed in 1920s – 1930s
- Benzedrine inhaler – nasal decongestant
- Amphetamine used as appetite suppressant, treatment for narcolepsy
- 1970: amphetamine made Schedule II drug
- Primary mechanism: Enters pre-synaptic neurons via reuptake transporters leading to ↑ NE, DA (and some serotonin) release

![Chemical structures of Amphetamine, Methamphetamine, Dopamine, and Norepinephrine]
Evolution of designer stimulants

- Early 1980s: Designer amphetamines widely used to circumvent drug laws
- Mid-1980s: Drug laws amended to cover analog substances used for mind-altering purposes
- Newer designer drugs circumvent analog act by labeling “not for human consumption”
  - Sold as “research chemicals”, “plant food”, “bath salts”, etc

![Chemical structures of Amphetamine, Methamphetamine, and Methylendioxy-methamphetamine (MDMA)]
Designer Amphetamines (cont’d)

- Chemist Alexander Shulgin synthesized MDMA & others in 1970s & 80s
  - Consultant for DEA until they raided his lab in 1990s
- Author of PIKHAL, *Phenethylamines I Have Known and Loved* (1991)
- Substitutions determine drug properties, whether more hallucinogenic or sympathomimetic

“2C” drugs
(dimethoxyphenethylamines) →

- **2C–E**
- **2C–B**
- **2C–I** aka “smiles”
Cathinones

- From leaves of khat plant
- Active ingredient: cathinone
- Khat–chewing common in Somalia & Yemen
- Khat has short shelf–life
- Synthetic cathinones became popular in Europe in 1990s and early 2000s
  - Aka bk phenethylamines

![Cathinone chemical structure]

![Chewing khat in Yemen]
## Synthetic cathinones used as DOAs

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Chemical Name</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butylone</td>
<td>1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one</td>
<td><img src="image" alt="Butylone Structure" /></td>
</tr>
<tr>
<td>Dimethylcathinone</td>
<td>(RS)-2-dimethylamino-1-phenylpropan-1-one</td>
<td><img src="image" alt="Dimethylcathinone Structure" /></td>
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<tr>
<td>Ecathinone</td>
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<td><img src="image" alt="Ecathinone Structure" /></td>
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<tr>
<td>Ethylone</td>
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<tr>
<td>3-Fluormethylcathinone</td>
<td>(RS)-1-(3-fluorophenyl)-2-methylaminopropan-1-one</td>
<td><img src="image" alt="3-Fluormethylcathinone Structure" /></td>
</tr>
<tr>
<td>4-Fluormethylcathinone</td>
<td>(RS)-1-(4-fluorophenyl)-2-methylaminopropan-1-one</td>
<td><img src="image" alt="4-Fluormethylcathinone Structure" /></td>
</tr>
<tr>
<td>Mephedrone</td>
<td>(RS)-2-methylamino-1-(4-methylphenyl)propan-1-one</td>
<td><img src="image" alt="Mephedrone Structure" /></td>
</tr>
<tr>
<td>Methcathinone</td>
<td>α-methylamino-propiophenone</td>
<td><img src="image" alt="Methcathinone Structure" /></td>
</tr>
<tr>
<td>Methedrone</td>
<td>(RS)-1-(4-methoxyphenyl)-2-(methylamino)propan-1-one</td>
<td><img src="image" alt="Methedrone Structure" /></td>
</tr>
<tr>
<td>Methyleneoxyprovalerone (MDPV)</td>
<td>(RS)-1-(Benzod[1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one</td>
<td><img src="image" alt="MDPV Structure" /></td>
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<tr>
<td>Methylone</td>
<td>(±)-2-methylamino-1-(3,4-methyleneoxyphenyl)propan-1-one</td>
<td><img src="image" alt="Methylone Structure" /></td>
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<tr>
<td>Pyrovalerone</td>
<td>(RS)-1-(4-methylphenyl)-2-(1-pyrrolidinyl)pentan-1-one</td>
<td><img src="image" alt="Pyrovalerone Structure" /></td>
</tr>
</tbody>
</table>
Cathinones (cont’d)

- Bupropion is the only cathinone used therapeutically (Wellbutrin®)
- Low abuse potential as an oral drug
- Sometimes abused by nasal insufflation (snorting) or IV administration
  - Bypasses first pass effect resulting in higher serum levels
Cathinones often labeled “not for human consumption”

Source: Gibbons, Clin Toxicol  2012
Calls to PCs in 1st half of 2011 > 10 X number of calls for all of 2010

September 2011: DEA announced temporary scheduling of mephedrone, methylone, and MDPV

Multiple states have banned SCs
Synthetic cathinones: clinical features

- Effects expected to be similar to older sympathomimetics
- Pharmacology & pharmacokinetics less well known
- Ingredients often not listed
  - MDPV, mephedrone, & methylone most common agents found in recent analysis of US “bath salt” samples (1)
  - Other substances may be present
- Most common routes of administration
  - Insufflation, injection, ingestion
- Most common clinical features:
  - Agitation, violent behavior, tachycardia (1)

Other designer stimulants

- “Masked amphetamines” have phenethylamine hidden in an extra 5 or 6 membered ring (1)
- Methylenedioxy-2-amino-indane (MDAI), methylenedioxy-2-amino-tetralin (MDAT), others
  - Thought to be more serotonergic
- Bromodragonfly (2) and DOI (3) a/w peripheral vasoconstriction

Other designer stimulants (cont’d)

- **25I-NBOMe**: New derivative of 2C-I associated with delirium and seizures (1)
- **Desoxypipradol** developed by Ciba-Geigy in 1950s to arouse patients from anesthesia (“Weckamine”)
  - Found in 2010 UK cluster of “ivory wave” abuse (2)
  - Chemically similar to DA/NE reuptake inhibitor methylphenidate
- Drugs sold as “LSD” often contain designer stimulants

Other designer stimulants (cont’d 2)

- Dimethylamylamine (DMAA) aka Geranamine, developed as nasal decongestant in 1940s
  - Structurally similar to methamphetamine
- Sold as dietary supplement, weight loss aid
- Associated with intracranial hemorrhage

Tryptamines

- Structural similarity to serotonin (aka 5-hydroxytryptamine)
- Natural (psilocin) and man-made (DMT, etc)
- Interact with serotonin receptors/transporters
- Primarily hallucinogenic
- Some also have sympathomimetic activity
- Treatment: supportive care, benzos prn
Tryptamine structures

Serotonin

Tryptamines I Have Known and Loved, Alexander & Ann Shulgin, 1997

Hill, Clin Toxicol 2011
Phencyclidine (PCP)/ketamine

- PCP (Phenylcyclohexylpiperidine): Dissociative anesthetic in use until mid-1960s
  - Dissociative effects thought due to glutamate antagonism
  - Abandoned due to post-op dysphoria & psychosis
  - Became popular as a street drug in 1970s
  - Tachycardia, delirium, hallucinations, nystagmus
  - Effects can last 24–48 h (T ½ 18–24 h)
  - Treatment: Supportive care, benzos prn

- Ketamine introduced in 1970: Potency & T ½ ~10% compared with PCP

- Methoxetamine analog of ketamine available on internet
  - Potency & duration of action intermediate between PCP & ketamine

Rosenbaum, J Med Toxicol 2012
Hofer, Ann Emerg Med 2012
O TC meds

- Dextromethorphan (DXM)
  - $\uparrow$s CNS serotonin activity (serotonin syndrome if combined with other serotonergic drugs)
  - Glutamate antagonist similar to PCP or ketamine
  - PCP–like dissociative effects (from metabolite)
  - Available as Robitussin & in other cold/cough meds
    - Some may contain acetaminophen
  - Robo–tripping, Tussing, Pharming popular among adolescents

Robo–tripping

Dextrorphan
(DXM metabolite)

DXM $\rightarrow$
Dextromethorphan (cont’d)

- L-isomer is opioid levorphanol but DXM has minimal opioid activity except at very high doses
- Short T ½ (3–5 h) except in slow metabolizers
- Metabolized by CYP 2D6 to active metabolite
- Can give false + for PCP on UDS
- Coricidin: DXM + chlorpheniramine (antihistamine)
  - Aka Skittles, Cap’n Crunch, Triple Cs
  - Can have AMS from DXM or anticholinergic delirium from antihistamine
- Treatment
  - Supportive care
  - Benzodiazepines as needed
  - Check for acetaminophen
Marijuana substitutes

- Synthetic cannabinoids developed in 1990s as potential analgesics
  - JWH–018, JWH–073, JWH–250, many others
  - Became DOAs in late 2000s

- Sprayed on herbs or dried leaves

- Marketed as incense or potpourri but typically smoked (K–2, Spice, etc)

- Illegal in most European countries

- DEA banned some synthetic CBs in Mar 2011
Marijuana substitutes (cont’d)

- Not detected by marijuana drug screen
- Delirium, tachydysrhythmias, and seizures have been reported
- Treatment: Supportive care, benzos prn seizure or agitation, look for coingestants
- Seizures with synthetic CB products
  - May be due to
    - ↑ potency of synthetic CBs
    - Other pharmacologic properties of these agents
    - Adulterants/contaminants
    - Absence of anticonvulsant substances present in marijuana plant
Case 1 conclusion

- 9 year old who took brother’s ADHD pills
- Methylphenidate 18 mg X 10
- Given IV fluids and multiple doses of lorazepam
- Discharged home on afternoon of hospital day 3
15 year old girl riding in Cadillac
In girl’s pocket ED nurses found empty blister packs of Coricidin HBP
  ◦ Dextromethorphan 30 mg/chlorpheniramine 4 mg
Parents found empty box in her bedroom
Confusion resolved after 8 hours without treatment
Referred for substance abuse counseling
Key points

- Misuse of pharmaceuticals is the fastest growing drug abuse problem among adolescents
  - Includes opioids, stimulants, antidepressants, neuroleptics, as well as OTC cold/cough preparations
  - May be perceived as safer than street drugs
  - Easy access in home, from friends, or health care provider

- Most common site of abuse appears to be at home

- Parents and children should be educated on risks of abuse and casual medication sharing
  - Parents to be alert for decline in schoolwork, loss of interest in usual activities, behavioral changes
  - Securing and monitoring of medications
Useful resources

- Substance Abuse and Mental Health Services Administration (SAMHSA) National Survey on Drug Use & Health: www.oas.samhsa.gov/nhsda.htm
  - 2010 is most recent year for which full survey results are available
- Nebraska Regional Poison Center: www.nebraskapoison.com/Prescription-Drug-Abuse.aspx
  - Journal articles
  - Presentations and handouts for parents and educators
Key points – treatment approaches

- Naloxone (but not flumazenil) for drug intoxication with CNS/respiratory depression
  - Start with low dose if chronic opioid use suspected
  - Repeated dosing or infusion may be needed

- Supportive care, cooling & benzodiazepines are mainstays for treating stimulant toxicity
  - Escalating doses of benzos
  - Check temperature; external cooling as needed
  - Direct vasodilators for vasospasm or ↑↑ BP not improved with benzos (avoid β-blockers)
  - Similar approach for hallucinogens, DXM & other dissociatives

- Consider anticholinergic toxicity if dry skin, axillae & mucous membranes
  - Initial treatment similar to stimulants
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Questions?

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How embarrassing -- we've got the same designer drugs
Thank you!

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