Emerging Drugs of Abuse

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Objectives

- Review the patterns and epidemiology of drug abuse
- Recognize the clinical manifestations of the novel drugs of abuse
  - Highlight the differences seen among specific agents
- Describe the limitations of the laboratory in identifying these agents

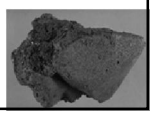
The Big Four

- Methamphetamine
- Marijuana
- Cocaine
- Heroin

Table 1. Drug Seizures at Arizona POEs, in Pounds, FY2009–FY2010

Drug	FY2009	FY2010
Marijuana	105,000	119,000
Methamphetamine	787	730
Cocaine	3,300	3,300
Heroin	190	263

Source: U.S. Customs and Border Protection Office of Field Operations.



Trends in Drugs of Abuse

- Illicit drugs are not recession proof
  - In Phoenix prices of meth dropped from $15,250/kg to $14,000/kg
- Officials also report a growing threat from controlled prescription drugs
- What are my options if I want to avoid those pesky cartels or other legal snags?

Designer Drugs and the Internet

Designer Drug

- Early 1980s - Dr. Gary Henderson of UC-Davis coined the term "designer drugs"
- Refers to chemicals created for recreational use to evade drug legislation usually by modifications of the molecular structures of existing drugs
- For example the Controlled Substance Act of 1970 made amphetamines Schedule II
- Abuse subsequently declined in the 70's
- 1980's the so-called "designer" amphetamines came into vogue

A New Wave of Drugs

- The search for a "legal high" resulted in an explosion of recreational designer drugs
- They posses stimulant, entactogen or hallucinogenic effects
- Reliable clinical and experimental data is not available
- Epidemiologic information is scarce
  - Wave hit UK and Europe first
- The internet adds another layer of complexity
  - www.erowid.org

Emerging or Novel Drugs

- Synthetic cathinones
  - Bath Salts
- Piperazine derivatives (BZP)
  - "Legal Ecstasy"
- Synthetic cannabinoid agonists
  - K2 or Spice
- *Salvia divinorum*
- Kratom- Mitragynine
- Methoxetamine
  - "Legal ketamine"

Case Presentation

- 22 y.o. male presents to ED by EMS
- HR 113, BP 167/84, T 38.0 (R), RR 22, Sats 94%
- Flushed, hot, diaphoretic, in distress
- Cardiac - tachy to 180s (narrow complex QRS)
- Neuro - confused and combative
- Intubated and after midazolam, placed on propofol gtt
- Transferred to BGSMC-Toxicology-ICU

Sympathomimetic Toxidrome

- Hyperactivity
- CNS excitation
- Pressured speech
- Agitation
- Tremor
- Seizures
- Hyperthermia
- Diaphoresis
- Tachycardia
- Hypertension
- Tachypnea
- Mydriasis
- Metabolic acidosis

Case

- On arrival, sedated with pupils reactive, normal reflexes, no clonus.
- HR 85, BP 123/70, T 36.9, Sat 100% on 70% O_2
- WBC – 26,000
- CPK - 6,000+ (peak 31,688)
- UA - Large blood, RBC 1-2
- Bicarb - 15, AG 20
- AST/ALT - 149/87 (peak 576/179)
- UDS – negative
- Extubated 30 hrs after presentation, with mild asp pneumonia

Patient said he used "Bath Salts"

Bath Salts

- Newer popularity in USA
  - –Originated from China and India
- Popular in Europe since 2007
  - –Banned in Britain in April 2010
- Falsely marketed as "research chemicals," "plant food," or "bath salts"
- Sold in smoke shops, head shops, convenience stores
- In capsules, tablets, and powders
  - –generally snorted or ingested
- Contain synthetic cathinones

Naked and Agitated

- 18-year-old man began battling a horde of imaginary insects inside a coffee shop bathroom after consuming a controversial drug
- Caused him to wage a private, bloody battle with the insects he felt were eating him alive. At some point during his violent struggle, he managed to shed quite a bit of his clothing.

Bath Salts

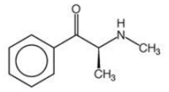
- Treatment: supportive
- Benzodiazepines
- Aggressive Hydration
- Haloperidol

Khat

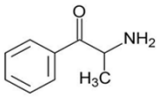
- Leaves of the *Catha edulis* shrub
- Consumed in East Africa and the Arabian peninsula
- Contains a number of chemicals among which are two controlled substances
  - cathinone and cathine
- As the leaves mature or dry, cathinone is converted to cathine, which significantly reduces its stimulatory properties

Methcathinone

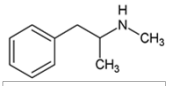
- Known as "cat" is often confused with khat
- A synthetic Schedule I substance with similar chemical structure to the cathinone
- Produced in clandestine laboratories and sold as a methamphetamine alternative
  - Manganese toxicity from production of permanganate and pseudoephedrine



Methcathinone

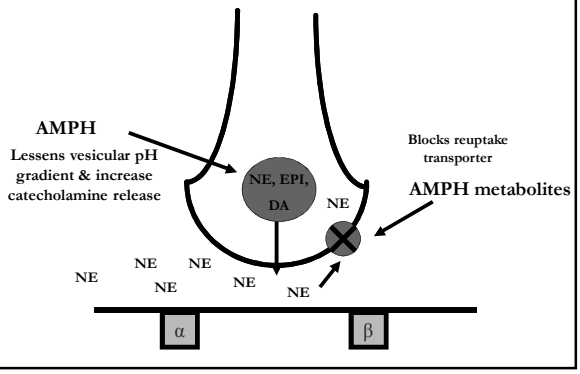


Cathinone



Methamphetamine

Catecholamine Excess



Clinical and Adverse Effects

- Increased alertness, improved attention, decreased fatigue, euphoria
- Depressed appetite, weight loss, insomnia
- Tachycardia, HTN, palpitations, tremor, diaphoresis, agitation
- Increased DA release
  - Choreoathetosis, tics, paranoid psychosis
- Increased 5HT release or agonism
  - increased hallucinations
- Overdose results in sympathomimetic toxidrome

Bath Salt's Increasing Popularity

- Banner Good Samaritan Poison and Drug Information Center and Bath Salts
  - In 2010 there were 2 cases
  - In 2011 there were 274 cases
- AAPPC
  - 2010: 303 calls about synthetic cathinones
  - Jan - June: 3,470 calls
- National Forensic Information System (NFLIS)
  - 14 reports of seizures from 8 states in 2009
  - 2010: 290 seizures from 21 states
- By July of 2011, 28 states had passed laws to control synthetic cathinones

Four Distinct Chemical Families

- A. Piperazines
- B. Phenylethylamines
- C. Tryptamines
- D. Piperidines

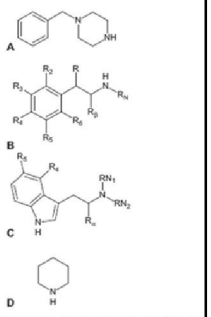


Fig. 1. Basic chemical structures of the piperazines (A), phenethylamines (B), tryptamines (C) and Piperidine (D).

Phenylethylamines

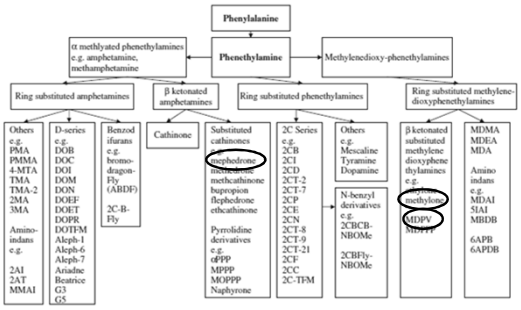
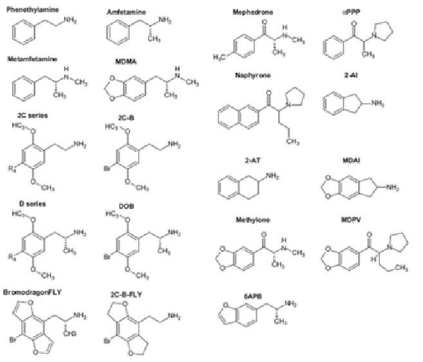


Fig. 4. Classification of the phenthylamines.

Drugs of Abuse Gaining Popularity



g. 3. Skeletal formulae for phenethylamines (note all are presented as the d stereoisomer irrespective of activity for ease of comparison).

Detection

- Immunoassays don't detect these agents
- Can be detected by GC-MS
- Currently, Banner Good Samaritan screens for:

Butylone
Flephedrone
MDAI (5,6-methylenedioxy-2-aminoindane)
MDPV
Mephedrone
3',4'-Methylenedioxy-pyrrolidinobutiophenone (MDPBP)
4-Methylethcathinone (4-MEC)
Naphyrone
Pentedrone
Pentylone
α-Pyrrolidinovalerophenone (PVP)
α-Pyrrolidinovalerophenone meta 1
α-Pyrrolidinovalerophenone meta 2

Clinical Effects

- Tachycardia, hypertension, diaphoresis vasoconstriction
- Euphoria, increased alertness, anxiety, agitation, insomnia, bruxism, trismus, seizures
- Symptoms may persist 24-48 hrs
- Reports of psychosis
- Deaths reported in Europe

"Bromo-dragonfly"

- Greater potency and adverse effects
- Dose is 0.2-1 mg
- Onset of action up to 6 hrs
- Duration of action 2-3 days
- Severe prolonged arteriolar vasoconstriction mediated via 5HT2 and alpha agonism
  - Agitation, hallucinations, severe limb ischemia, seizures, hepatic and renal failure
  - Linked to a number of deaths in Scandinavia

PMA and PMMA

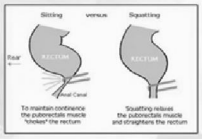
- Paramethoxyamphetamine (PMA) and paramethoxymethamphetamine (PMMA)
  - "Death" and "Flatliner"
- Greater morbidity and mortality
- Severe hyperthermia is prominent feature

Goals

- Review some ethanol withdrawal
- Review potential novel approaches
- Learn something new

ARE YOU POOPING WRONG?

In a 2003 study, 28 healthy people volunteered to time themselves doing their business in three alternate positions: sitting on a standard toilet, sitting on a low toilet, and squatting.

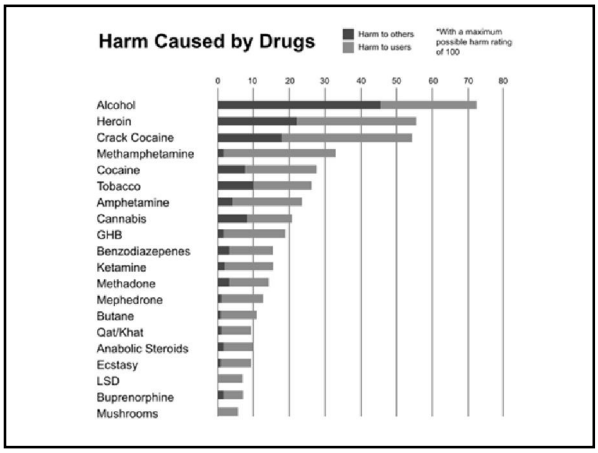


They not only recorded how long it took them, but also how much effort it took. Squatting, the study concluded, takes less time and effort.

"Simply put, it straightens out the colon."

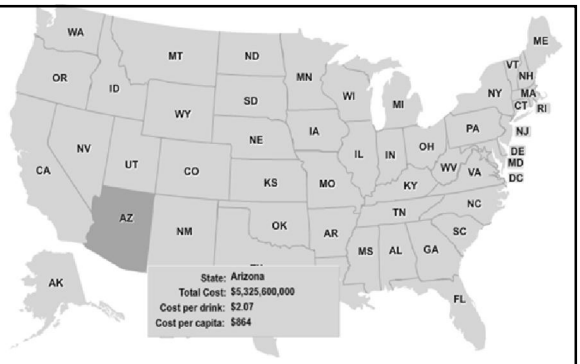
When we're standing, the colon (where waste is stored) gets pushed up against the puborectalis muscle, which keeps fecal continence until it's time to hit the bathroom. Sitting down only partially relaxes that muscle. Squatting fully relaxes it, essentially straightening out the colon. That, in turn, eases the elimination pooping process.

Medical Observer | Source: Everydayhealth



Excessive Drinking Costs U.S. $223.5 Billion

- In 2006, about $1.90 per drink



Source: Sacks, et al. *American Journal of Preventive Medicine* 2013

[Notes and text description of this map are also available.]

Case

- 70-yo M with unknown PMHx was brought into ED after being found down. Pt was found to have displaced hip fracture and was taken to OR for ORIF. Pt initially did well post-op, but 48 hrs after admission pt started having tachycardia, hypertension, fever, and agitation.
- What are some differential diagnosis?

Case Presentation

- A 21-year-old female is brought to the ED
- She reportedly ingested 5 tablets of an unknown club drug

Case

- She is delirious and combative requiring restraints
- Diaphoretic with axillary temp is 105.5ºF
- Hr 178, BP 120/70, pupils are dilated
- Muscular rigidity legs > arms

Case

- Cooling with ice and wet sheets
- IV fluids
- Level of consciousness continues to decline requiring intubation
- Develops 2nd degree heart block requiring temporary pacing

Case

- Labs: K^+ 4.5, HCO3 18, CPK 259, BAC 78
- Temperature increases to 108ºF
- Anuric, hypotensive, coagulopathic
- Severe metabolic acidosis ensues (pH 7.06)
- K^+ 7.3 despite repeated doses of bicarb, insulin and dextrose and calcium.
- Hemodialysis planned
- Patient dies within 5 hours of her arrival.

Serotonin Syndrome

- Pathophysiology not completely understood
- Excessive stimulation of 5-HT_{1A} and 5-HT_{2A}
- Clinical diagnosis with symptoms ranging from mild to life-threatening
- Classic triad
  - Altered mental status
  - Autonomic instability
  - Neuromuscular effects

Piperazines

- 1-benzylpiperazine (BZP)
- 1-phenylpiperazine
- Marketed as herbal or natural high
- Fully synthetic (no examples in nature)
- First reported in California in 1990s

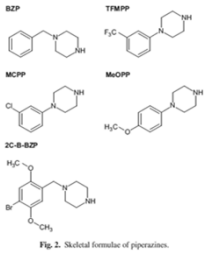


Fig. 2. Skeletal formulae of piperazines.

1-Benzylpiperazine (BZP)

- Acts identically to amphetamine
- Peak plasma concentrations in ~75 min
  - Conc. 262 ng/ml; 80% excreted as urinary sulphate conjugates
- Elimination half-life ~5.5 hrs
- Detection in plasma up to 30 hrs after ingestion

BZP

- Acute toxicity similar to d-amphetamine
  - 1/10 the potency
  - sympathomimetic toxidrome, metabolic acidosis, seizures, psychosis, hyponatremia
- 2 severe cases of BZP toxicity with multi-organ system failure
- No isolated deaths but fatalities with BZP and MDMA reported in Sweden and Switzerland

Cognitive-Behavioral

- Confusion/disorientation
- Agitation
- Coma/unresponsive
- Anxiety
- Hypomania
- Drowsy/lethargic
- Seizures
- Insomnia
- Hallucinations
- Dizziness

Autonomic Dysfunction

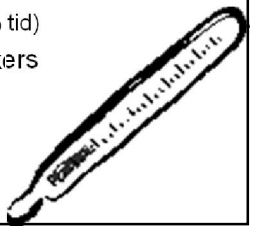
- Hyperthermia
- Diaphoresis
- Tachycardia
- Hypertension
- Tachypnea
- Mydriasis
- Flushing
- Hypotension
- Diarrhea
- Abdominal cramps
- Salivation

Neuromuscular Dysfunction

- Myoclonus
- Hyperreflexia
- Muscle rigidity LExt>>UExt
- Tremor
- Hyperactivity/restlessness
- Ataxia/incoordination
- Shivering/chills
- Nystagmus
- Babinski
- Opisthotonos
- Trismus

Treatment

- Aggressively treat hyperthermia
  - Ice packs, Cool Mist, Cool IV fluids
- GABA Agonists- benzodiazepines
- Serotonin Antagonists
  - Cyproheptadine (4-8 mg po tid)
- Nondepolarizing NM blockers
- Treat hyperkalemia



Case Presentation

- 14 y.o. male develops nausea after smoking an herb he purchased on-line
- Exam reveals tachycardia
- UDS negative
- Symptoms improve with IVF, benzodiazepines

JWH-018

- Synthesized by John W Huffman in 1995 purely for experimental purposes
- Aminoalkylindole that acts as a potent cannabinoid receptor agonist
  - 4-5 X more potent than THC
- Sold as an herbal mixture to burn as incense
  - Spice, spice gold, spice silver, spice diamond, yucatan fire, sense, chill X, smoke, genie, Algerian blend, K2
  - Concentrations vary 0.2 to 3%

Other Synthetic Cannabinoids

- Additional synthetic cannabinoids include:
  - CP-47,497 (CP = cyclohexylphenol)
  - CP-55,940
  - JWH-015 (JWH = John W. Huffman)
  - JWH-073
  - JWH-133
  - JWH-398
  - HU-210 (HU = Hebrew University)
- JWH-018 is the most used

Cannabinoid Receptors

- CB_1 found in CNS/PNS
  - Responsible for elevating mood, anxiety, cognition
- CB_2 found in spleen, macrophages.
  - Responsible for reducing inflammation-induced pain

"SPICE"

- Do not know what effects the other components may have
- Common herbal components of spice include:
  - Beach bean (*C. maritima*, *C. rosea*)
  - White and blue water lily (*N. alba*, *N. caerulea*)
  - Dwarf skullcap (*S. nana*)
  - Indian warrior (*P. densiflora*)
  - Lion's ear/tail (*L. leonuru*)
  - Blue/Sacred lotus (*N. nucifera*)
- Banner PCC cases: 51 in 2010 vs 206 in 2011

Mitragyna speciosa "Kratom"

- Mitragynine is a partial opioid agnonist similar to morphine
- A minor alkaloid, 7-hydroxymitragynine, is more potent than morphine
- Activates supraspinal mu and delta opioid receptors
- Low dose produces euphoria, high dose produces opioid effects
- Used by narcotic abusers to ameliorate withdrawal symptoms and by individuals with chronic pain syndromes
  - $10-40 per ounce

Case Presentation

- 32 y.o. man with a history of hallucinogenic drug use presented after injecting methoxetamine intramuscularly
- Police and paramedics found patient agitated, but able to give some history and oriented to self and location only
- HR 105, BP 140/95, RR 16, afebrile
- Intermittently in a dissociative state
- Pupils 6 mm and reactive with rotatory nystagmus
- Returned to baseline mental status after 8 hrs

Methoxetamine

- A ketamine congener available from on-line venders (eg, buy-methoxetamine.com)
- Routes: orally, insufflated, intramuscular, rectal, intravenous
- White, odorless powder (may be other forms)

Methoxetamine

- 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone
  - an arylcyclohexylamine congener of ketamine and phencyclidine
- Likely manufactured in China and shipped to UK for general distribution
- Suspect:
  - NMDA receptor blockade
  - dopamine reuptake inhibition

Summary

- Overall Signs and Symptoms
- Treatment

QUESTIONS?