Monoamine Agonists of Abuse:
Stimulants, Hallucinogens, and Club Drugs

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Dr. Charlie Reznikoff has no disclosures

Overview

- How to categorize intoxicants by action
  - What is a “club drug”?
- How are stimulants and hallucinogens related and different; what is an empathogen?
- How to manage acute intoxication on hallucinogens (and ketamine)
- What is GHB?

Categories and Examples of Addictive Drugs

- Sedatives
  - Benzos, Barbs, Alcohol, GHB

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- Dissociatives
  - Ketamine (arylcycloalkylamine), PCP (phencyclidine), DXM (dextromethorphan)

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  - LSD, Psilocybin, DMT, Mescaline

Which are “club drugs”?

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The problem with the term "Club Drug"

It defines a drug by where it is used and who uses it.

Define drugs of abuse like an Internist:

by their mechanism of action.

Categorize Addictive Drugs by Receptor Action

- Sedatives
  - Gaba agonists
- Dissociatives
  - NMDA antagonists
- Cannabinoids
  - CB1 agonists
- Opioids
  - Mu opioid receptor agonists
- Stimulants
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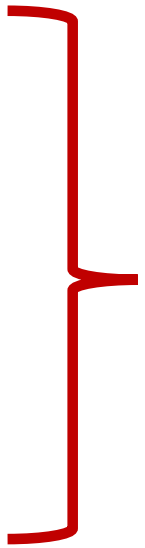


Each actives monoamine systems

Monoamine Spectrum

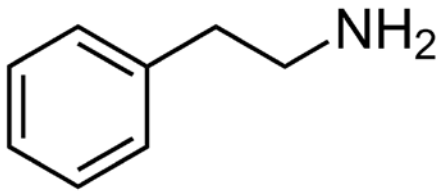
Stimulant:
Dopaminergic
Adrenergic
Addictive
CV/SZ/SI risks

Hallucinogen:
Serotonergic
Mild N.epi
Nonaddictive
Psychiatric risk

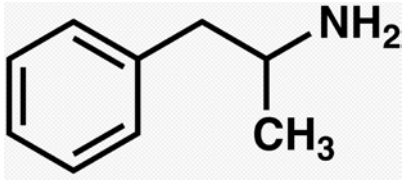
Empathogen:
Balanced effects
Addictive?
Harmful?

Monoamine Spectrum

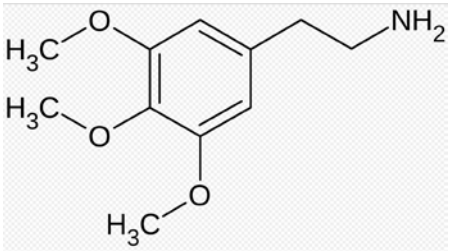
(*e.g.* phenethylamine)



Amphetamine

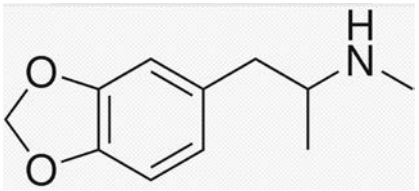


Mescaline

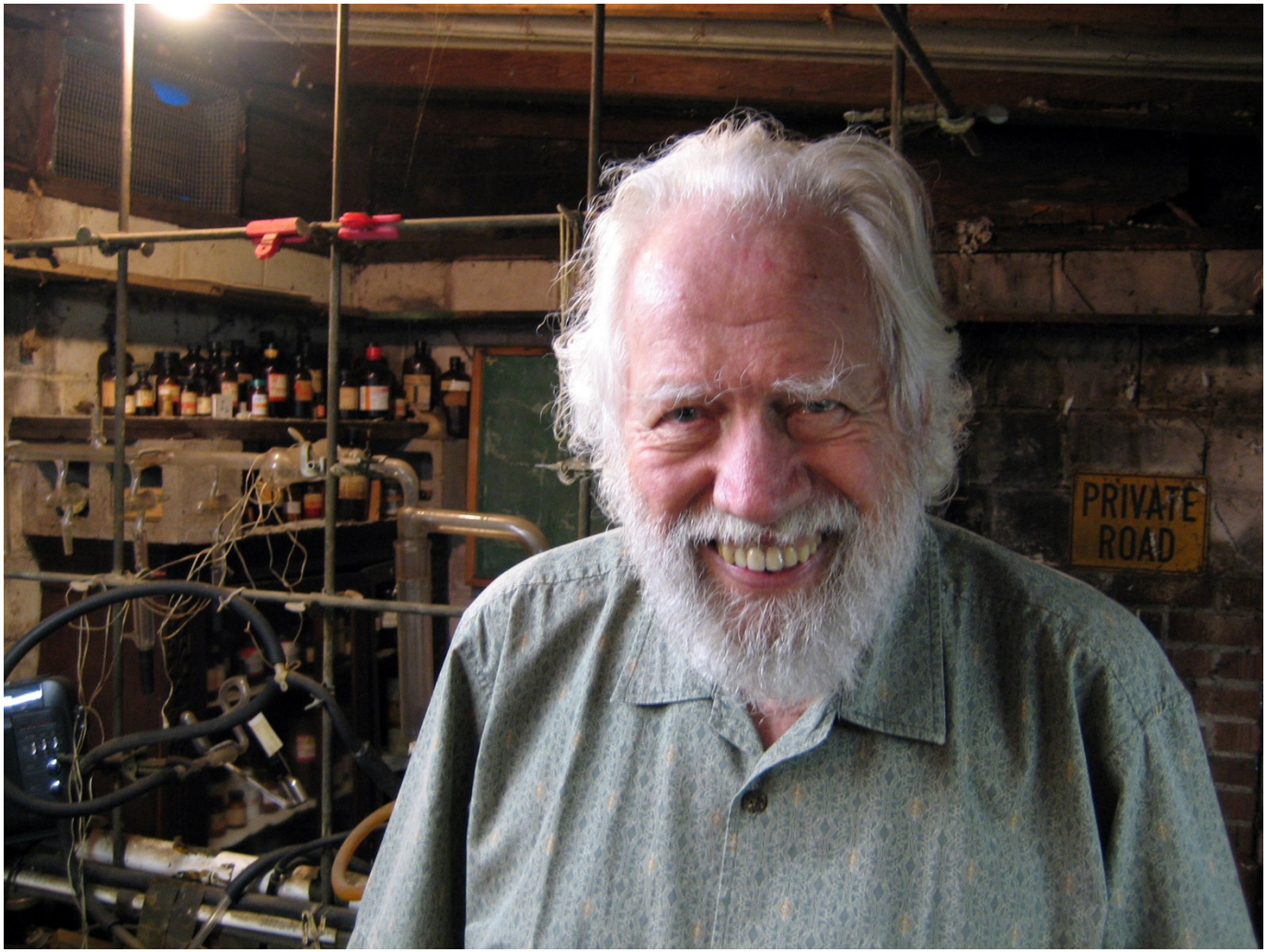


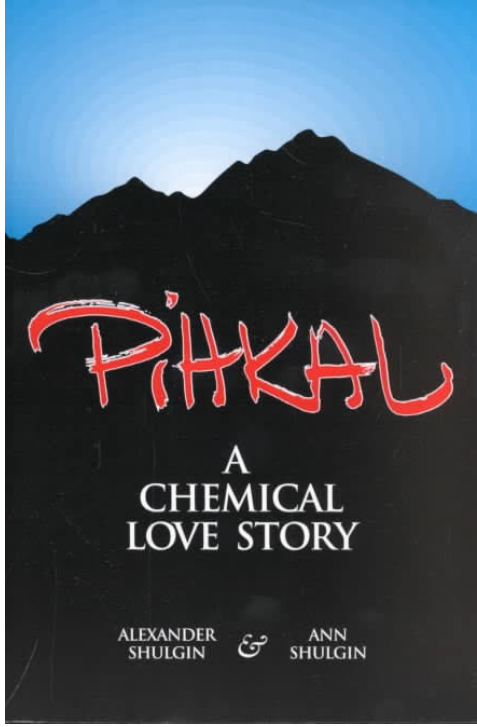
MDMA

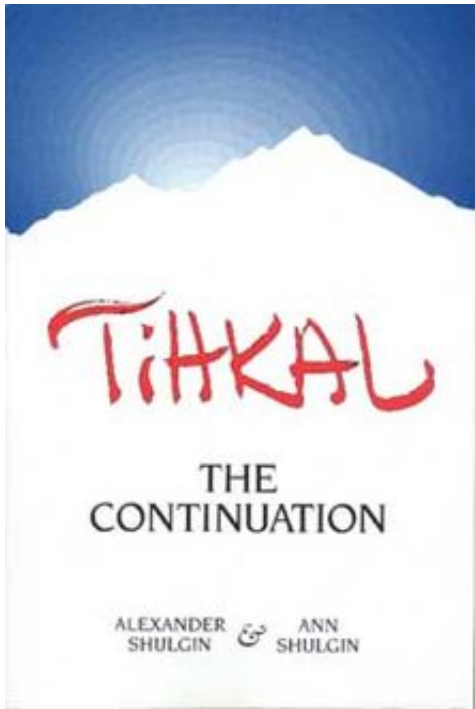
(3,4-methylenedioxymethamphetamine)



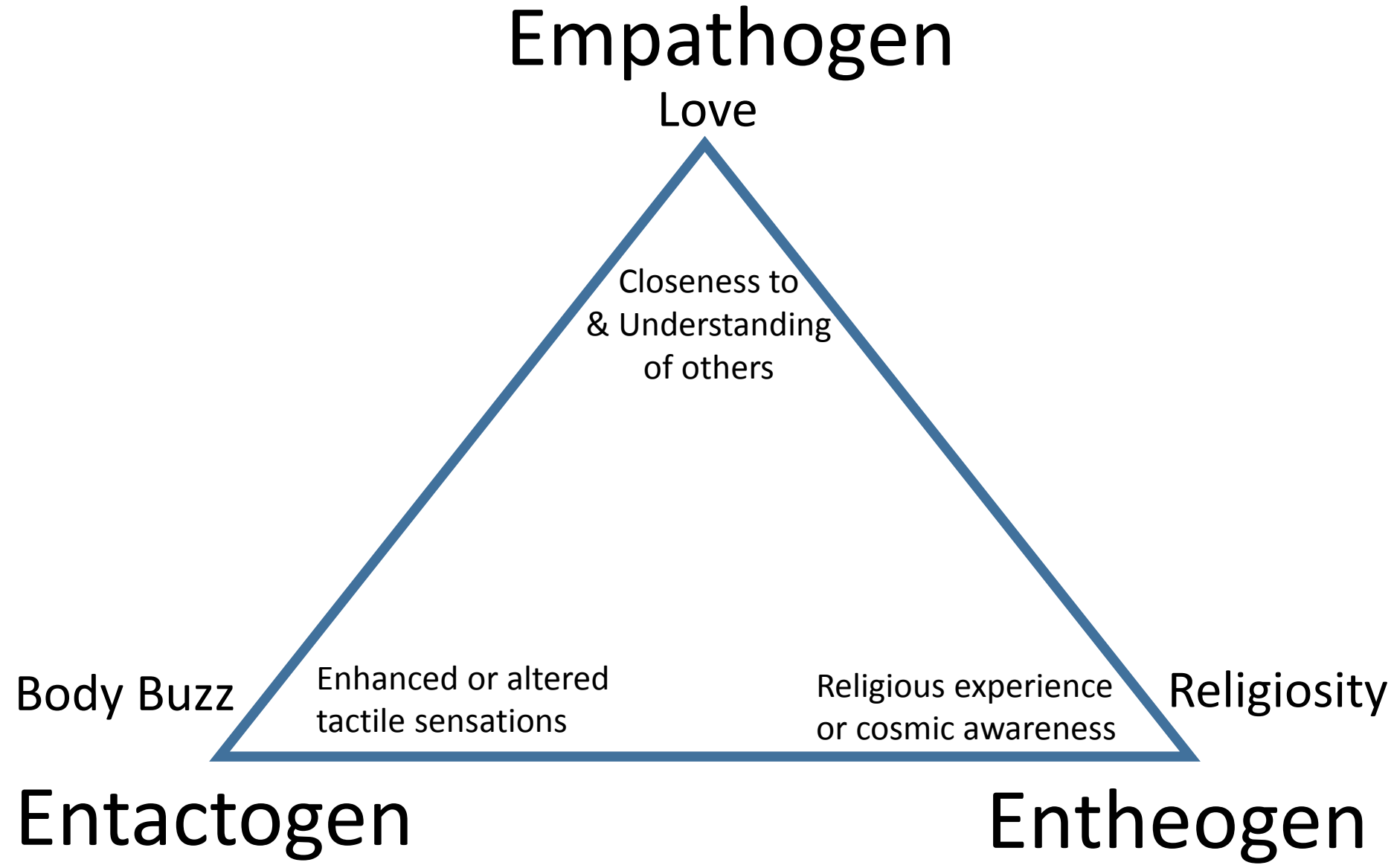
Sasha Shulgin invented 230 Phenethylamine and Tryptamine intoxicants







Middle Spectrum Monoamine Agonist Actions & Names



Cathinones: another base structure from which to make novel monoamine agonists

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Synthetic Cathinones ("Bath Salts")

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Revised February 2018

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- Health Effects of Specific Drugs
- Effects of Drug Use
- Prevention and Treatment
- Survey Data

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What are synthetic cathinones?

Synthetic cathinones, more commonly known as "bath salts," are human-made stimulants chemically related to cathinone, a substance found in the khat plant. Khat is a shrub grown in East Africa and southern Arabia, where some people chew its leaves for their mild stimulant effects. Human-made versions of cathinone can be much stronger than the natural product and, in some cases, very dangerous.[1]

In Name Only

Synthetic cathinone products marketed as "bath salts" should not be confused with

Synthetic cathinones usually take the form of a white or brown crystal-like powder and are sold in small plastic or foil packages labeled "not for human consumption." They can

Additional Drug Facts

NIH NIDA
NIDA FOR TEENS
THE SCIENCE BEHIND DRUG ABUSE

easyread.drugabuse.gov

Monoamine agonists

- Phenethylamines
  - Amphetamines, mescaline, Molly
- Cathinones
  - Khat, bath salts, mephedrone
- Tryptamines
  - DMT, psilocybin, foxy methoxy

U.S. · **Published** March 17, 2011 · **Last Update** November 17, 2014

Overdose Leaves Minnesota Teen Dead, 10 Hospitalized

By | **Associated Press**

BLAINE, Minnesota -- One teen died and 10 teenagers and young adults were hospitalized Thursday after an apparent mass overdose on a designer hallucinogen at a suburban Minneapolis home, authorities said.

Investigators said the state Bureau of Criminal Apprehension has identified the drug as 2C-E. It appeared the hallucinogen, which is sometimes known on the street as "Europa" and has no approved medical use, was legally ordered over the Internet for a spring break party, said Paul Sommer, a sheriff's office commander.

A 19-year-old man whose name was not immediately released died hours after officers responded to reports of an overdose at the house, investigators said. Officers found several people there who were ill shortly after midnight. Others who fled the house were later found to also be suffering the effects of an overdose.

Two 30-year-old Oregonian men attempted to purchase 2CE online from china and received Aniline instead. They had severe methemoglobinemia.

In Oklahoma two youth died after ordering 2CE and instead receiving “Bromo Dragonfly” a more potent substance

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OREGON PUBLIC HEALTH DIVISION • OREGON HEALTH AUTHORITY

YOU CAN'T ALWAYS GET WHAT YOU WANT: DESIGNER DRUGS, METHEMOGLOBINEMIA AND THE INTERNET

They thought they were going out for a good time. On an August evening in 2011, a 30-something Oregon man (patient A) collapsed in a fast food restaurant and was taken by ambulance to a local emergency room. He reported feeling lightheaded and nauseated 15 minutes after sharing a soft drink with his friend (patient B). He was cyanotic* and confused. His pulse oximetry reading was 86% despite 100% oxygen by nonrebreather mask.

Blood drawn for lab testing was chocolate-brown. Arterial blood gas: pH 7.43, pCO_2 35 mm Hg, pO_2 222 mm Hg, bicarbonate 23 mmol/L, SaO_2 96.7%. His methemoglobin level was 66.7% (normal, 1%–3%) and peaked six hours after ingestion at 79.6%.

Patient B, also a 30-something male, had shared the soft drink with patient A and was also deeply cyanotic in the ER. His methemoglobin level was 49.5% and peaked eight hours after ingestion at 74.4%.

The Oregon Poison Center (OPC) was consulted and advised treatment with methylene blue.[1] Methemoglobin is an oxidized form of hemoglobin, and a metabolite of methylene blue reduces methemoglobin to hemoglobin.

After several doses of methylene blue, both patients' methemoglobin levels began to fall. Alas, so did their hemoglobin levels. Patient B's hemoglobin fell from 14 g/dL to 10 g/dL, but he left AMA without further treatment. Patient A's fell from 14 to 6 g/dL; low haptoglobin and LDH>2000 suggested acute oxidant-stress-induced hemolysis. Glucose-6-phosphate dehydrogenase (G6PD) concentration was normal. Several blood transfusions and multiple plasmapheresis sessions later, his hemoglobin stabilized.

Chemicals of two classes cause methemoglobinemia: nitrates and aromatic amines. Local anesthetics like benzocaine, and sulfonamide antibiotics like dapsone, are common culprits. But the list is long and varied, and includes cyclophosphamide, chloroquine, and aniline dyes.[2]

PUBLIC HEALTH INVESTIGATION

Under interrogation by the ER physician, patients A and B confessed to having bought "2C-E," a psychoactive recreational chemical, from a Chinese web site. FDA tested the yellow liquid and found aniline — a commonly used industrial solvent — and no trace of 2C-E. When ingested, aniline causes methemoglobinemia that can lead to hemolytic anemia.[3]

The patients denied sharing the product with others. Nonetheless, out of concern that aniline might have been mislabeled and sold to others seeking 2C-E, investigators from the Oregon Public Health Division (OPHD) and OPC actively searched for unexplained cases of methemoglobinemia since January 2011. OPC queried poison center directors nationally and searched the National Poison Data System for reports of aniline poisoning. OPHD notified CDC and looked for cases using Oregon's Health Alert Network and CDC's Epidemic Information Exchange. No additional cases were identified.

DESIGNER DRUGS

Despite the passage in 1986 of the Controlled Substances Analogue Enforcement Act (CSAEA),[4] use of novel psychoactive recreational drugs has mushroomed† in the United States. To circumvent CSAEA, manufacturers design drugs that have structures distinct from regulated substances but that retain psychoactive effects. These products may evade surveillance and regulation through advertisement using code words like "research chemicals," "plant food," "pond cleaner," or "bath salts."

Designer drugs have seductive names like "Meow Meow," "K2 Spice," and "Vanilla Sky."[5] They are peddled domestically in smoke shops and gas stations, and through the Internet from domestic and international sources. They are ingested, smoked or inhaled. Designer drugs come in three popular flavors: synthetic amphetamines, synthetic cathinones, and synthetic cannabinoids.

Synthetic amphetamines include the "2C" family of phenethylamine derivatives, which produce psychedelic effects similar to those of methamphetamine. Drugs of this class, which include "ecstasy" — 3,4-methylenedioxymethamphetamine (MDMA) were designed and popularized by Berkeley chemist Andrew Shulgin, PhD.[6]

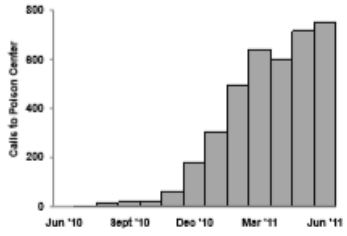
Synthetic cathinones are β-keto phenethylamine derivatives related to the psychoactive substance in *khat*, a narcotic leaf chewed in East Africa; they are sold as "plant food" or "bath salts."

Synthetic cannabinoids, which mimic the effects of δ-9-tetrahydrocannabinol, are sold as "herbal incense" products (e.g., "spice," "JWH").

THE INTERNET: NOT FOR AMATEURS

The availability of psychoactive chemicals and other hazardous ingestibles for order over the Internet poses a risk for obtaining products (either advertently or in-) that are inherently toxic or that have been adulterated (whether intentionally or un-). From 2010 to 2011, calls to poison centers about exposures to "bath salts" increased nationally from 303 to 6,072 (Figure).[5] In Minnesota last year, teens at a party overdosed on 2C-E: several suf-

Figure. "Bath salts": Exposure calls to poison control centers, United States, Jun 2010–Jun 2011



* Per the ED physician, "blue as a smurf"

† Not just psilocybin derivatives.

www.oregon.gov/oha/ph/DiseasesConditions/CommunicableDisease/CDSummaryNewsletter/Documents/2012/ohd6107.pdf

Methamphetamines used to make ersatz “pills”

All club drugs should be assumed to be methamphetamines

Emerging Trend: Methamphetamine in Pill Form

Methamphetamine in pill form has appeared in several states in 2018 and into 2019. Many incidents have involved pill forms that resemble MDMA tablets, while others have been counterfeit pharmaceuticals with methamphetamine present or as the primary substance. Several seizures in Illinois, New Jersey, Ohio, Virginia, and South Carolina have yielded supposed MDMA tablets containing methamphetamine.

Counterfeit Adderall pills containing methamphetamine were seized in Michigan in 2019. The pills were of the same color and markings as legitimate prescription Adderall, but contained methamphetamine, caffeine, and acetaminophen (see Figure 49). This may indicate that methamphetamine traffickers are targeting prescription stimulant users, similar to the counterfeit MDMA tablets, in order to gain access to a larger user market.

In April 2019, the Pinellas County, FL Forensic Lab shared information with DEA's Southeast Laboratory about a

Figure 49. Counterfeit Adderall Tablets Containing Methamphetamine seized in Michigan

Source: Michigan State Police

Imagine hundreds of novel synthetic drugs in each category

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- Dissociatives
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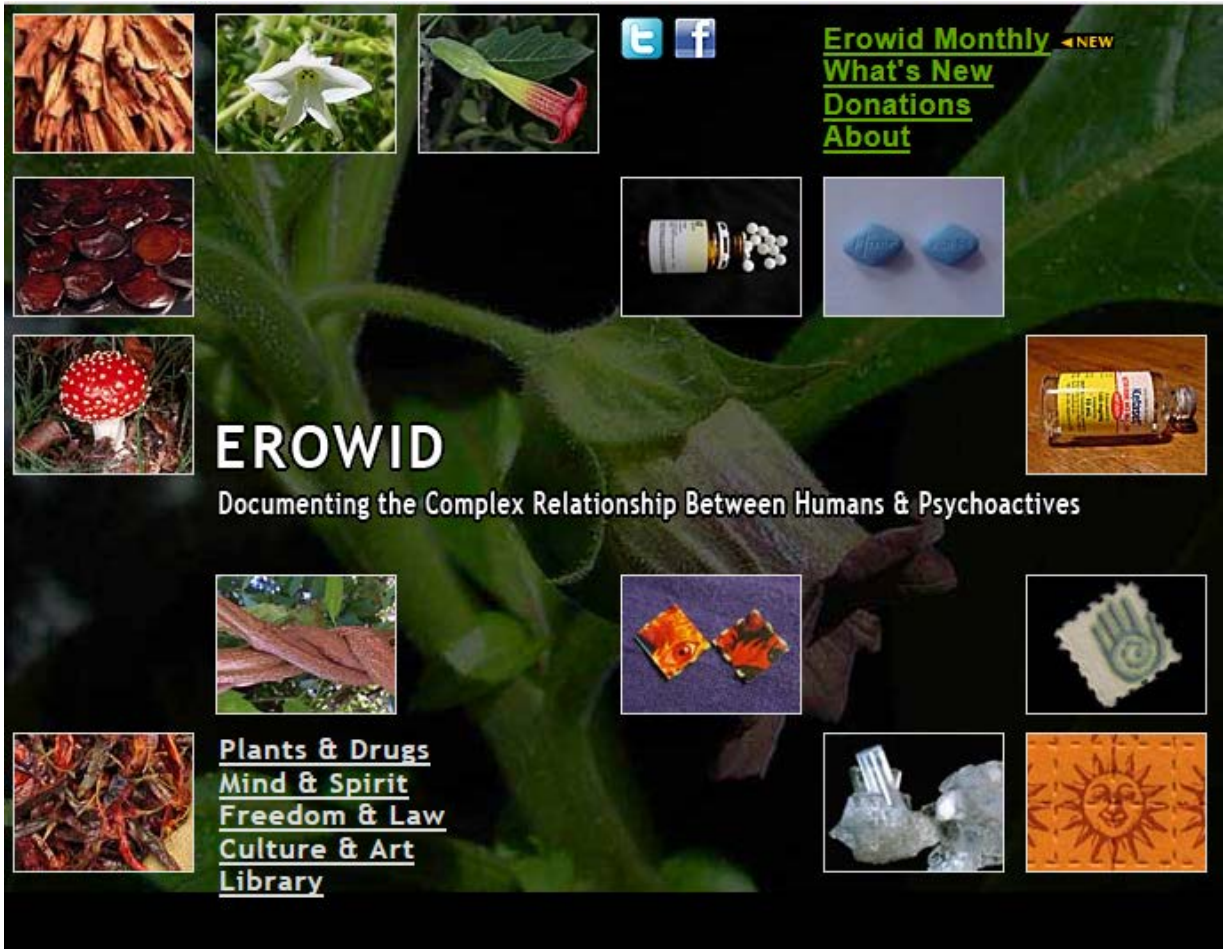
The future of addictive drugs is synthetic compounds cooked in clandestine labs.

Erowid: The Wikipedia of drugs

A good source for info about novel drugs.

I gave up learning the new drug names.

I know the classes of drugs and their presentation and syndromes.



https://www.erowid.org/

How are dissociatives (ketamine) different from hallucinogens (LSD)?

- Ketamine (NMDA antagonist) creates a dissociative state– the cognition and perception are dissociated from each other
  - Users may lack insight and become frightened
  - Offering reassurance interpreted as more confusing and threatening perceptual input
  - Keep stimulus low (light, noise, vitals) & fingers crossed
- LSD (serotonin agonist) alters perceptual experience without dissociating it from cognition
  - Retained insight their experience is the result of LSD
  - Healthcare workers should offer calm reassurance
  - Those with underlying psychosis may become unstable

What is GHB or “G”?

- Gaba agonist (like benzos, barbs)
- Sedative properties: amnesia, anxiolysis, disinhibition, muscle relaxation, ataxia, soporific
- FDA approved (Xyrem) for narcolepsy
- Many illicit uses:
  - Come down from stimulant use
  - Properly dosed, G causes mellowing
  - Date rape drug (colorless/flavorless undetectable by tox)
  - Stimulates IGF- body builders use for anabolic effects
- Classic overdose:

  Young individual presents unarousable, intubated, and 24 hours later abruptly awakes and self-extubates

Summary

- Stimulants, empathogens and hallucinogens exist on a spectrum of activity and effects
- Phenethylamines, tryptamines, and cathinones can be chemically modified into many novel intoxicants
- Many poorly characterized agents on this spectrum
- Purity concerns, unknown actions of designer drugs
- Other club drugs (G, K) should be understood by their receptor action

Thank you!
Questions?