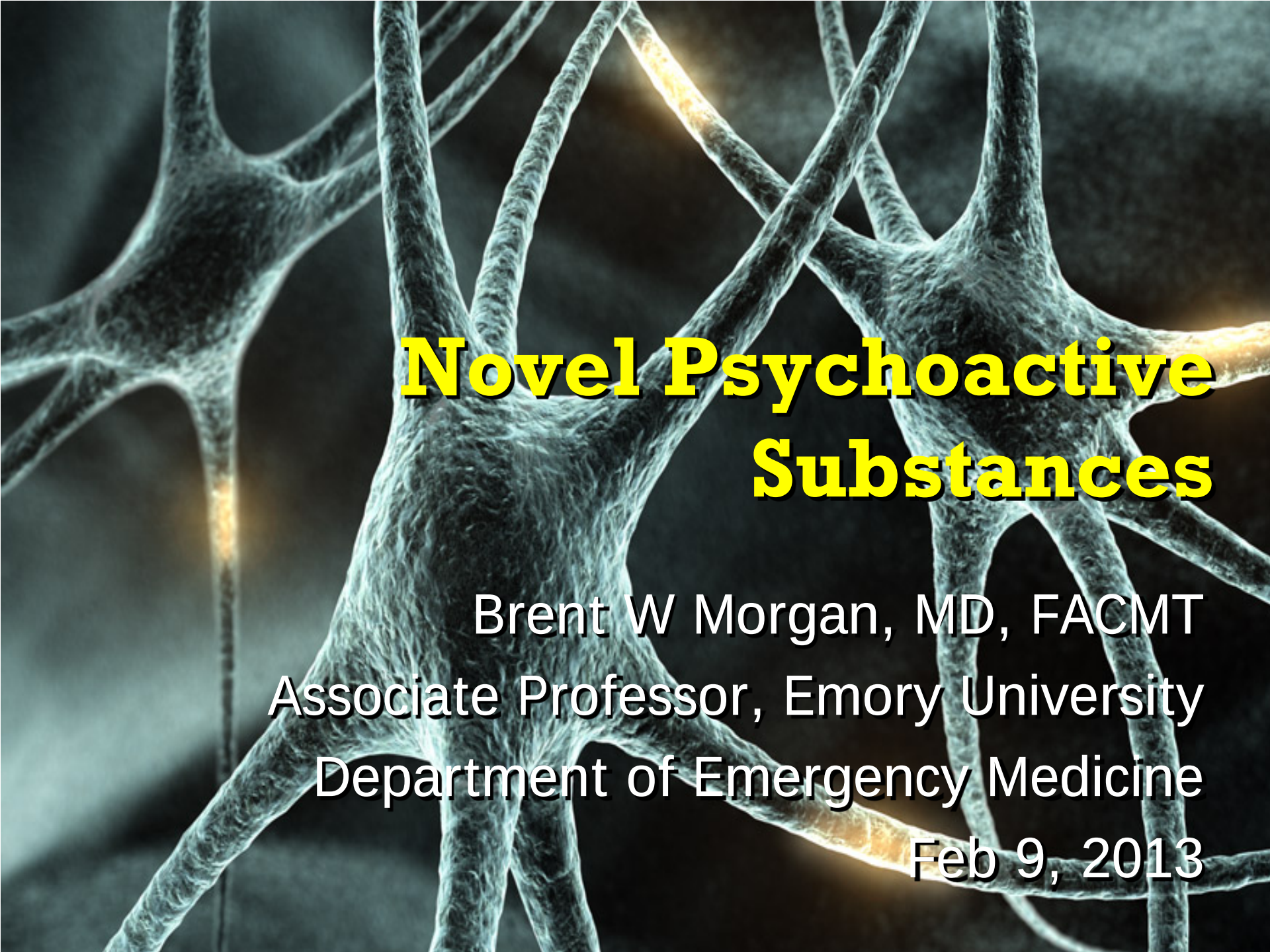


Novel Psychoactive Substances

Brent W Morgan, MD, FACMT
Associate Professor, Emory University
Department of Emergency Medicine

Feb 9, 2013

Disclosure

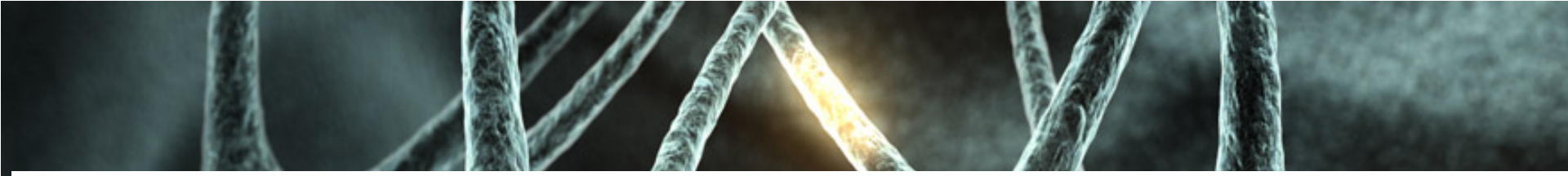
- I have no financial relationships with any commercial interest related to the content of this presentation
- Legal review
- ECN reviews

Objectives

- 1. Cite the novel psychoactive substances and describe how to recognize the use of these drugs in clinical practice.
- 2. Describe the common symptoms of novel psychoactive substances and complications that are encountered.
- 3. Describe the current management of an acute toxic event suspected or known to be due to novel psychoactive substances.

Novel Psychoactive Substances

- Unprecedented Proliferation
- Europe: 41 new psychoactive substances identified in 2010
- Majority: Synthetic
  - Cannabinoids
  - Amphetamine like stimulants
  - Opioid-like substances
  - Halluncinogens

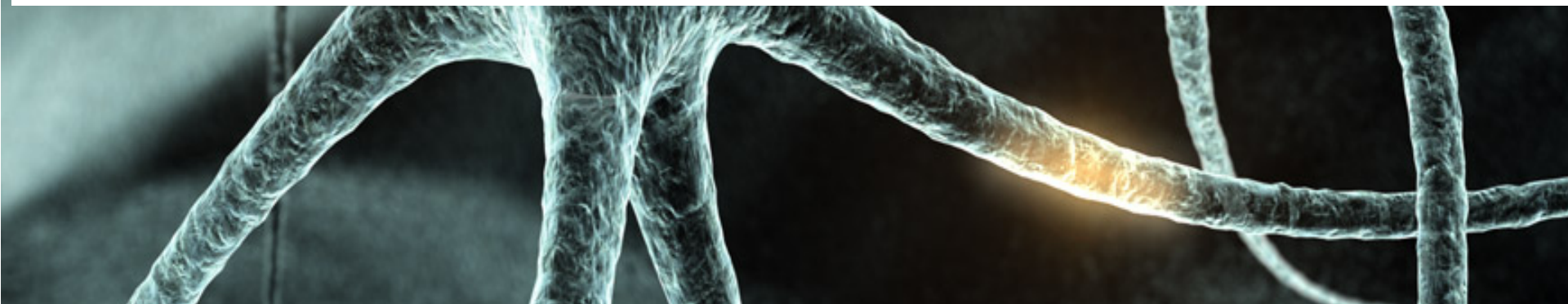


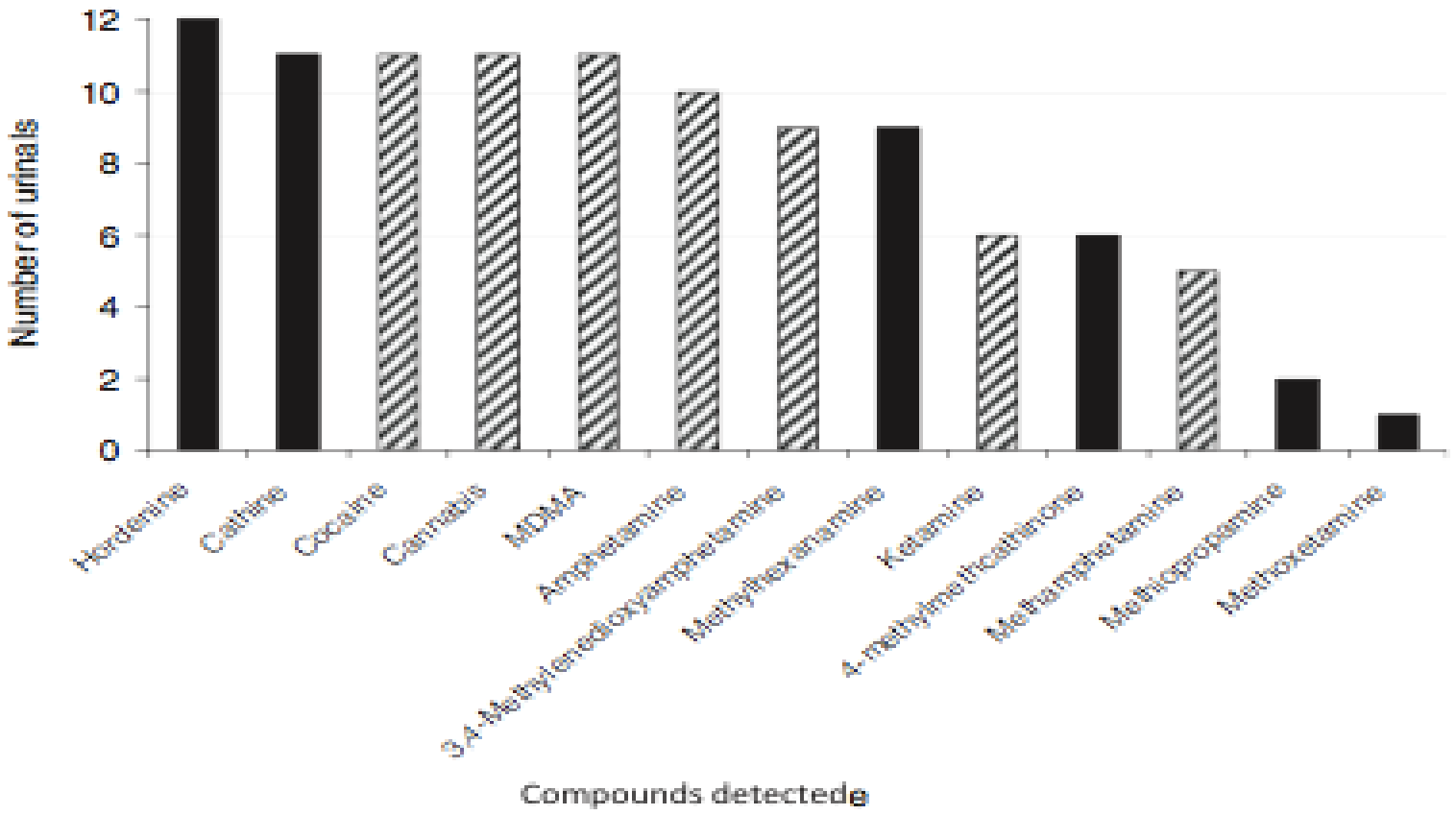
Q J Med 2013; **106**:147–152
doi:10.1093/qjmed/hcs219 Advance Access Publication 22 November 2012

Analysis of anonymous pooled urine from portable urinals in central London confirms the significant use of novel psychoactive substances

J.R.H. ARCHER[1], P.I. DARGAN[1,2], S. HUDSON[3] and D.M. WOOD[1,2]

From the [1]Clinical Toxicology, Guy's and St Thomas' NHS Foundation Trust and King's Health Partners, Westminster Bridge Road, London, SE1 7EH, [2]King's College London, Strand, London, WC2R 2LS and [3]HfL Sport Science, LGC Health Science, Newmarket Road, London, CB7 5WW, UK




Number of urinals
12
10
8
6
4
2
0
Hordenaine
Caffeine
Cocaine
Cannabis
MDMA
Amphetamine
3,4-Methylenedioxyamphetamine
Methylhexanamine
Ketamine
4-methylmethcathinone
Methamphetamine
Methiopropamine
Methoxetamine
Compounds detected

Patient Presentation

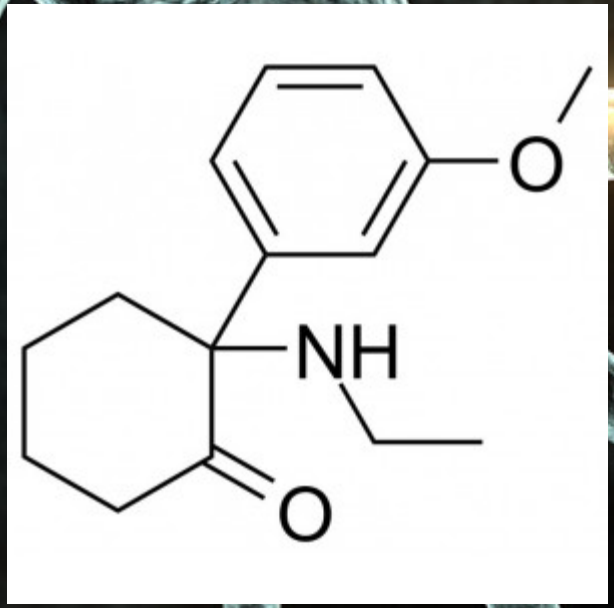
- 1/18/13 0039
- Oconee Regional Medical Center
- 19 yom
- “300 mg MXE”
- Pt is unresponsive, no gag reflex pinpoint pupils.
- Pt was given 2mg of narcan-no response.
- Seizure Activity, pt intubated.
- EKG=wnl. Skin warm and dry.
- Vitals: P-89, BP-143/87, RR-14 O_2 sat 100%
- ASA/APA neg, Ethanol 128, CMP WNL

Outcome

- Extubated at 1700, recovered
- HR 63 117/73 afebrile FiO2 45%,
- Neurology eval for new onset seizure,
- Agreed to go to outpatient rehab

Methoxetamine (MXE)

- **3-MeO-2-Oxo-PCE**
- Ketamine derivative
- Rational drug design: its N-ethyl group was chosen to increase potency.
- Ketamine is a noncompetitive NMDA receptor antagonist
- Also binds to opioid mu and sigma receptors at high doses.



Methoxetamine has a 3-methoxy group instead of 2-chloro group on the phenyl ring of ketamine and an n-ethyl group instead of the n-methyl group on the amine portion of the molecule

Methoxetamine

- First identified in November 2010.
- July 2011,
  - Sold on 58 websites
  - 145–195 euros for 10 grams.
- Sold as a stand alone fish tank cleaner and can be found over-the-counter in many stores across the UK and US

- Methoxetamine's effects are described by some as similar to ketamine or high-dose DXM, while others report not finding it similar to those substances. A number of accounts describe compulsive redosing and unintentional consumption of more than was initially planned.

Ketamine & Methoxetamine

- In overdose, the most common effects are sedation and respiratory depression.
- Tachycardia, HTN palpitations and chest pain.
- Nausea, vomiting, diarrhea
- Nervous System
- Seizures (rare)
- Respiratory Arrest
- Perceptual distortions, dissociative/catatonic states,hallucinations, paranoia, agitation, memory loss, slurred speech, cerebellum toxicity and rotatory nystagmus.

Cannabinoids

- **Cannabinoids** are a class of diverse chemical that activate cannabinoids receptors.
- Endocannabinoids
- Phytocannabinoids
- Synthetic cannabinoids

Synthetic Cannabinoids

- Legit research seeking cannabinoid receptor agonist with analgesic and anti-inflammatory effects without the psychotropic effects
- 7 major groups: Hundreds developed
- Mixed with variety of herbs

Some Brand Names

- Spice, K2
- Chill zone cherry
- Chaos mint
- Tai fun blackberry
- Smoke
- Clover Spring
- Aztec thunder
- Exclusive Sensation
- Zen
- Sensation vanilla
- Natures organic truskawka (strawberry)

Synthetic Cannabinoids

- CB_1 & CB_2 receptor agonist
- Higher binding affinity than Δ9-THC
- Full agonists

Clinical Effects

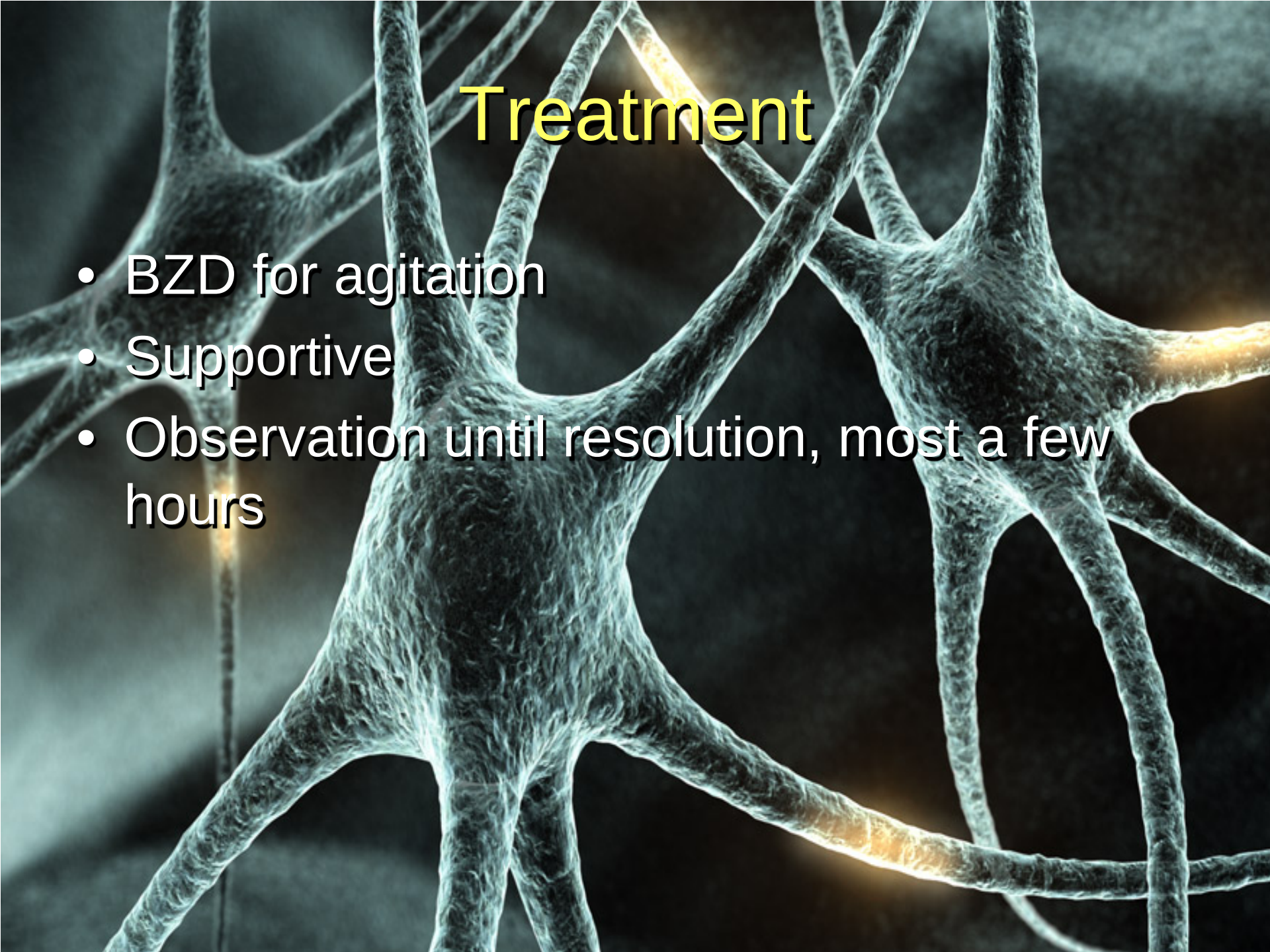
- Anxiety
- Paranoia
- Agitation
- Delusions
- Tachycardia
- Diaphoresis
- Conjunctival Injection
- Xerostomia
- Cycling Vomiting
- Pulmonary Infiltrates
- AKI
- Possible Withdrawal symptoms

Detection

- Do not cross react with current Δ9-THC immunoassays
- Commercial assays
- Can be detected with GC/MS or LC/MS
- Persistence Unknown

Legality

- In the US, as of March 1, 2011, five cannabinoids, JWH-018, JWH-073, JWH-200,CP-47,497, Cannabicycldhexanol were made Schedule I
- **Synthetic Drug Abuse Prevention Act of 2012**



Treatment

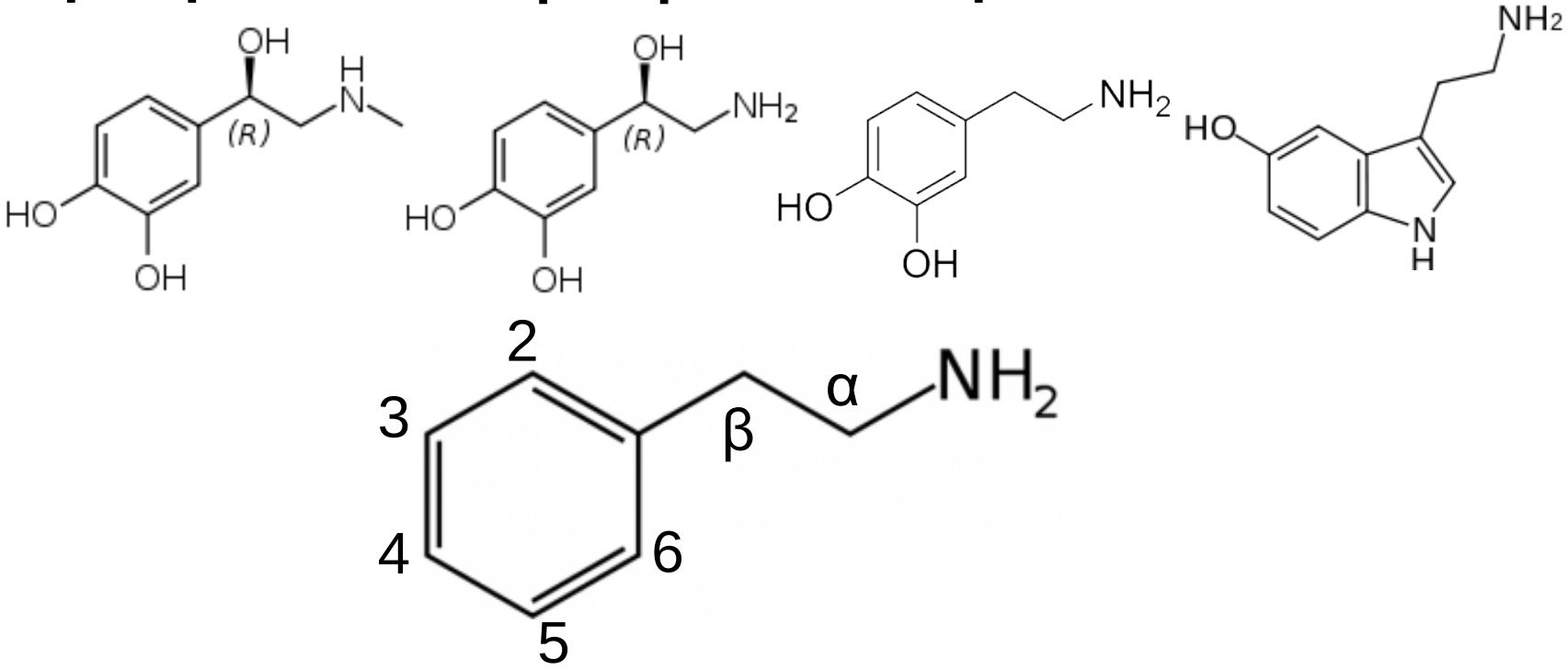
- BZD for agitation
- Supportive
- Observation until resolution, most a few hours

Phenethylamines

- 1: A naturally occurring compound found in both the animal and plant kingdoms. It is an endogenous component of the human brain.
- 2: Any of a series of compounds containing the phenethylamine skeleton, and modified by chemical constituents at appropriate positions in the molecule.

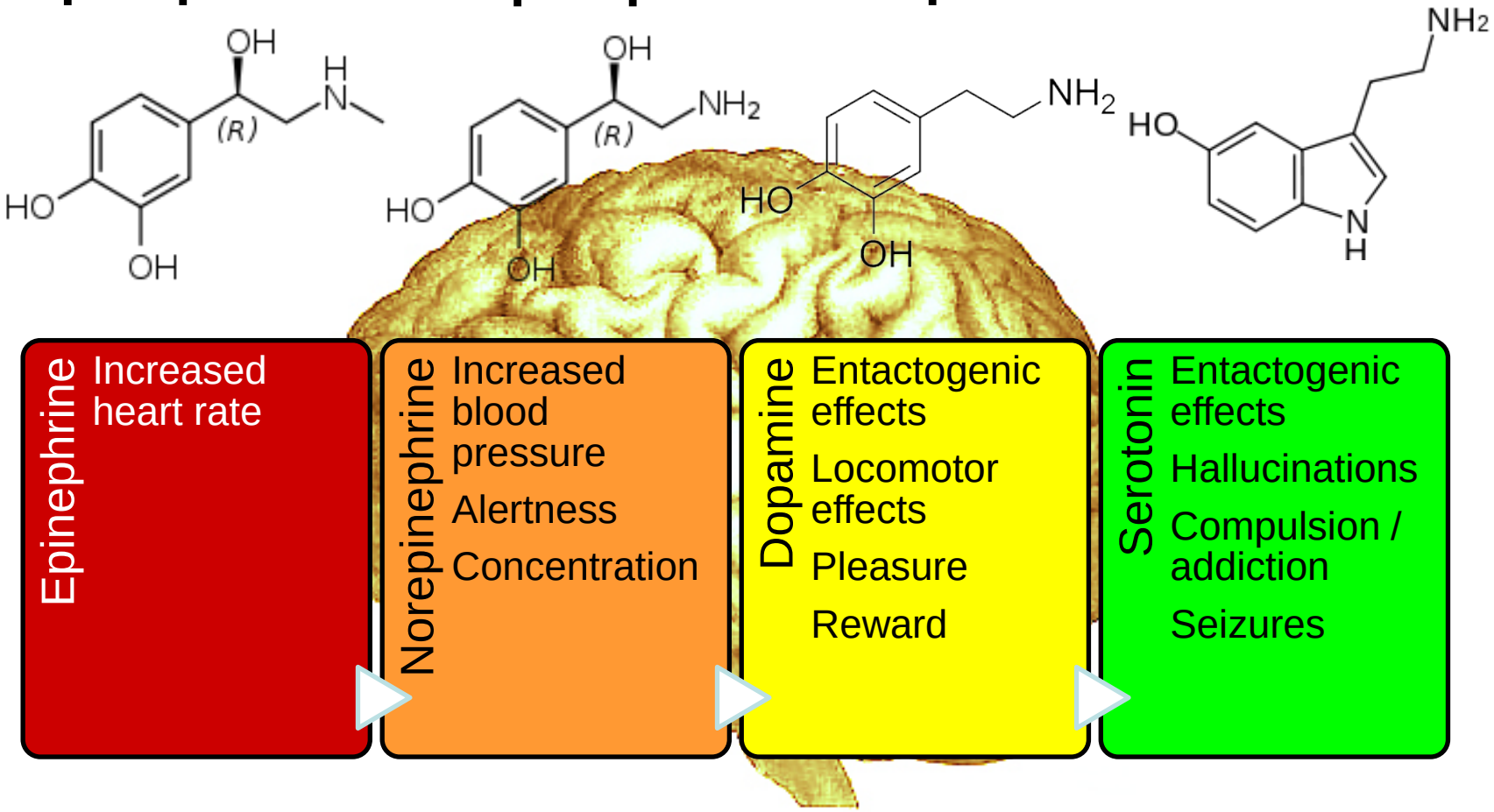
Phenethylamines (2Cs)

Epinephrine **Norepinephrine** **Dopamine** **Serotonin**



Brain Neurotransmitters

Epinephrine **Norepinephrine** **Dopamine** **Serotonin**

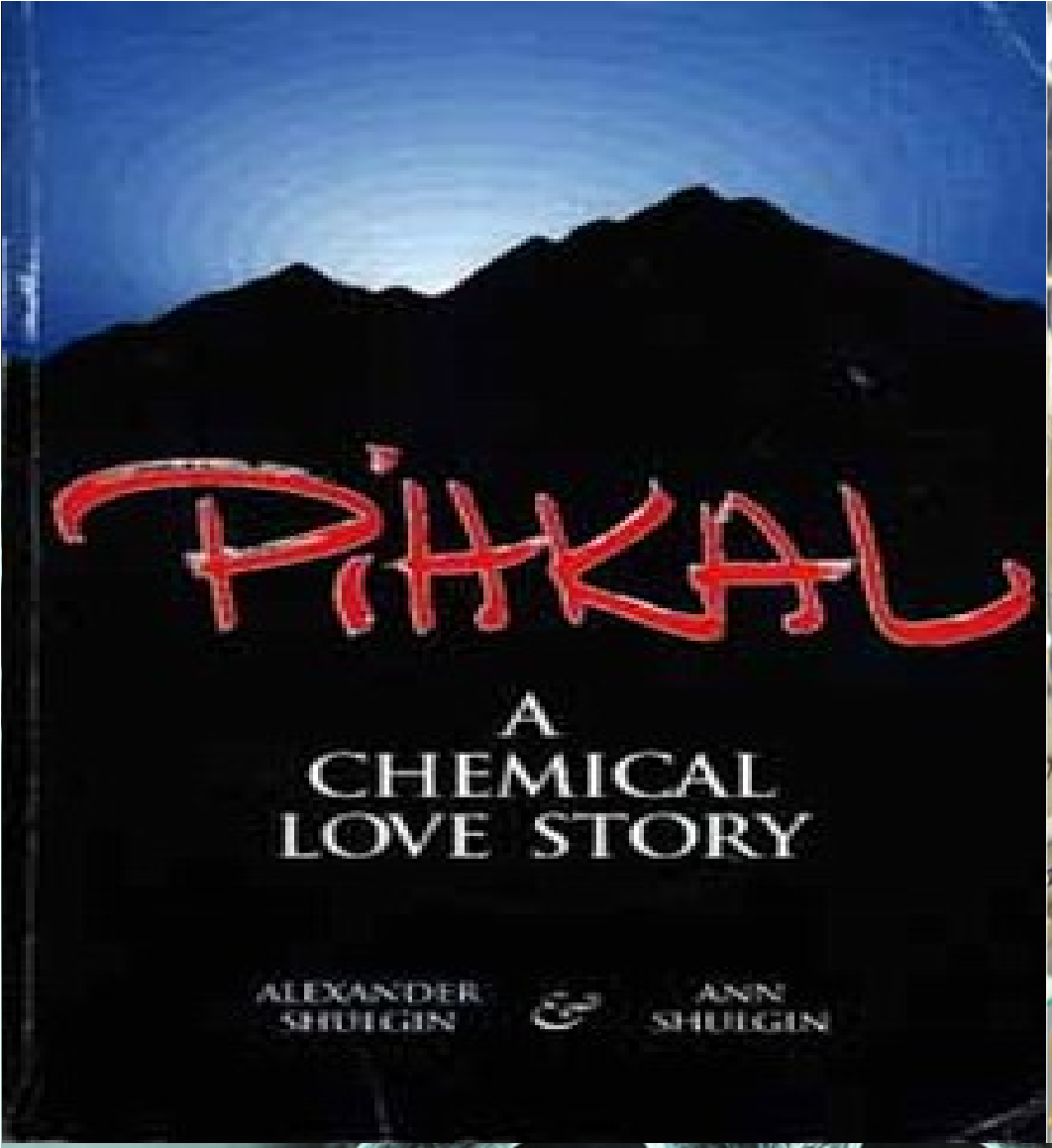


Epinephrine
- Increased heart rate

Norepinephrine
- Increased blood pressure
- Alertness
- Concentration

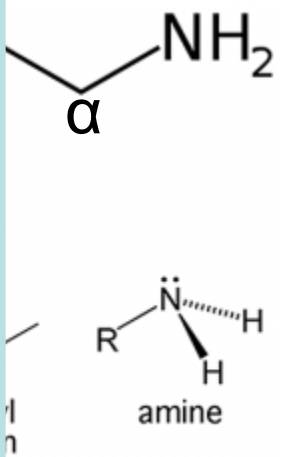
Dopamine
- Entactogenic effects
- Locomotor effects
- Pleasure
- Reward

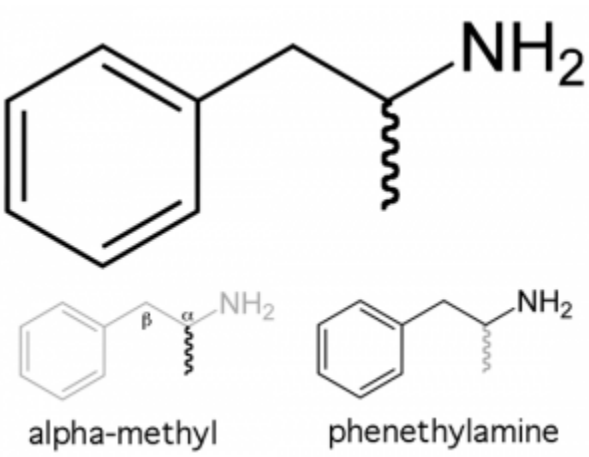
Serotonin
- Entactogenic effects
- Hallucinations
- Compulsion / addiction
- Seizures



Phenethylamines I Have Known And Loved

α-Methylation



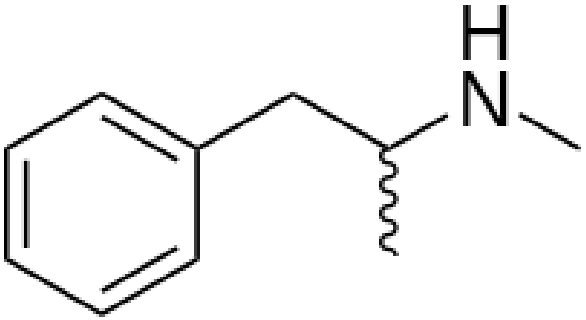


Adding alkyl chains at the α position:

1. Increases lipophilicity (BBB penetration)
2. Inhibits MAO breakdown
3. Potentiates hallucinogenic properties

Amphetamines

Methamphetamine

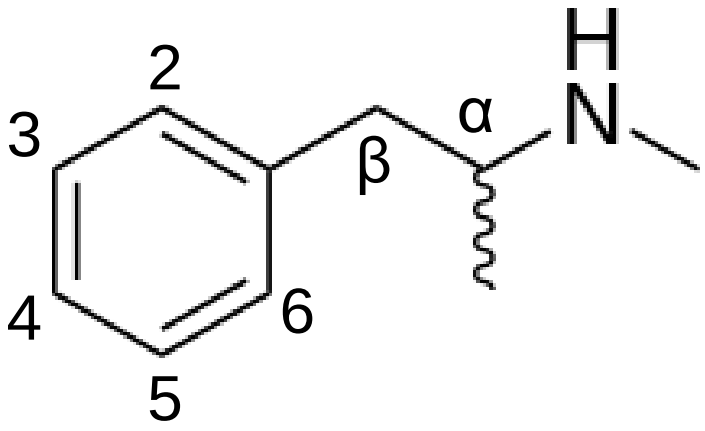


Adding n-substitutions:

1. Decreases sympathomimetic effects
2. Increases lipophilicity
3. Increases duration of action


5-HT2A

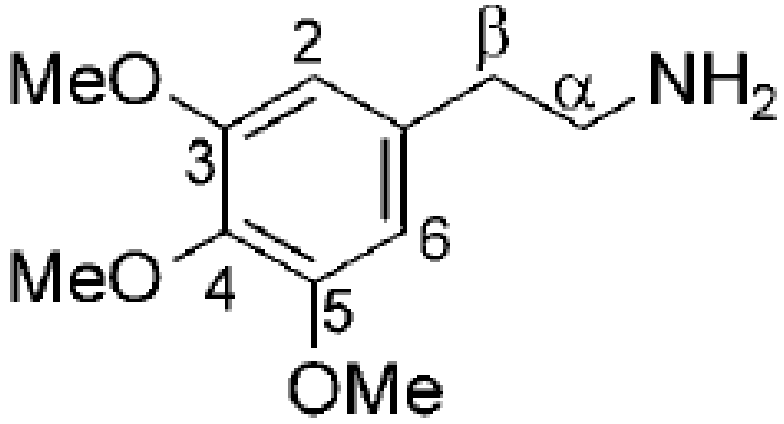
Phenethylamines



Phenyl ring substitutions:

1. Halogenating position 4 = ↑ hallucinogenic properties
2. Substitutions at 2,4,5 maximize 5-HT_{2A} effects
3. Methyoxy substitutions ↑ serotonergic effects

Phenethylamines



Phenyl ring substitutions:

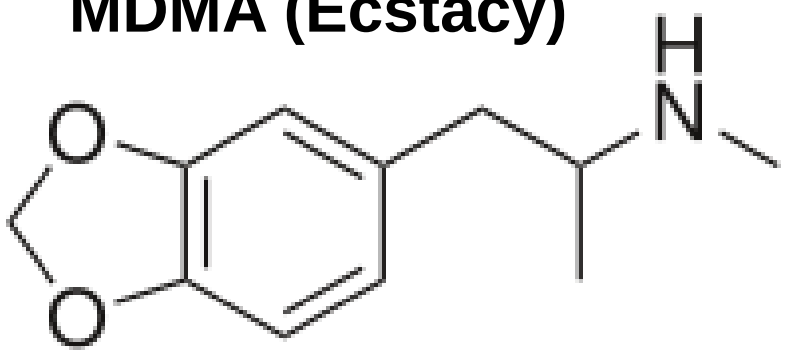
1. Halogenating position 4 = ↑ hallucinogenic properties
2. Substitutions at 2,4,5 maximize 5-HT_{2A} effects
3. Methyoxy substitutions ↑ serotonergic effects
4. Mescaline or 3,4,5-trimethoxyphenethylamine

Phenethylamines

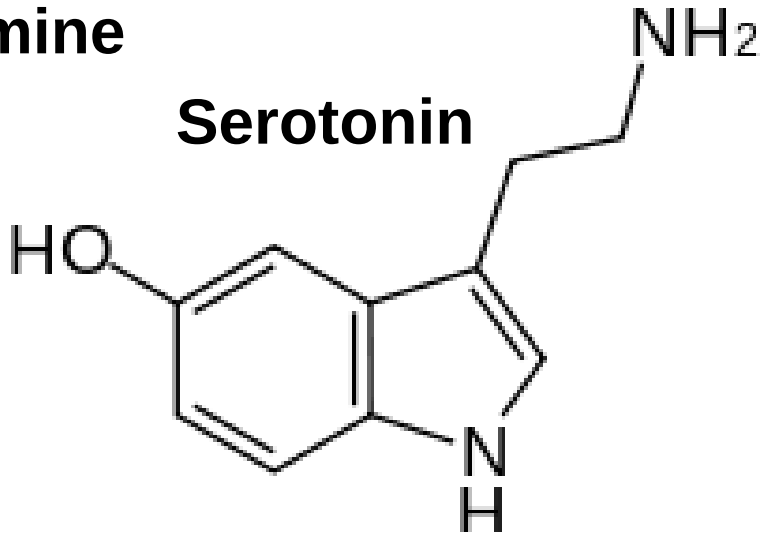
Entactogens

Methylenedioxymethamphetamine

MDMA (Ecstacy)



Serotonin



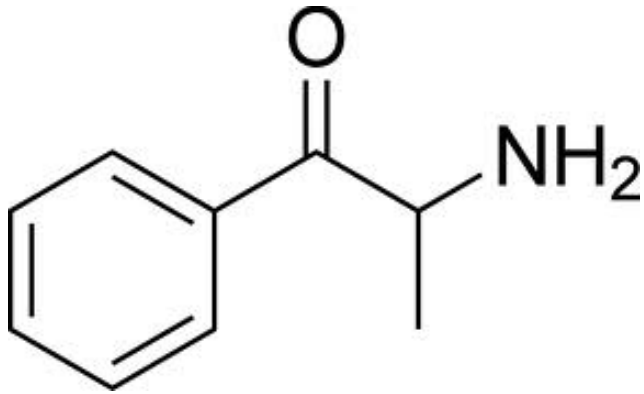
Methoxy substitutions:

1. Very potent serotonergic properties
2. Intense entactogenic effects

Cathinones

http://curiso.com/artist-takes-every-drug-known-to-man-draws-self-portraits-after-each-use/

Cathinones

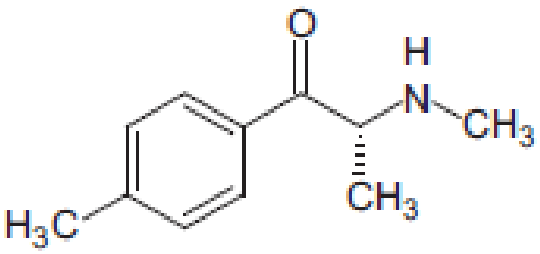


Cathinone

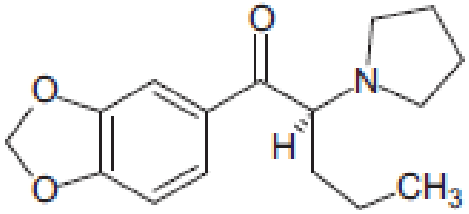
Bath salts are not made from Khat.

Synthetic Cathinones

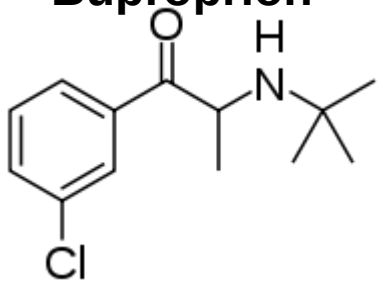
Mephedrone



MDPV

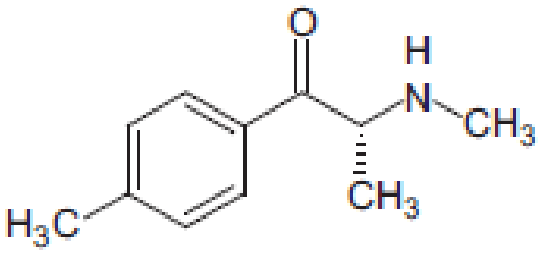


Buproprion

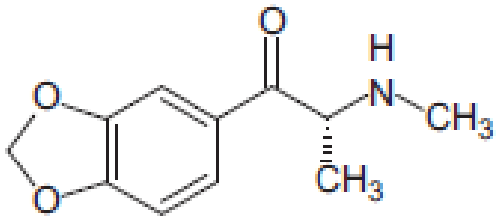


Synthetic Cathinones

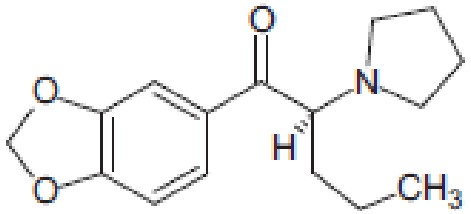
Mephedrone

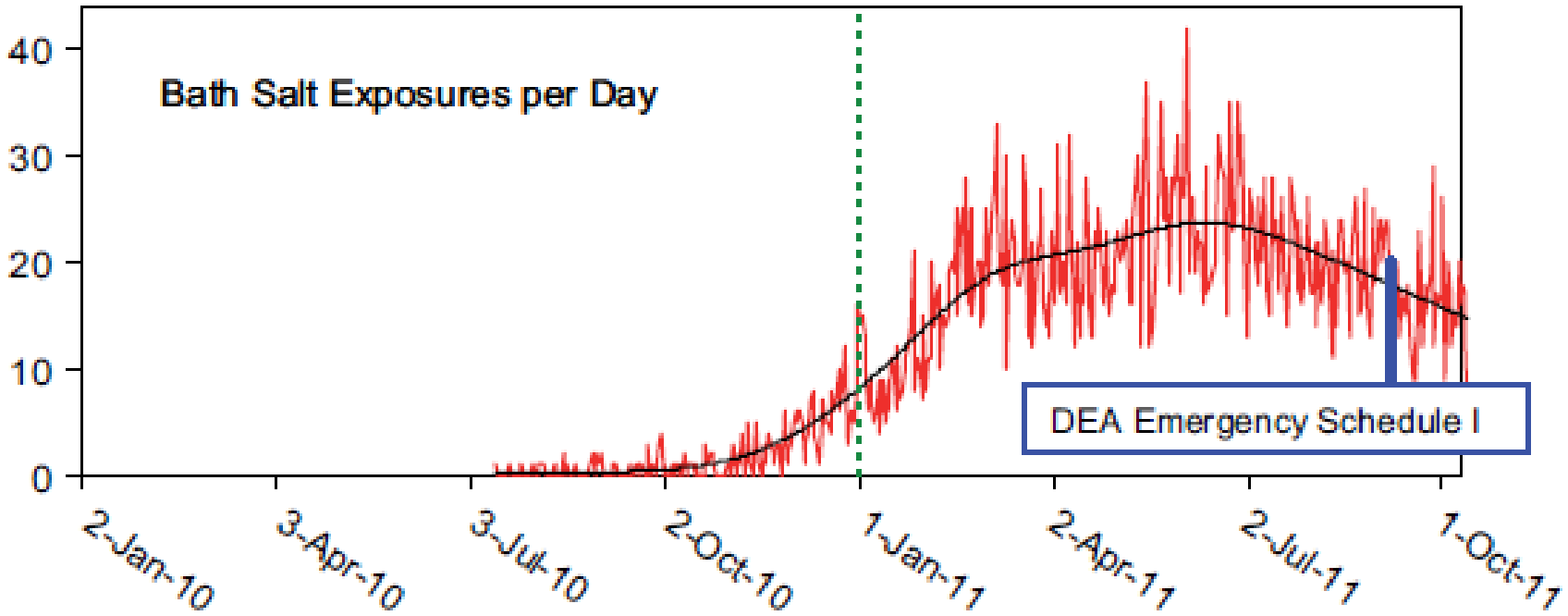


Methylone

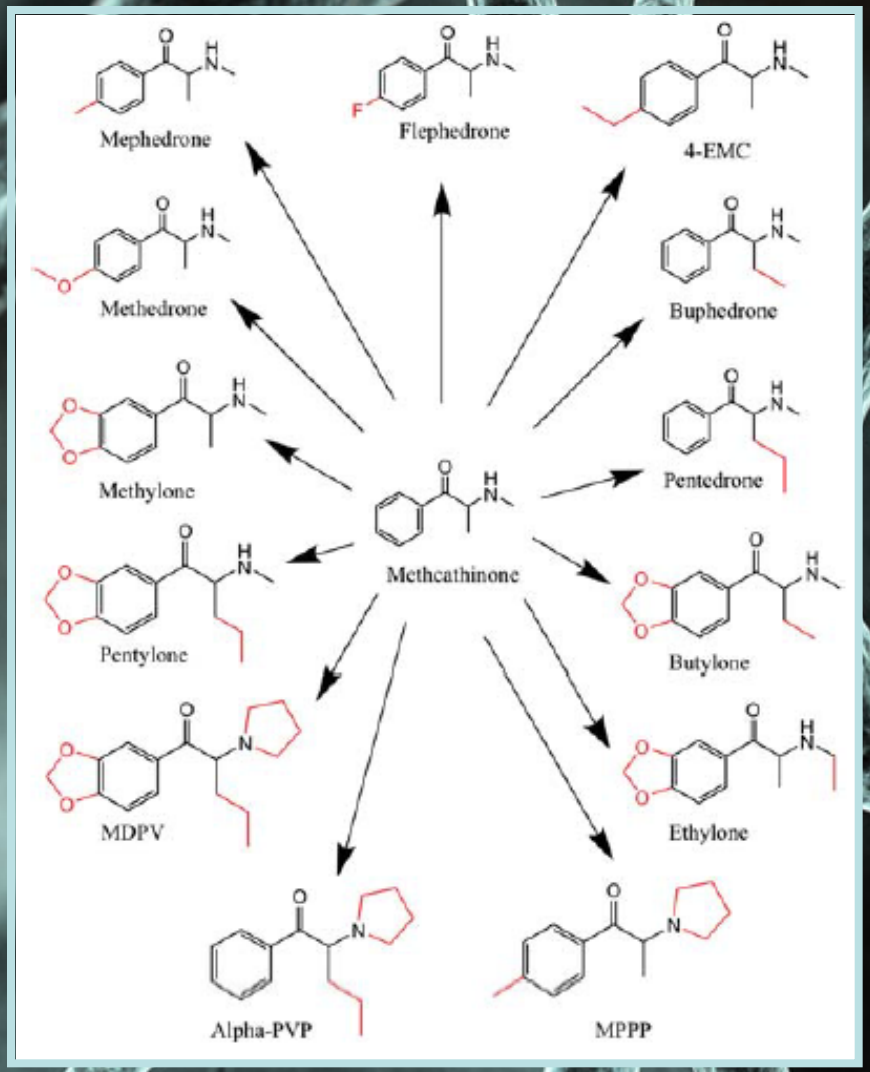


MDPV





Synthetic Cathinones



Synthetic Cathinones

ABSTRACTS

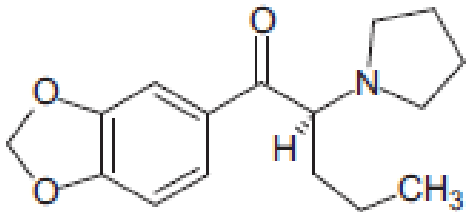
2012 Annual Meeting of the North American Congress of Clinical Toxicology (NACCT) October 1–6, 2012 Las Vegas, NV, USA

1. Comprehensive drug analysis of "bath salts" purchased in the United States

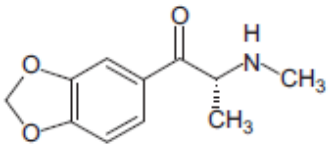
Aaron Schneir[2], Binh T. Ly[2], Craig Smollin[1], Stephen Thornton[2], Michael Darracq[2], Cyrus Rangan[3], Steve R. Offerman[4], Rais Vohra[5], Christian Tomaszewski[2], Roy R. Gerona[1]

[1]*University of California, San Francisco, San Francisco CA USA;* [2]*UCSD Medical Center;* [3]*Los Angeles County Departmen of Health, CA USA;* [4]*Kaiser Permanente South Sacramento;* [5]*UCSF Fresno*

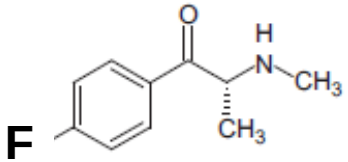
MDPV



Methylone



Flephedrone



What's in Bath Salts:

1. 9 different compounds
2. 5 mg to > 1 g

Synthetic Cathinones

Route	Onset	Duration
Insufflation	10-20 min	1-2 hrs
Ingestion	15-45 min	2-4 hrs
Intravenous	10-15 min	30 min

Synthetic Cathinones

Clinical Effects:

- Sympathomimetic toxidrome
  - Tachycardia, hypertension, hyperthermia
- Agitation (82%), Violent-combative (57%), Hallucinations (40%)
  - one death from self-injury
- Seizures
  - One death from status epilepticus
- Hyponatremia (118-125 mEq/L)
  - Two deaths from cerebral edema

Synthetic Cathinones

285. Fatalities following parenteral injection of MDPV sold as "hookah cleaner"

Ronald I. Kirschner[2], Henry C. Nipper[1], Patricia K. Studts[3], Kathy L. Jacobitz[4]

[1]*Creighton University Medical Center, Omaha NE USA;* [2]*University of Nebraska Medical Center, Omaha NE USA;* [3]*Creighton Medical Laboratories, Omaha NE USA;* [4]*Nebraska Regional Poison Center, Omaha NE USA*

288. Psychosis from a bath salt product containing flephedrone and MDPV with serum, urine, and product quantification

Stephen L. Thornton[1], Roy R. Gerona[2], Christian A. Tomaszewski[1]

[1]*University of California – San Diego, San Diego CA USA;* [2]*University of California – San Francisco, San Francisco CA USA*

290. Clinical presentations and medical complications after exposure to substances labeled as "bath salts": A ToxIC preliminary report

Blake A. Froberg[4], Michael Levine[1], Kristin M. Engebretsen[2], Nathanael J. McKeown[5], Mark Kostic[6], Christopher D. Rosenbaum[3], Daniel E. Rusyniak[4]

Tachycardia (70%)
Hypertension (35%)
Hyperthermia (15%)
Acidemia (37.5%)
Hypokalemia (27.5%)

293. Comparison of synthetic cathinone and methylenedioxymethamphetamine (MDMA) exposures

Mathias B. Forrester[1], Liza Leung[2], Kurt Kleinschmidt[2]

[1]*Department of State Health Services, Austin TX USA;* [2]*University of Texas Southwestern, Dallas TX USA*

Table 1. Results for abstract 293.

	Synthetic cathinones (%)	MDMA (%)	RR, 95% CI
Tachycardia	45.5	27.2	1.67, 1.3–2.1
Agitation	37.3	18.1	2.06, 1.53–2.77
Hypertension	19.2	9.4	2.03, 1.30–3.16
Hallucinations	17.8	9.4	1.88, 1.20–2.95
Confusion	12.3	3.0	4.10, 1.93–8.62
Vomiting	9.4	4.1	2.30, 1.18–4.48
Chest pain	7.5	7.9	1.05, 0.59–1.87
Dizziness	6.8	2.7	2.48, 1.1–5.6
Dyspnea	6.4	2.7	2.34, 1.03–5.34
Treatments			
IV fluids	50.0	34.0	1.47, 1.2–1.8
Benzodiazepines	38.4	21.5	1.78, 1.35–2.34
Oxygen	9.6	4.2	2.31, 1.17–4.54
Other sedation	6.8	1.9	3.63, 1.38–9.53

Testing for Cathinones

- Find Forensic Testing
- Postmortem Toxicology
- DRE Toxicology
- Synthetic Cannabinoids Testing (K2, Spice)
- Designer Stimulants Testing ("Bath Salts")
- Crime Lab
- Expert Services
- Backlog Reduction

Designer Stimulants Testing MDPV, Mephedrone and Methylone ("Bath Salts")

Routine drug tests do not detect the synthetic stimulants found in "bath salts" and "plant food." NMS Labs now offers ***quantitative*** testing for these key ingredients - MDPV, Mephedrone and Methylone*.

Mephedrone, MDPV and Methylone

Called "bath salts" or "plant food" by illicit drug users and makers, these designer drugs are dangerous stimulants and hallucinogens. Although labeled as "not for human consumption," these substances often come in pill or powder form and are snorted, injected or smoked by users.

NMS LABS ONLINE TEST CATALOG

Select by first letter or code number

A B C D E F G H I J K L M
N O P Q R S T U V W X Y Z
0 1 2 3 4 5 6 7 8 9

Sample Type

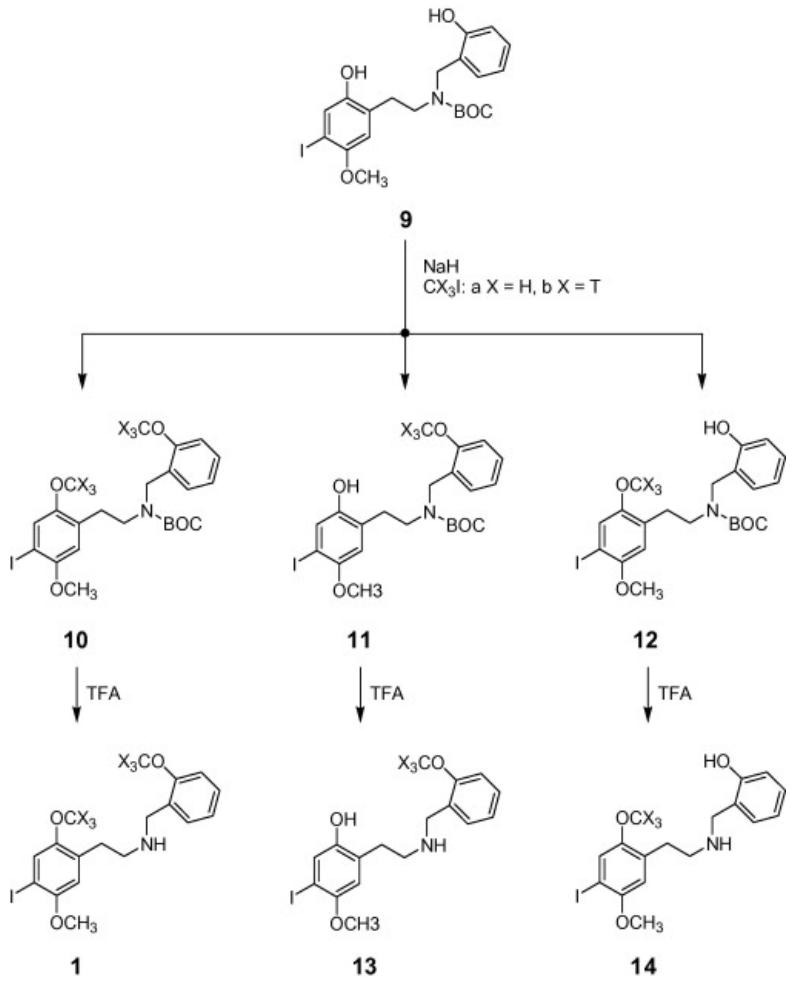
SEARCH

NBOMe

NBOMe

- N – benzyl substitution with OMe groups on the ring
- Discovered in 2003
- Initially surfaced in Russia
- Currently unscheduled*

NBOMe



- Not a homogenous group
- Potent 5-HT_{2A} agonists
- 25I, 2C-I, 2C-B, 2C-C compounds

NBOMe

Clinical Effects:

- Sympathomimetic toxidrome
  - Tachycardia >> hypertension
- Hallucinations / agitation
- Seizures

284. Case series of 25I-NBOMe exposures with laboratory confirmation

Adam Kelly, Bernard Eisenga, Brad Riley, Bryan Judge

Grand Rapids Medical Education Partners/Michigan State University, Grand Rapids MI USA

Table 1. Data for abstract 284.

Patient	Heart rate (bpm)	BP (mmHg)	Serum CPK (U/L)	Serum HCO_3 (mmol/L)	Serum glucose (mg/dL)	Seizure activity	Intubated	Urine [25I-NBOMe] (ng/mL)	Urine drug screen
A	122	121/56	n/a	22	239	no	no	2	caffeine
B	108	140/60	826	22	484*	yes	yes	n/a	n/a
C	153	148/49	292	13	286	yes	yes	36	caffeine
D	184	107/82	30000	11	79	yes	yes	28	caffeine nicotine

n/a = specimen not available or test not performed.
* = Patient B has known diagnosis of type 1 diabetes mellitus.

296. Severe poisoning following self-reported use of 25-I, a novel substituted amphetamine

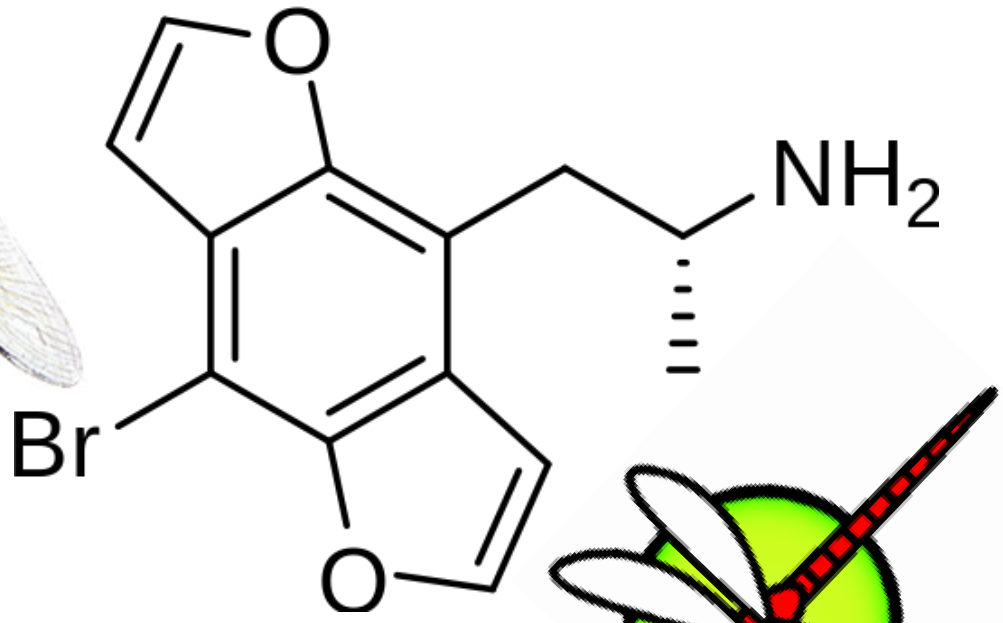
Rutherfoord S. Rose, Kirk L. Cumpston, Paul E. Stromberg, Brandon K. Wills

Virginia Commonwealth University Health System, Richmond VA USA

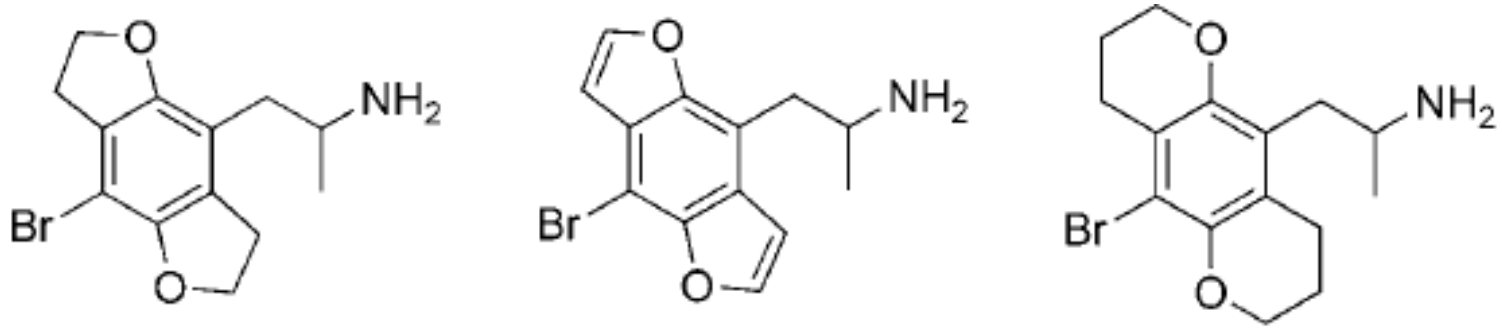
Tachycardia (90%)
Hypertension (70%)
Agitation (60%)

Hallucinations (50%)
Seizures (20%)

Bromodragonfly



BromoDragonFly

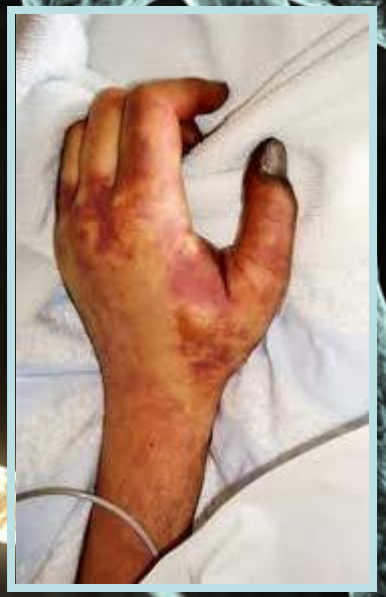


1. High affinity for 5-HT receptors
2. Potent hallucinogens
3. Potent vasoconstrictors

BromoDragonFly

Clinical Effects:

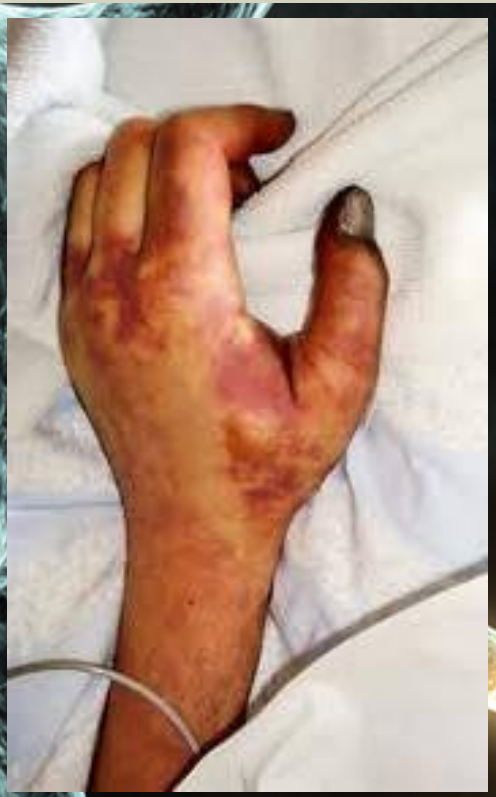
- Slow Onset, long duration
- Sympathomimetic toxidrome
  - Tachycardia, hypertension, hyperthermia
- Severe vasoconstriction
  - Delayed effects
- 5 deaths in Sweden

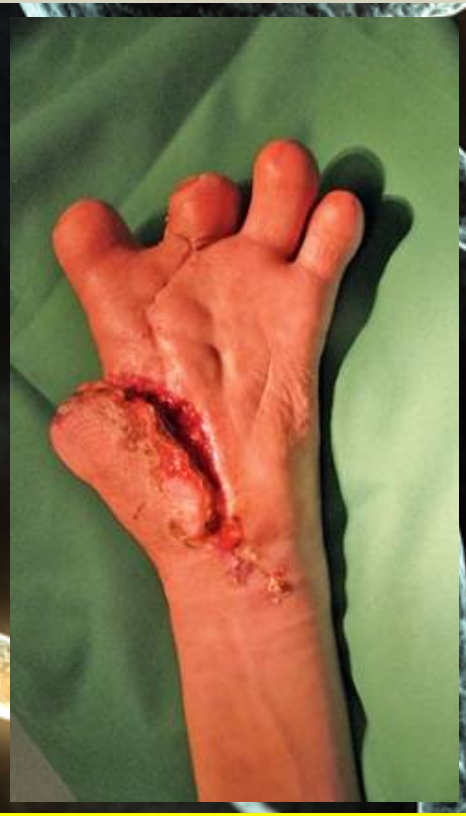


BromoDragonFly

Bromo-Dragonfly Death and Hospitalization in Sweden

by Erowid, Suave, and Abrad
v1.0 Aug 16, 2008





Management

Benzos, Benzos, Benzos

Pharmacokinetics of Benzos

	Diazepam	Midazolam	Lorazepam
Onset of action (IV)	Rapid	Rapid	Rapid
Duration of action	1-2 hr	30-80 min	2-4 hr
T peak CSF conc	3.7 min	3.7 min	7.0 min
T EEG Δ	0.89 min	0.29 min	3.8 min
Duration EEG Δ	7.5 min	6.3 min	28.3 min
Active metabolite	Yes	Yes	No

Management

- Benzos, Benzos, Benzos
- Aggressive cooling
- Control sejzures
- Look for rhabdomyolysis
- Look for serotonin syndrome

Summary

- Cathinones = Sympathomimetic + serotonin (agitation, hallucinations)
- NBOMe = Cathinones w/ ↑ tachycardia and seizures
- BromoDragonFly = Cathinones w/ vasoconstriction
- Benzos, Benzos, Benzos + call Poison Control

Kratom

Kratom Trees – Mitragyna Speciosa

Kratom

- Native to SE Asia
- Used for centuries
- Stimulate (NE, 5-HT) and Analgesic properties (Mu, Delta)

Kratom

- Leaves chewed, smoked or drink as tea
- 2-6 grams: "therapeutic" use include mild euphoria and CNS stimulation
- > 6 grams: stupor, vertigo, rombergism nausea and vomiting, rare seizure
- Duration 4-6 hours
- Chronic use can produce skin discoloration, anorexia, weight loss, addiction and withdrawal

Kratom

- Not regulated by the United States federal government.
- DEA includes the botanical in its "Drug and Chemical of Concern" list.
- It is sold online, in “tobacco or head shops” throughout the country as raw or crushed leaves that can be put into empty capsules, made into tea, eaten, or smoked.

Salvia Divinorum

- Oaxaca, Mexico
- Mazatec Indians
- Intense very short-term hallucinogenic experience

Salvia Divinorum

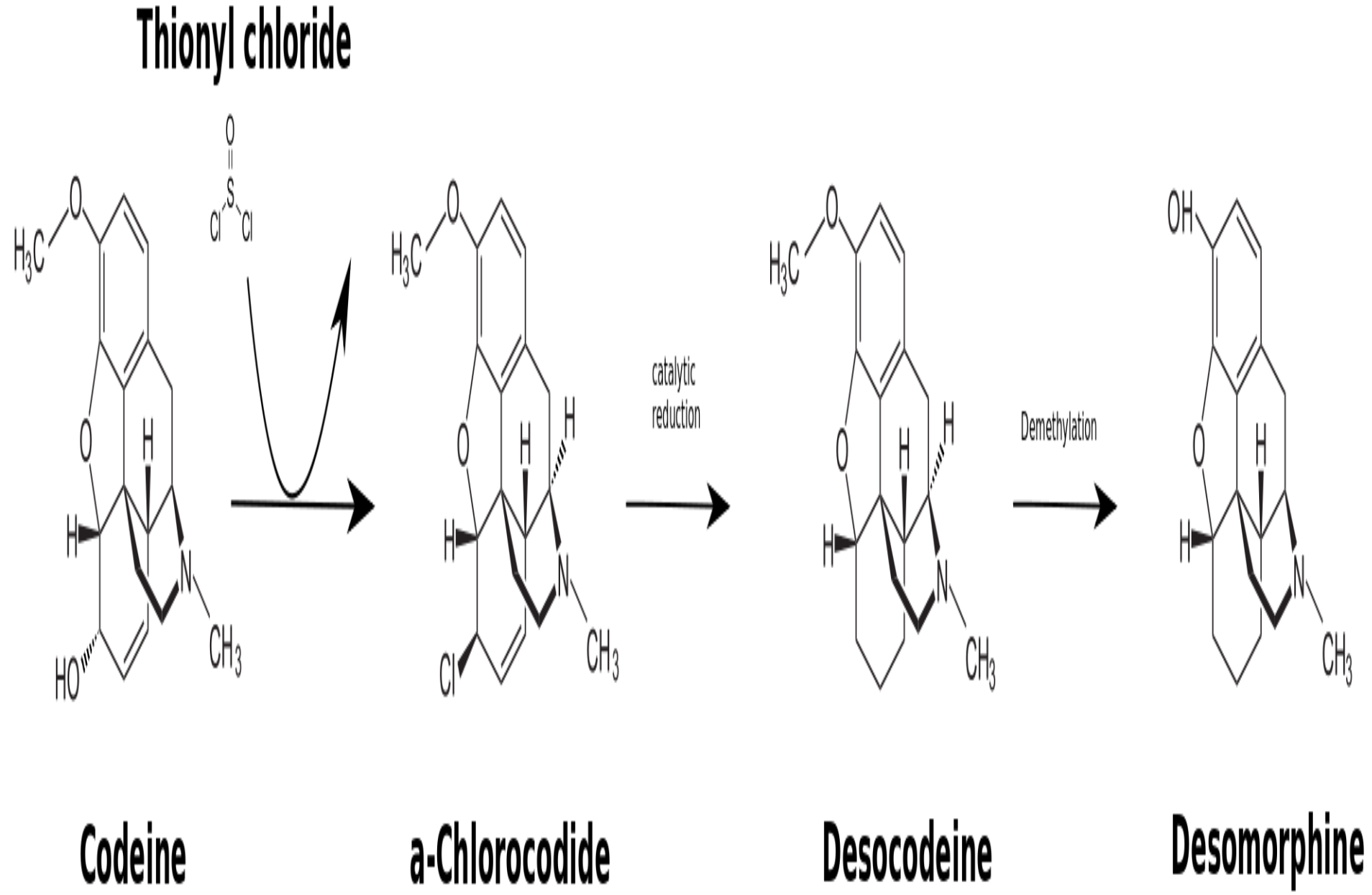
- Route
- Rapid onset
- Duration 5 minutes-2 hours

Salvia Divinorum

- Synesthesia
- Uncontrollable laughter
- Past memories, such as revisiting places from childhood memory
- Sensations of motion, or being pulled or twisted by forces
- Merging with or becoming objects
- Overlapping realities: perception of being in several locations at once

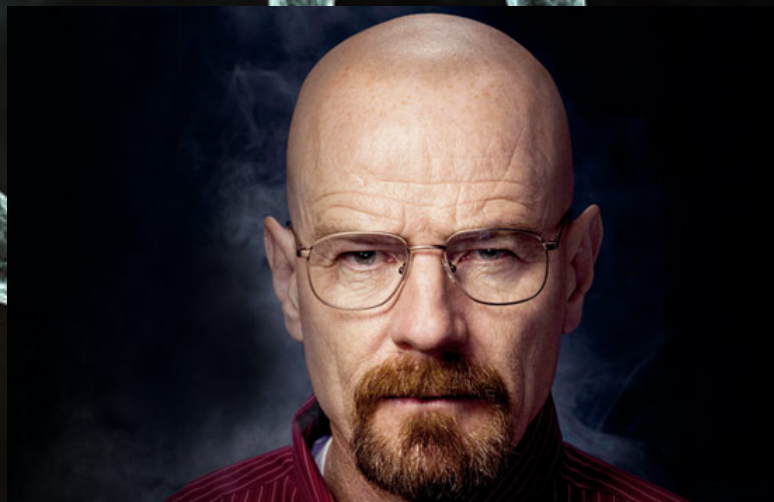
Desomorphine
Krocodile

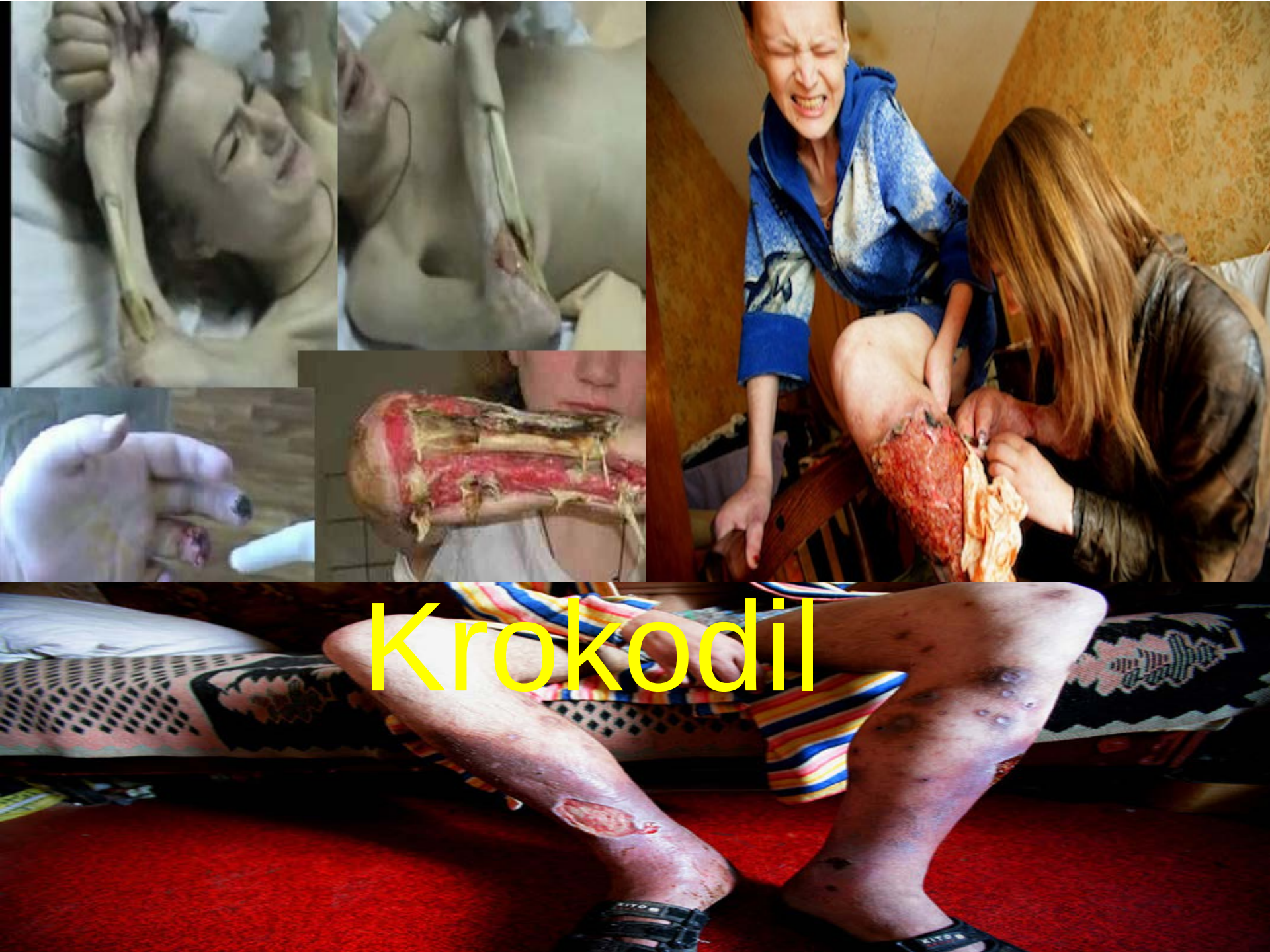
- Invented in 1932
- Derivative of Morphine; 8-10 x
- 2010 outbreak in Russia


Thionyl chloride
catalytic reduction
Demethylation
Codeine
a-Chlorocodide
Desocodeine
Desomorphine

Krocodile

- Codeine availability
- 30-60 minutes to prepare with over-the-counter ingredients
- Similar to Heroin, shorter duration
- Many impurities
- Severe Tissue Damage
- Life span 2-3 years




Krokodil

Questions?