

Clinical and Pharmacological Aspects of Bath Salt Use



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New Drugs 2014 Scientific And Technical Update
on New Psychoactive Substances
Rome

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Objectives

Khat, *catha edulis*

History of synthetic cathinones

Pharmacology

Desired effects

Adverse effects

Toxicity

Treatment

Catha edulis

- Khat (catha edulis) is a drought-tolerant evergreen shrub, leaves contain cathinone and cathine
- Khat chewing is common in the Horn of Africa and in Arabian Peninsula, where the *Catha edulis* plant is endemic
- Cathinone structurally related to amphetamine
- Cathinone is found in large quantity in younger leaves
- Used similar to coffee
- Khat ingestion does not provide the full reinforcing properties since chewing is slow, restricting the amount of active principles absorbed and delaying the onset of the rewarding effects

Graziani M et al. 2008



History of Synthetic Cathinones

- Chemical structures of some have been known but only recently abused
- Methcathinone, a methylated analogue of cathinone, was synthesized in 1928
- Synthesis of mephedrone and MDPV were first described in 1929 (Sanchez, 1929)
- Synthesis of MDPV were first described in 1967 (Emerson & Cisek, 1993)
- Methylone is a more recent analogue, patented 1996 (Jacob Peyton III, 1996)
- First synthetic cathinone drug developed in 1990s, with reports of abuse in the early 2000s (C German et al 2014)
- Legal and regulatory efforts 2007 & 2008
- Law enforcement seizures provide early warning

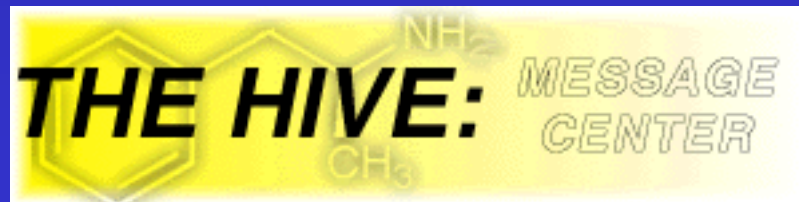


“...after that, a fantastic sense of well-being that I haven’t got from any drug before except my beloved ecstasy.”

- Kinetic, underground chemist

Mephedrone gained initial popularity in 2003 through website “The Hive” that served as a forum for discussing psychoactive chemicals

Archives on Vaults of Erowid



Synthetic Cathinones

MDPV

Mephedrone

Methylone



Sold as plant food, bath salts, research chemicals

Advertised as legal highs, legal meth, cocaine, or ecstasy

Administration: orally, intranasally, injected, smoked or rectal administration

Cathinones shorter $t_{1/2}$ than methamphetamine
conversion to ephedrine isomers

Brenneisen et al 1990

Bath Salts

Synthetic drugs are formulated for their potent stimulant and hallucinogenic properties

- Classification: psychoactive properties, chemical structure, biologic targets

Szily & Bitter 2013

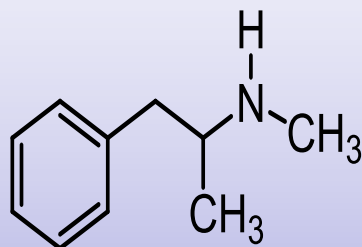
- Manufacture and sales and distribution
- Routes of administration
- Methods of detection
- Adverse events and toxicity
- Tolerance and withdrawal
- Addiction liability



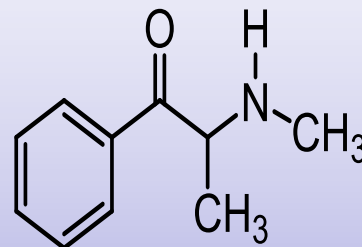
Examples of Synthetic Stimulants

DRUG NAME	DESCRIPTION
Mephedrone	4-methyl-methcathinone; “Miaow” Similar to cocaine and MDMA (ecstasy)
Methylone	β -MDMA: 3,4-methylenedioxy-methcathinone; “Explosion” Similar to cocaine and MDMA (ecstasy)
MDPV	3,4-methylenedioxyprovalerone; MDPV; “NRG-1” (Brandt, 2010); “Ivory Wave” Stimulant with rapid onset; 2-4 hour duration of action
BZP	1-benzyl-piperazone Similar to amphetamine 1/10 potency of <i>d</i> -methamphetamine

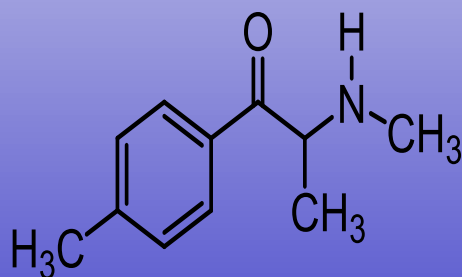
Synthetic Cathinones are β -keto ('bk') Analogs of Amphetamine



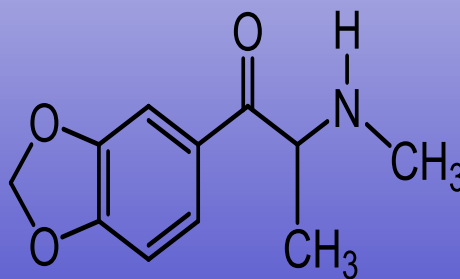
Methamphetamine



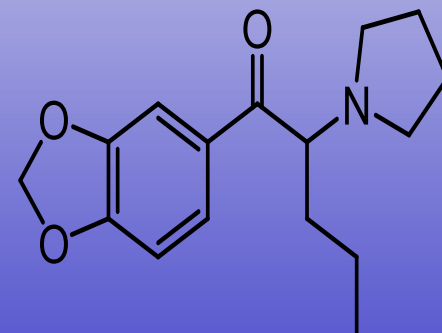
Methcathinone



4-Methylmethcathinone
(Mephedrone)



3,4-Methylenedioxymethcathinone
(Methylone)



3,4-Methylenedioxypyrovalerone
(MDPV)

Prosser, JM & Nelson LS 2012

“Classic” Stimulants

Direct action on synapse

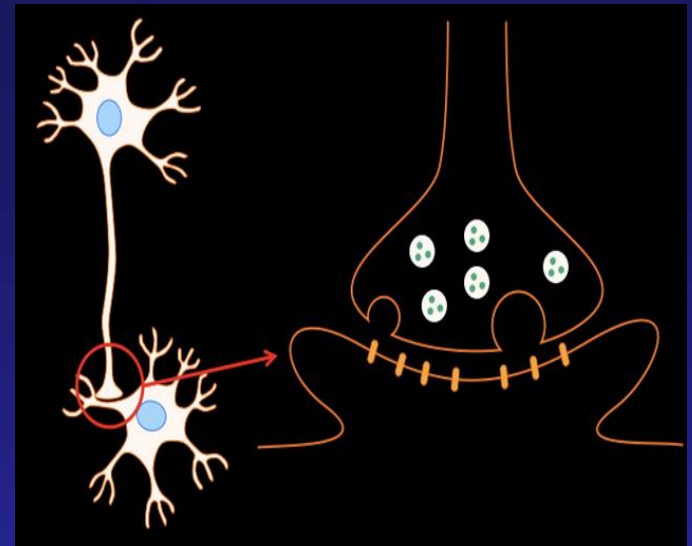
Amphetamine, cathinone: induce dopamine release

Cocaine, methylphenidate (Ritalin): block dopamine removal

MDMA: additional effects on serotonin

Dopamine effects less, so less “rewarding,” in animal self administration

Synthetic stimulants are variations on this theme, BUT:
“Very subtle structural modifications can yield profoundly different behavioural, neurochemical, and neurotoxicological effects.”



Bath Salts: Double Punch on Brain Receptors

Two components of bath salts, Mephedrone and MDPV, produce opposite effects at DAT that are comparable with METH and cocaine, respectively

Mephedrone is nearly as potent as METH; however, MDPV is much more potent than cocaine and its effect is longer lasting

Bath salts containing Mephedrone (or a similar drug) and MDPV might then be expected initially to release DA and subsequently prevent its reuptake via DAT

Such combined action possibly underlies some of the reported effects of bath salts abuse



Synthetic Cathinones

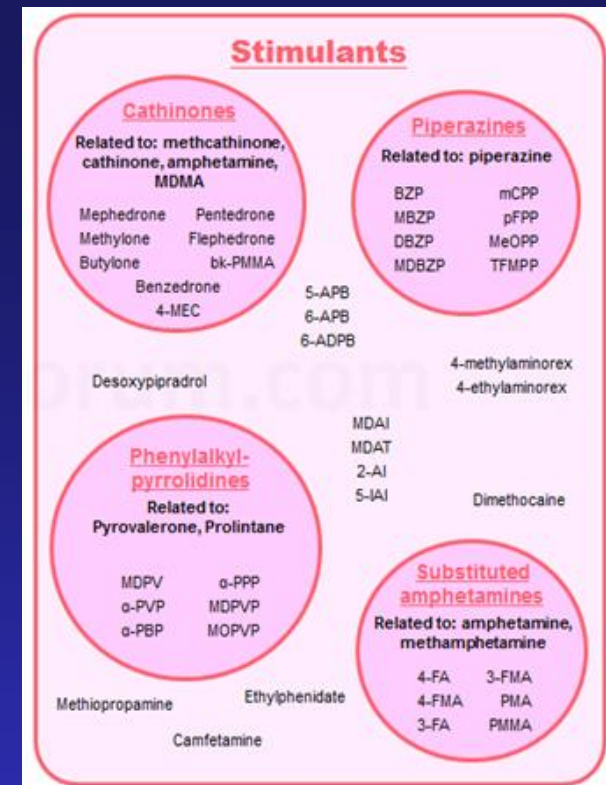
Block transporters

Rank at **Dopamine transporter**:

MDPV/pyrovalerone >>
cocaine, amphetamine/MA,
methcathinone, naphyrone >
mephedrone

Rank at **Serotonin transporter**: MDMA, naphyrone > MBDB,
cocaine, ethylone, mephedrone, butylone >> rest

Rank at **Norepinephrine transporter** (fight/flight): MDPV,
pyrovalerone > amph/MA, methcathinone > cathinone,
mephedrone, flephedrone, naphyrone > MDMA, cocaine,
methylone



Synthetic Cathinones

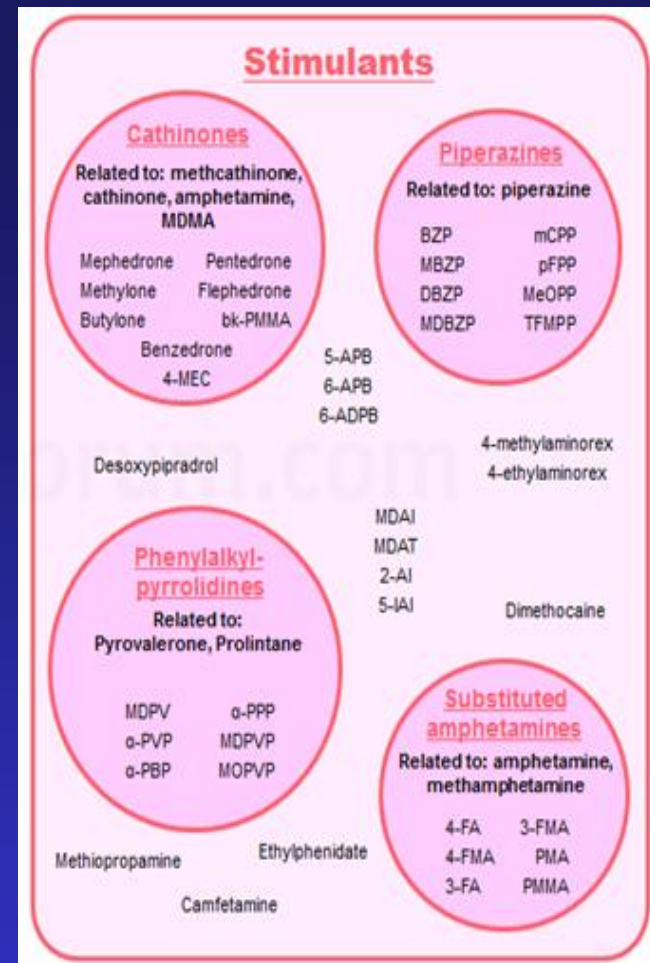
Also release

Dopamine: Amph/MA, cathinone, methcathinone, mephedrone, > MDMA (potency low)

Serotonin: MDMA, methylone, ethylone, butylone, mephedrone

Amph/MA, methcathinone

Pyrovalerone, MDPV: **NO** dopamine or serotonin release, but still extremely good at blocking removal – 10x cocaine



Physical and Neuropsychiatric Effects of Bath Salts

	Desirable	Adverse
Physical	Alertness Analgesic effects Increased energy Stimulation	Cerebral edema Diaphoresis Hyperreflexia Hypertension Hyperthermia Jaw tension Muscle spasms Mydriasis Myocardial infarction Respiratory distress Seizures Tachycardic
Neuropsychiatric	Creativity Empathy Euphoria Sociability Productivity Mental clarity Sexual arousal Sharpened awareness	Aggression Agitation Combative behavior Dysphoria Hallucinations Insomnia Paranoia Psychosis Suicidal thoughts

Effects of Mephedrone

Intended Effects:

Euphoria

Stimulation

Enhanced music
appreciation

Decreased hostility

Improved mental function

Mild sexual stimulation

Avoid drug testing

Unintended (Adverse) Effects:

Bruxism (teeth grinding)

Dilated pupils

Poor concentration

Problems focusing visually

Poor short-term memory

Hallucinations

Delusions

SOURCE: J. Randall Webber, MPH, CADC,
“Emerging Drugs of the 21st Century, July 2013.”

Effects of Methylone

Central Nervous System
stimulation

Euphoria or dysphoria

Anxiolysis/Anxiogenesis

Increase in sociability

Insomnia

Restlessness

De-realization/

De-personalization

Hallucinations

Psychosis

Tachycardia

Hypertension

Hyperthermia

Sweating

Dilated pupils

Nystagmus

Trismus (inability to open the
mouth)

Bruxism (teeth grinding)

Anorexia

Nausea and vomiting

Synthetic Stimulants: Cognition



Same changes in mental state as classic stimulants:
impulsive acts, decision-making, judgment □ can
lead to risky behavior like unsafe sex, aggression,
impaired driving

Single human study: 20 mephedrone users snorting in
own homes (vs. drug-free visit, vs. controls)

Regardless of under the influence vs. not: worse
memory than controls, some personality differences
(schizotypy, depression)

High caused drug-wanting, “speedy” effects, increased
speed of movement, worse working memory

Clinical Symptoms of Synthetic Cathinone Use in Patients Admitted to the Emergency Department (N=236)

Agitation	82%
Combative/Violent behavior	57%
Tachycardia	56%
Hallucinations	40%
Paranoia	36%
Confusion	34%
Myoclonus/Movement disorders	19%
Hypertension	17%
Chest pain	17%
CPK elevations	9%

Spiller et al Clinical Toxicology 2011

Cheng et al Am Academy of Emergency Med 2012

Synthetic Stimulants: Physical Concerns

Norepinephrine (fight/flight) system: hyper-active movement, body temperature regulation, cardio-vascular effects

Especially MDPV

Better than cocaine (x10) at producing hyper-active movement, increased heart rate & blood pressure

Itself does not disrupt body temperature regulation (like MA or MDMA does), but heart rate/blood pressure interact with ambient temperature (Fantegrossi et al 2013)

Neurotoxicity (“brain damage”): some evidence for serotonin and dopamine depletion in animals

Mephedrone NOT toxic to dopamine cells (several reports)

****BUT:** Mephedrone enhances toxic effects of amph/MA and MDMA! □ co-administration frequent, even if accidental (Angoa-Perez et al 2013)

Bath Salts: Adverse Psychological Effects

Mood: depression, dysphoria, euphoria, anxiety

Thought: suicidal ideation, homicidal ideation, intensification of sensory experiences, paranoid delusions, auditory/ visual/ tactile hallucinations,

Psychotic symptoms in 40% of cases where bath salt users presented to US emergency departments

Behavior: insomnia, increased energy, agitation, anorexia, catatonia, panic attacks, self-mutilation, self destructive behavior or violent behavior



MDPV Addiction Potential

Animal self-administration

Found to be more rewarding than methamphetamine and poses a substantial threat for compulsive use that is potentially greater than that for methamphetamine

Is there Withdrawal?

- Extended binges on MDPV have also been reported to produce severe **come down effects** similar to that of methamphetamine, characterized by

- depression
- lethargy
- headache
- anxiety
- postural hypotension
- lightheadedness
- weakness of the muscles
- severely bloodshot eyes
- usually subside within 4 to 8 hours

Miotto et al Drug and Alcohol Dependence 2013

Recognizing Synthetic Cathinone Intoxication

- Present with severe sympathetic stimulation:
 - Tachycardia
 - Hypertension
 - Hyperthermia
 - Seizures
- Present with profoundly altered mental status:
 - Severe panic attacks
 - Agitation
 - Paranoia
 - Hallucinations
 - Suicidal behavior



Sample Clinical Treatment Protocol for Synthetic Cathinone Users

- Supportive care
- Aggressive sedation with benzodiazepines (for agitation, seizures, tachycardia, and hypertension)
- Significant hyperthermia may require passive or active cooling
- Lab studies including electrolytes, renal and liver function tests, cardiac markers, and creatine kinase should be considered

Mas-Morey et al Journal of Pharmacy Practice 2012

Cheng, Yeo, Brown, & Regan. *American Academy of Emergency Medicine* 2012

New 'Bath Salts' Zombie-Drug Makes Americans Eat Each Others Face



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