

Spice, Bath Salts and Salvia, oh my!:
A review of “on-trend” synthetic substances of abuse

Snehal Bhatt, MD Assistant

Professor, Psychiatry

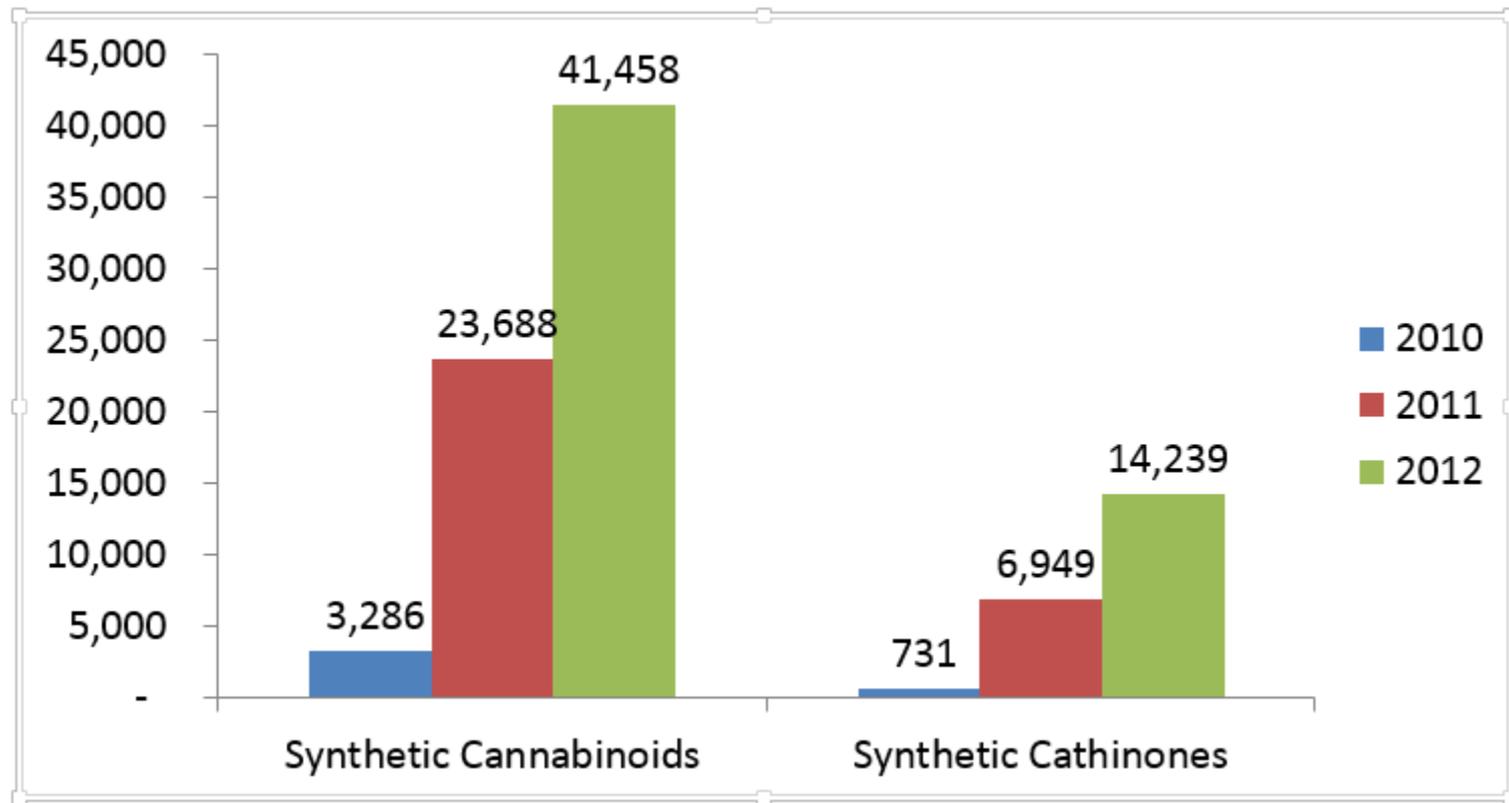
Medical Director, Addiction and Substance Abuse Programs

Objectives

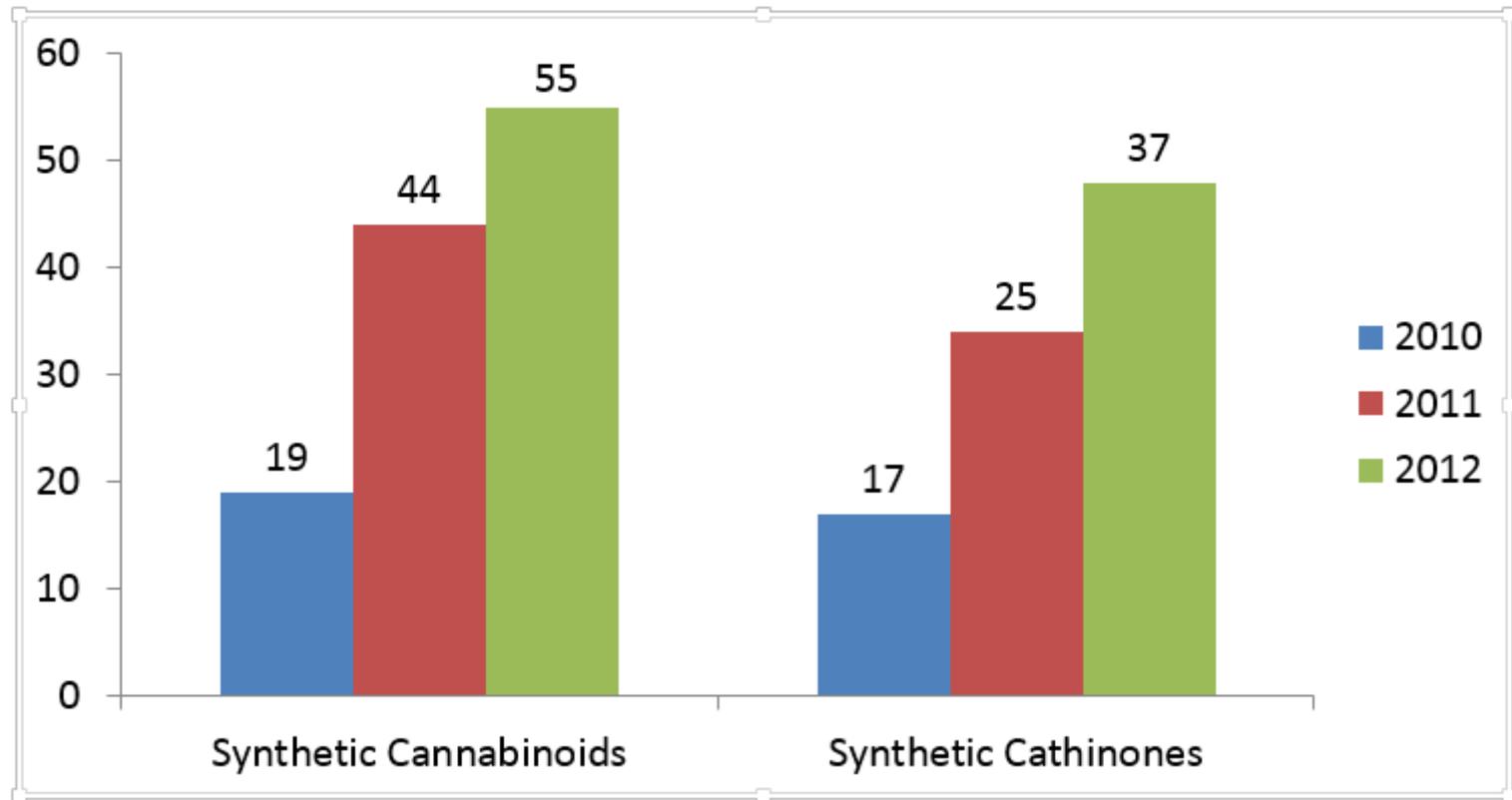
- Identify the mechanism of action of some prevalent synthetic drugs of abuse.
- Recognize the psychological and physiological effects of these substances.
- State how emerging drugs of abuse are forever changing and involve manipulation of basic chemical structures to avoid legal ramifications.
- Describe some of the management strategies for these substances.

**EPIDEMIOLOGY- THE PREVALENCE
OF SYNTHETIC DRUGS IS RISING**

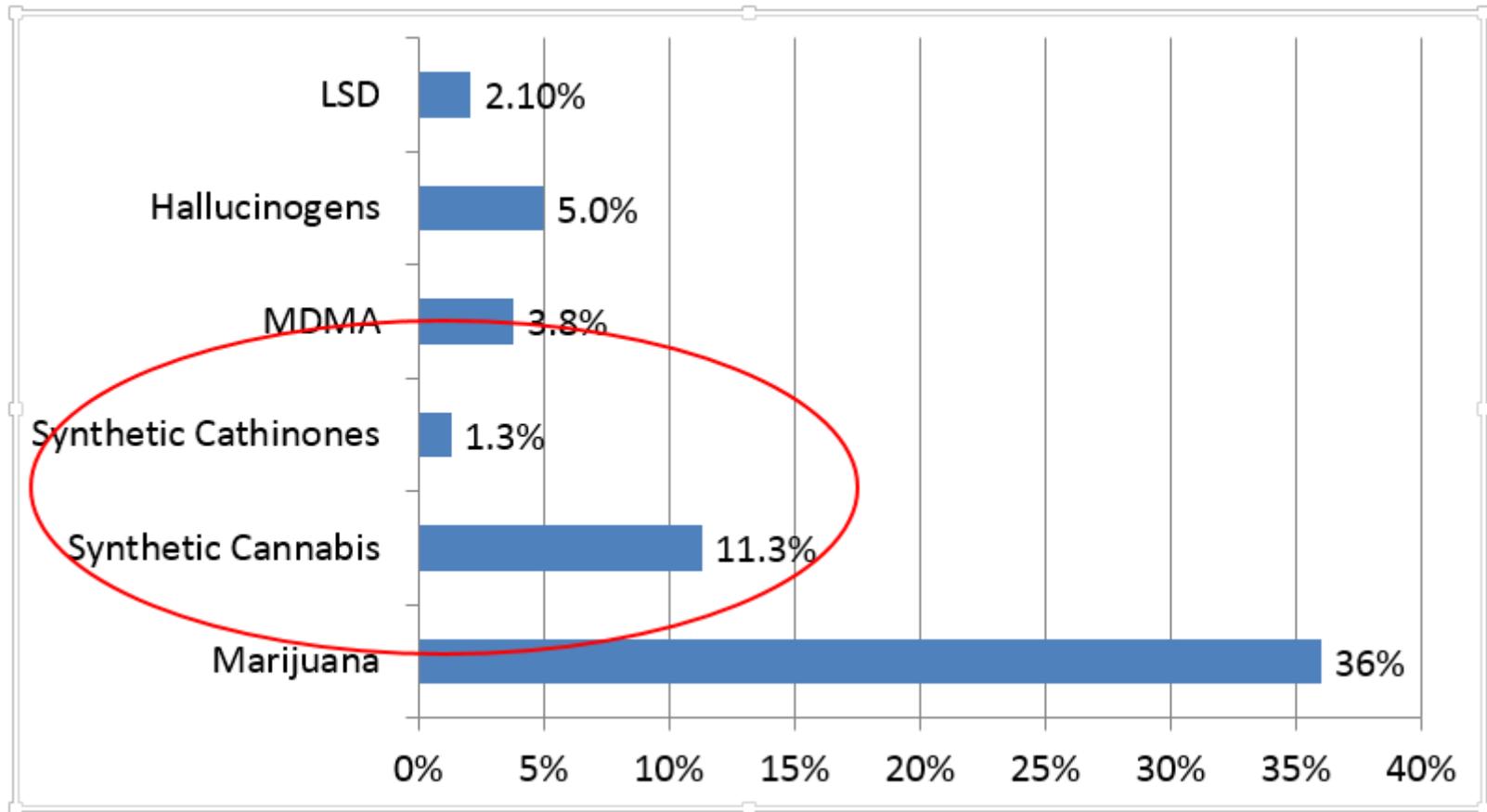
Emerging Drug Items Identified in U.S. NFLIS Forensic Labs: 2010-2012



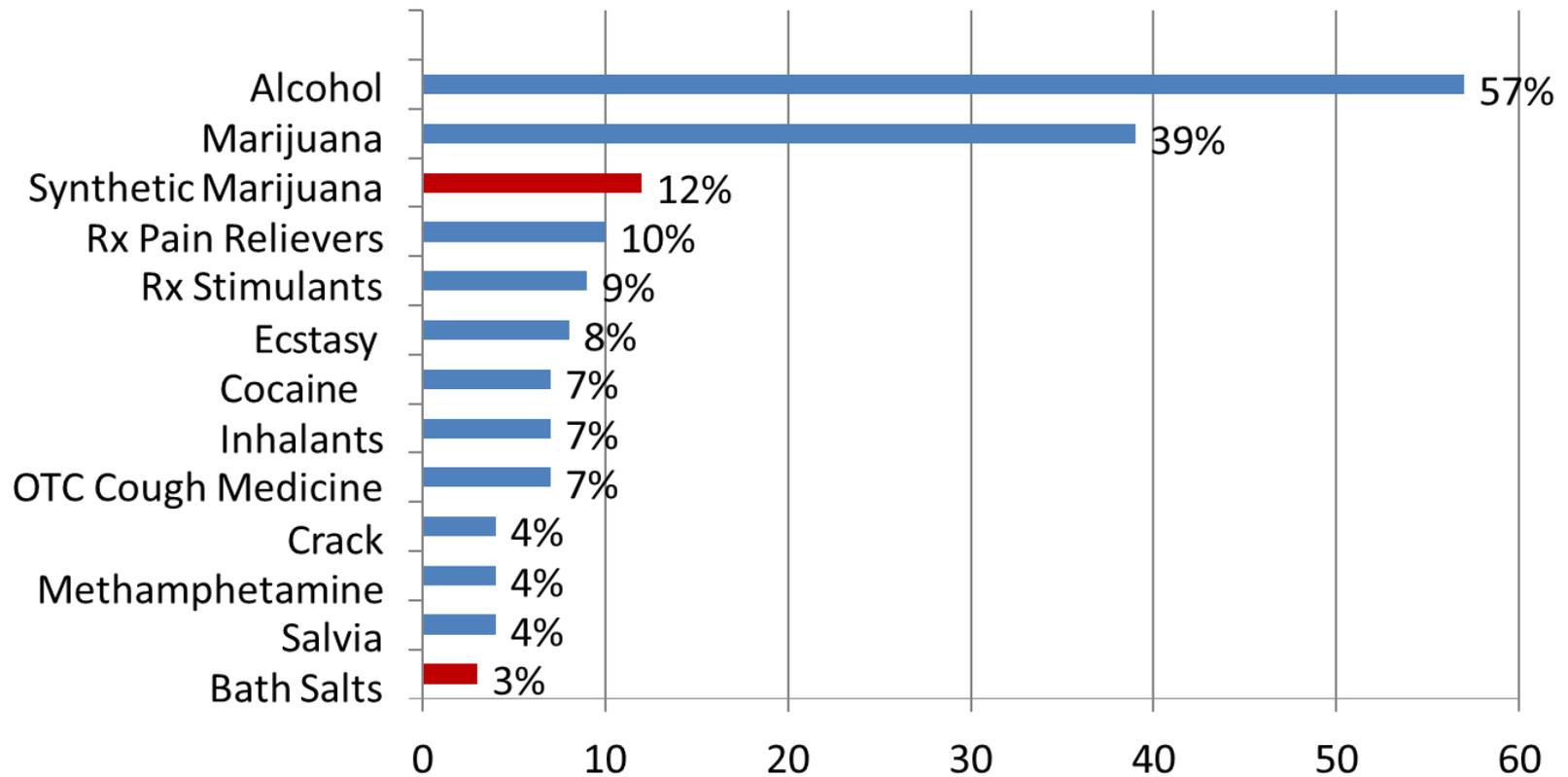
Number of Unique Types of Synthetic Drugs Identified Nationally: NFLIS (2010-2012)



Past Year Drug Use by 12th Grade Students: MTF, 2012



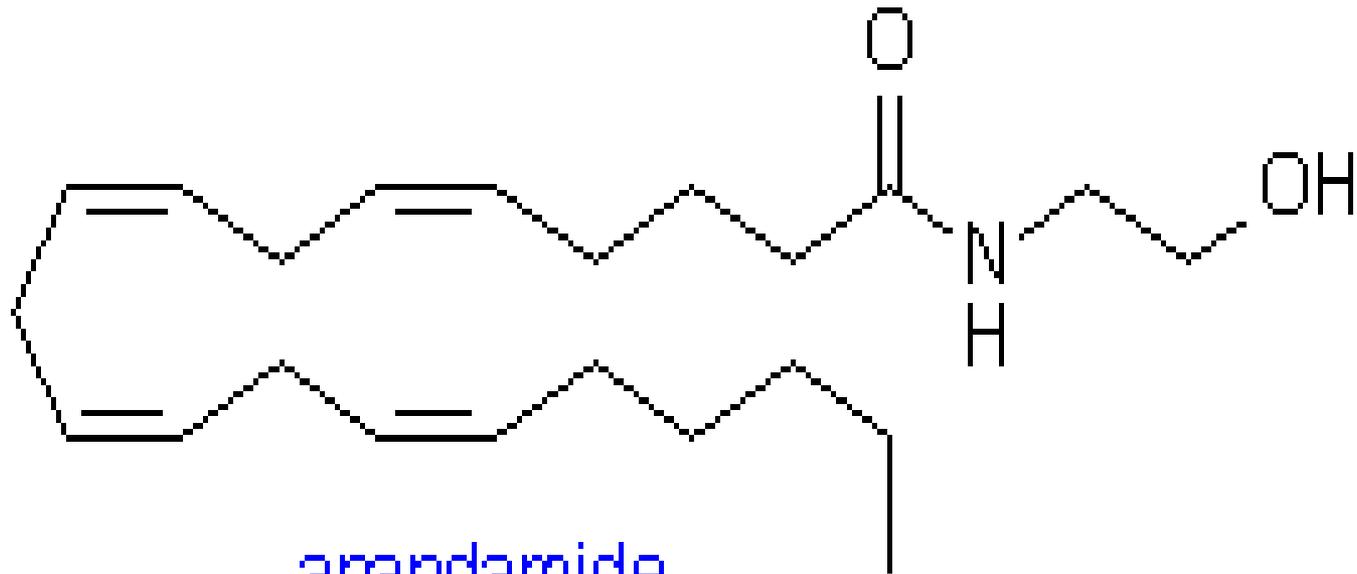
Percentage of U.S. Students (Grades 9 to 12) Reporting Past Year Alcohol and Other Drug Use, 2012 (N=3,884)



"SPICE" [SYNTHETIC CANNABINOIDS]

What is it? Is it safe?

Anandamide- Endogenous cannabinoid



anandamide

Anandamide- Endogenous cannabinoid

- “Ananda” = Sanskrit word meaning bliss, happiness, joy
- Anandamide and receptor sites are present in all mammals
- Anandamide and receptor sites are also present in birds, amphibians, fish, sea urchins, leeches, mussels, and even the most primitive animal with a nerve network, the Hydra, where it is involved in the “feeding mechanism”

Endocannabinoids are important!

- MODULATE:
- Learning and memory
- Social recognition
- Regulation of anxiety
- Regulation of pain threshold
- Regulation of appetite
- Emotional relevance determination
- Forgetting aversive memories

Major receptors

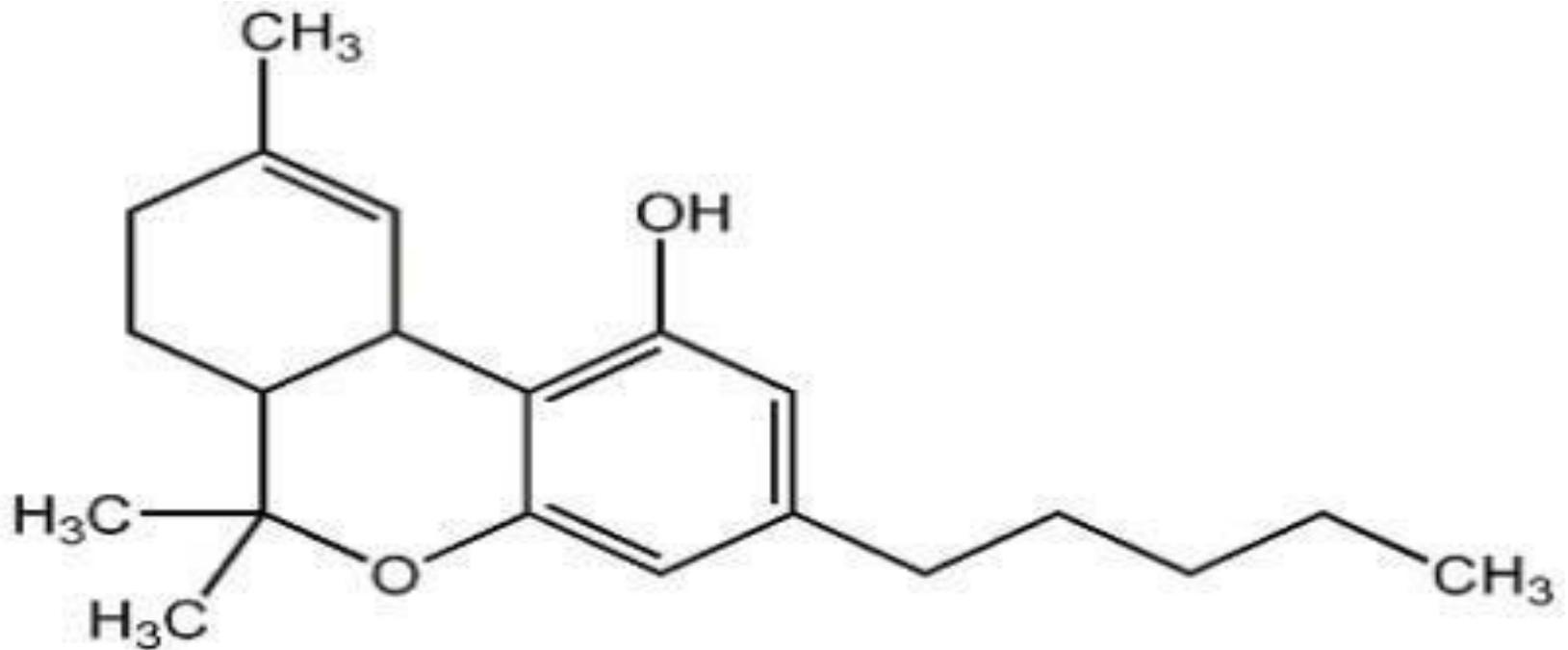
- **CB1 Receptors - 1988**

- Hippocampus – Memory and Learning
- Amygdala – Novelty, Emotion, Appetites
- Basal Ganglia – Motor
- Cerebellum – Real Time Coordination, Selective Attention and Time Sense
- **Nucleus Accumbens - Reward Mechanism (Addiction)**
- Cortex (Anterior > Posterior) – Frontal Lobe Executive Functions

- **CB2 Receptors - 1993**

- Macrophages
- Spleen, Intestines

Δ^9 -THC: Exogenous cannabinoid



Synthetic cannabis



Also called...

- Spice
- K2/K2Gold
- Tai Fun blackberry/vanilla/orange
- Exclusive original/mint/cherry
- Natures Organic cherry/strawberry
- Chill Zone
- Chill Out
- Sensation
- Chaos
- Zen
- Black Mamba
- Clover Spring
- Aztec fire
- Bombay Blue
- Blaze
- Yucatan Fire
- Mr. Smiley
- Krypton
- Moon Rocks
- Zohai
- Fake Weed

Synthetic cannabinoids

- “K2”
- “Spice”
- Sold at head shops and gas stations
- Initially marketed as legal natural herbs
- However, DEA reports show that it in fact contains synthetic cannabinoids not yet illegal and not detected in standard urine tests
- Essentially, it is a designer drug

Synthetic cannabinoids

- Many synthetic cannabinoids produced from the 1960s onwards to study cannabinoid receptors
- These are sprinkled onto dried herbs [inert] including: rose hips, marshmallow, red clover, lotus, wild dagga, skullcap, baybean, beach bean etc.
- The mixture is then smoked

History

- “Spice” initially marketed in 2004 in Europe by a now defunct company called The Psyche Deli, based in London
- Now, it refers to any such product
- Usually marketed as “herbal incense” or “herbal smoking blend”
- Came to US 2008-2010 once these were banned in Europe and Russia

Multiple “generations”

- FDA: fifth and sixth generation drugs are now available
- On average, a new substance may come out every 4-6 days!!!
- Urine tests only test for upto 17
- Makes it very difficult to control and test
- Most recent one, CRB-754, inhibits enzyme that breaks down endocannabinoids!

Pharmacology

- FULL agonists of CB-1 and CB-2 receptors [THC only a partial agonist]
- Stronger binding affinity
- HU-210: 100-800x more potent than THC
- CB47-497: 30x more potent than THC
- JWH-018: 5x more potent
- Usually quicker onset of action and shorter duration

Why popular

- Potency
- Difficulty in detection= attractive to athletes, military personnel etc.
- Ready availability
- Misperceptions of safety

Table 2

Comparisons between synthetic and natural cannabis effects (self-rated from 1 to 10).

Self-rated effect	Mean (SD)			Dependent samples <i>t</i> -test with effect size (Cohen's <i>d</i>)
	Synthetic	Natural	Difference	
Pleasurable effects when high	4.98 (2.49)	8.59 (1.70)	-3.61 (2.97)	$t(930) = -37.1, p < .001, d = -1.22$
Increase in appetite	3.79 (2.59)	6.89 (2.35)	-3.10 (2.92)	$t(858) = -31.1, p < .001, d = -1.06$
Sedation (sleepiness after use)	4.51 (2.57)	6.16 (2.05)	-1.65 (2.99)	$t(905) = -16.7, p < .001, d = -0.55$
Value for money	4.76 (3.00)	6.72 (2.27)	-1.96 (3.90)	$t(881) = -14.9, p < .001, d = -0.50$
Ability to function after use	5.47 (2.76)	6.85 (2.34)	-1.38 (3.10)	$t(884) = -13.3, p < .001, d = -0.45$
Impairment in memory	4.26 (2.78)	4.59 (2.42)	-0.33 (2.70)	$t(852) = -3.60, p < .001, d = -0.12$
Addictiveness	2.62 (2.51)	2.97 (2.42)	-0.36 (2.92)	$t(836) = -3.56, p < .001, d = -0.12$
Consistency of product	5.93 (3.17)	6.35 (2.36)	-0.42 (4.16)	$t(837) = -2.92, p < .01, d = -0.10$
Hangover effects	3.49 (2.80)	2.79 (2.31)	0.70 (3.16)	$t(854) = 6.45, p < .001, d = 0.22$
Paranoia	4.75 (3.11)	3.89 (2.43)	0.86 (3.24)	$t(889) = 7.91, p < .001, d = 0.27$
Harmful effects on lungs	5.79 (2.85)	4.19 (2.36)	1.60 (2.87)	$t(868) = 16.4, p < .001, d = 0.56$
Negative effects when high	4.80 (2.89)	2.80 (2.00)	2.00 (3.13)	$t(859) = 18.7, p < .001, d = 0.64$

Characterization of exposures

- Hoyte et al. [2010]
- All -9-tetrahydrocannabinol homolog exposures reported to the National Poison Data System between January 1, 2010, and October 1, 2010, were extracted
- 1,898 exposures
- Tachycardia 37.7%
- 52 seizures [3.8%]; 2 cases of status epilepticus
- 78.4% effects lasted < 8 hours
- 92.9% non-life-threatening
- The most common therapeutic intervention was intravenous fluids [

Table 2. Ten most common clinical effects.

Symptoms	N=1,353 (%)
Tachycardia	541 (40)
Agitation/irritability	317 (23.4)
Vomiting	207 (15.3)
Drowsiness/lethargy	183 (13.5)
Confusion	164 (12)
Nausea	139 (10)
Hallucination/delusion	127 (9.4)
Hypertension	110 (8.1)
Dizziness/vertigo	99 (7.3)
Chest pain	64 (4.7)

Key differences from marijuana

- Significant more irritability/agitation
- Seizures [epileptogenic agents such as *O desmethyltramadol*, an active metabolite of tramadol, found in herbal formulations]

Reports of kidney damage

- Sixteen cases of kidney damage reported by CDC
 - All admitted to hospital
 - Five required hemodialysis
- Fifteen of the patients were male; ranged in age from 15 to 33, no history of kidney disease
- In early Feb 2013, UA-Birmingham reported 4 cases of previously healthy young men, whose acute kidney injury was associated with synthetic marijuana
 - Symptoms of nausea, vomiting, and abdominal pain
 - All four men recovered kidney function, and none required dialysis

Testing

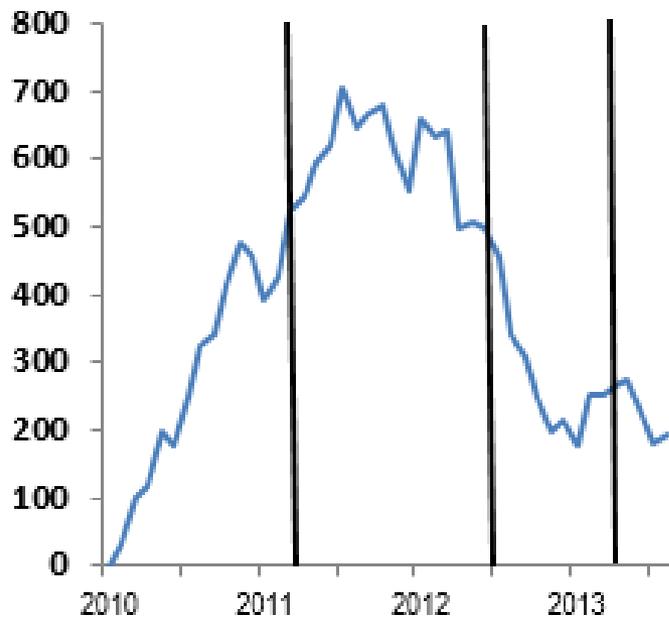
- NONE detected in standard urine tests
- GC/MS can detect upto 17 common ones
- LC-MS/MS can pick up several more
- Commercial blood tests can detect several
- Window: 48-72 hours
- Check with your local labs!

Management

- No antidote
- Contact 9-1-1 and transfer to ER
- Supportive care
- Benzodiazepines for agitation/anxiety
- In development: CB-1 antagonist [SR141716]-
may reverse the effects
- Naltrexone may also attenuate effects

Effects of legislation

The Effect of Federal Controls on Synthetic Cannabis Calls to Poison Centers



- March 2011: DEA places JWH-018, JWH-073, JWH-200, CP-47, 497, and CP-497 C8 homologues into temporary Schedule I.
- July 2012: Synthetic Drug Abuse Prevention Act places more than a dozen synthetic cannabinoid homologues permanently into Schedule I.
- April 2013: Notice of Intent published to temporarily schedule UR-144, XLR 11, and AKB48.

**“BATH SALTS” [SYNTHETIC
CATHINONES]**

Media sensationalism

- Summer 2012 Florida: 31 y/o man Rudy Eugene chewed down the face of homeless man Ronald Poppo
- Prompted media reports of zombie cannibalism caused by bath salts
- Ultimately turned out: man had no traces of synthetic cannabinoids, cathinones or LSD in his system!

Other media reports

- The man who slashed himself to remove the “wires” in his body
- The mother who left her demon-ridden 2-year-old in the middle of the highway
- The 21-year-old son of a family physician who, after snorting bath salts once, shot himself following 3 days of acute paranoia and psychosis, including hallucinations of police squad cars and helicopters lined up outside his house to take him away

KHAT



KHAT

- *Catha edulis*: Shrub native to East Africa and Southern Arabia
- Leaves chewed socially for mild stimulant effect
- Quite prevalent in Somalia, Ethiopia, Yemen [over 10 million users]
- 1st described in 11th century
- Active substance: cathinone
- Euphoria, elation, increased alertness
- Tachycardia, hypertension
- Effects 90 minutes to 3 hours, but “sessions” lasting many hours

From khat to designer drugs!

- Cathinone > methcathinone [1928]

Compound	Alternative names	Product names
Cathinone		Khat
Methcathinone	Ephedrine, β -keto-methamphetamine	
Mephedrone	4MMC (4-methylmethcathinone)	Bubbles, Meow Meow, MCAT
Methedrone	4-Methoxymethcathinone, β -keto-PMMA, PMMC	
Methylone	B-keto-MDMA, MDMC	Explosion, Impact
Naphyrone	Napthylpyrovalerone	Energy-1, NRG-1
Butylone	β -keto-MBDB	
MDPV	3,4-Methylenedioxypropylone	Bath salts, Ivory Wave, Vanilla Sky, Hurricane Charlie, Cloud 9, Scarface, Red Dove, White Dove, White Rush, White Lightning
4-Flouromethcathine	4-FMC, flephedrone	
3-Flouromethcathine	3-FMC	

History

- 1928: Methcathinone isolated
- 1988: Cathinone listed as Schedule I by UN Convention on Psychotropic Substances
- 1990s: outbreaks in Europe and US
- 1993: Schedule I substance by DEA
- 2007: Mephedrone appears in Australia and Europe

History

- 2009: Mephedrone appears in US
- 2010: MDPV and Methyone appear in US
- 2011 first 6 months: US poison controls 6x as many calls of “bath salt” exposure as 2010
- 2009-2010: 20 fold increase In drug seizures with synthetic cathinones
- September 2011: DEA issues a notice of intent to temporarily schedule three synthetic cathinones [mephedrone, methyone, and MDPV]

Marketing

- “legal highs”
- Cheap
- Sold in head shops and online
- “Not for human consumption”

Pharmacology

- Synthetic cathinones = β -ketophenethylamines
- Structurally similar to methamphetamines, but LESS potent

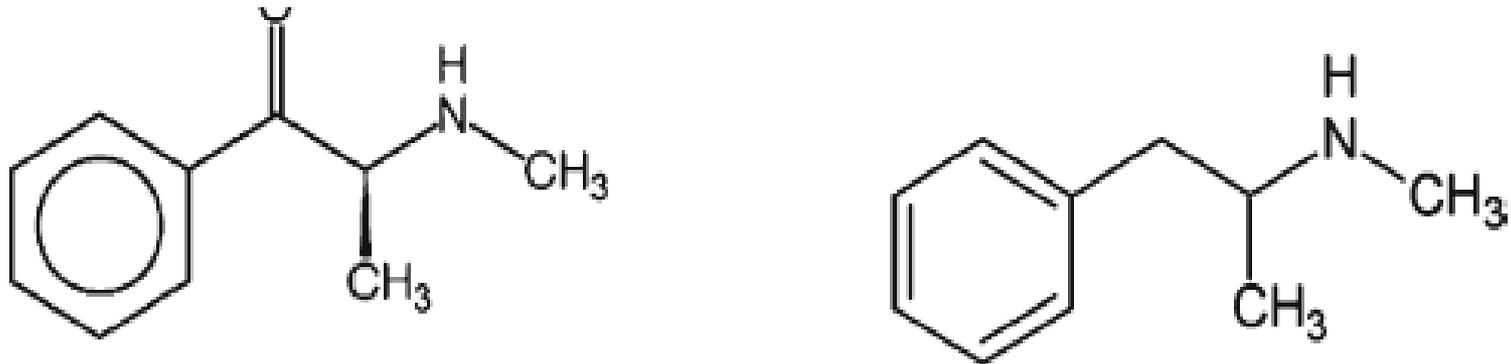
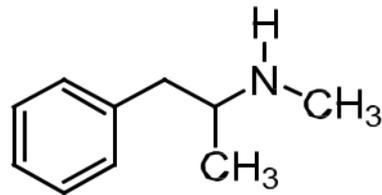
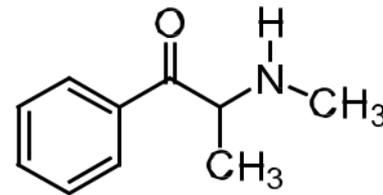


Fig. 2 Structural similarity of mephedrone (*left*) and methamphetamine (*right*)

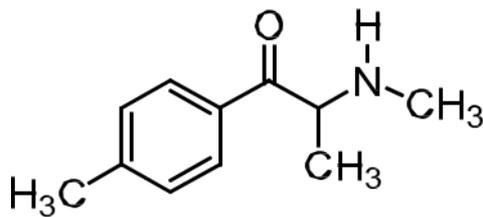
Molecular structures



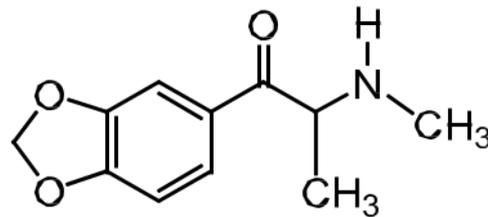
Methamphetamine



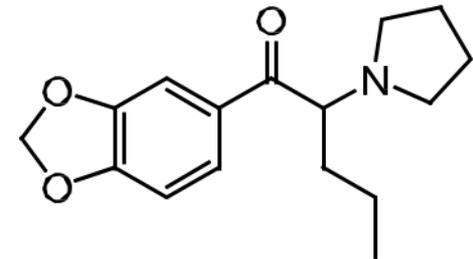
Methcathinone



**4-Methylmethcathinone
(Mephedrone)**



**3,4-Methylenedioxmethcathinone
(Methylone)**



**3,4-Methylenedioxypropylvalerone
(MDPV)**

Pharmacology

- strongly inhibit reuptake of dopamine [like cocaine], serotonin [like MDMA], and norepinephrine [MDPV; 10x more potent than cocaine]
- Like methamphetamine, increase pre-synaptic release of these substances [mephedrone]
- So, in a way, like a combination of cocaine and methamphetamine
- May also insert into DNA to exert toxicity

Pharmacology

- DA reuptake: MDPV >> cocaine, meth, methcathinone > mephedrone, methylone > cathinone > MDMA
- 5-HT reuptake: MDMA > cocaine, mephedrone >> meth, MDPV, methcathinone, cathinone
- NE reuptake: MDPV > meth, methcathinone > cathinone, mephedrone > MDMA, cocaine, methylone

Pharmacology

- DA release: meth, cathinone, methcathinone, mephedrone > MDMA
- 5-HT release: MDMA, methylone > mephedrone >>>>> meth, methcathinone

Use

- White or brown powder; often in capsules
- Nasal, oral, rectal, IV/IM
- Onset of action: 30-45 minutes
- Duration of action: 3-7 hours
- MDPV stronger than mephedrone

Clinical Effects

- Euphoria, alertness, energy, talkativeness, sexual arousal
- Compulsion to re-dose!
- Sessions can last hours to days!
- Aggression/psychosis
- Phenomenal physical strength [like PCP]
- Bizarre behaviour
- Self mutilation
- Paranoia
- Suicide attempts

Clinical Effects

- Dependence/craving
- Sympathomimetic toxicity
- Hypertension
- Tachycardia
- Hyperthermia
- Dehydration
- Seizures
- Palpitations
- Headaches
- Chest pain
- Bruxism
- MI
- Myocarditis [mephedrone]
- Serious infections reported
- Death

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%

Detection

- None detected on routine screening
- May cause false positive amphetamine screen
- GC-MS and LC-MS kits available commercially to detect mephedrone, MDPV and methylone

Clinical management

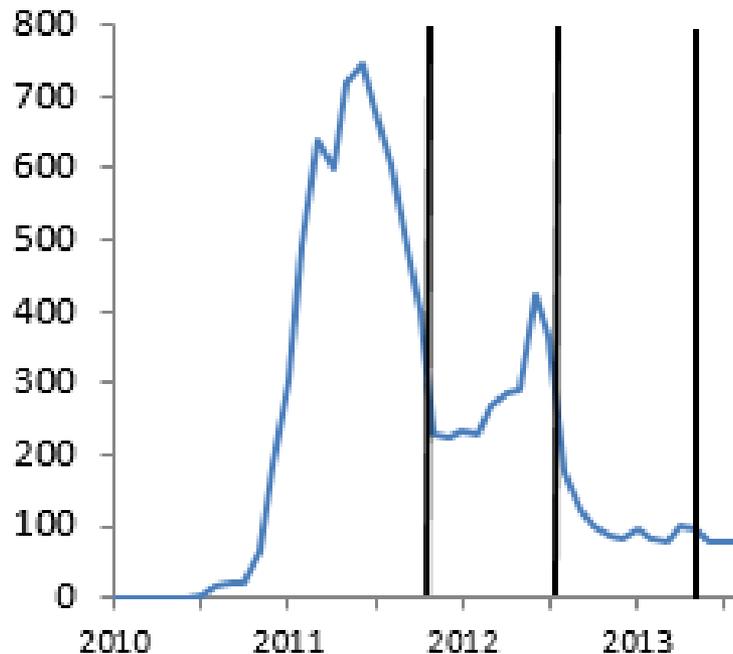
- Call 9-1-1; get to ER
- No antidote
- Supportive care; A-B-Cs
- Benzodiazepines for aggression/agitation
- Avoid B-blockers
- Sedation
- Passive or active cooling for extreme hyperthermia
- EKG/cardiac monitoring
- Serial temperature checks
- CPK, electrolytes, renal/liver functions, cardiac enzymes

Clinical Management

- Monitor until symptoms resolved
- 26% admitted to ICU
- 14% admitted to medical floor
- 9% admitted to psych floor
- 51% discharged from ER

Effects of legislation

The Effect of Federal Controls on Synthetic Cathinone Calls to Poison Centers



Federal Efforts to Ban Synthetic Cathinones:

- Oct 2011: DEA exercised its emergency scheduling authority to control some of the synthetic substances used to manufacture bath salts; these synthetic stimulants are now designated as Schedule I substances.
- July 2012: Congress passed and President Obama signed the *Synthetic Drug Abuse Prevention Act* (MDPV and mephedrone Schedule I).
- April 3013: DEA places methylone into Schedule I.

SALVIA DIVINORUM

Info

- Mint family
- Use dates back centuries
- Religious rituals and herbal healing by Mazatec people- chew leaves or make a tea
- Last decade: a surge in use among teenagers/young adults- smoke
- 2008 DEA report: 1.8 million had tried

Also called

- Diviner's sage
- Mystic sage
- Magic mint
- Sally D
- Maria Pastora
- Purple sticky

Pharmacology

- Salvinorin-A
- NOT a classical hallucinogen; no 5-HT₂ binding
- Kappa opioid agonist- hallucinations, diuresis, spinal analgesia, sedation, **depression, aversion**
- NO respiratory suppression
- Hallucinations within seconds; duration of effect 20-30 minutes

Clinical effects

- “unique” intense high
- Meditation/trance state
- Hallucinations
- Distortions of perception
- Synesthesia
- Out of body experiences
- Depression in some; anti-depressant effect in some!
- Extreme dysphoria and anxiety; fractured reality
- Often ingested with alcohol and cannabis

Clinical Effects

- NOT reinforcing
- Very little addictive potential
- In fact, may have some role as a modulator of reward pathway
- May also have utility as a treatment for depression and anxiety, or as an anti-inflammatory

Testing/Management

- No good available methods for testing
- Few case reports of emergency care
- No antidote
- Benzodiazepines
- Supportive care
- Naltrexone??

KRATOM

Info

- Legal plant product
- Used for centuries to treat opioid withdrawal
- Available on-line
- Derived from *Mitragyna speciosa*, a south asian tree
- Opioid-like effects: mild stimulant at low doses, and analgesia at higher doses
- DEA” ‘drug of concern”
- One of top 5 legal highs in UK

Pharmacology

- Tree has 25 alkaloids
- Mitragynine is the opioid-like alkaloid
- Structurally distinct from opiates, yet acts as mu and delta agonist
- 13x more potent than morphine
- Onset: 5-10 minutes
- Duration: several hours

Uses

- Available as powder, leaves, or gum
- Smoked or brewed into tea
- Treatment for muscle pain
- Relief of opioid withdrawal
- Supposed benefits: anti-inflammatory, analgesia, anti pyretic, antitussive, antihypertensive, hypoglycemic, anti-malarial, anti-diarrheal
- Adverse effects: tolerance/withdrawal; seizures; hepatic damage

Detection/management

- No readily available detection kits
- Management: airway management
- Naloxone
- Benzos for seizures
- Treatment for opioid dependence

PIPERAZINE DERIVATIVES

Info.

- Piperazine= antihelminthic agent
- Has amphetamine like effects
- BZP schedule I since 2004
- 2010: 26% of clubgoers in UK used these substances
- Also rising rates in US
- “Legal ecstasy”
- “Benzo Fury”
- “MDAI”
- “Head Rush”
- “XXX Strong As Hell”
- “Exotic Super Strong”

Common piperazines

Table 3 Common piperazines and chemical names

Abbreviated name	Chemical name
BZP	1-Benzylpiperazine
CPP	1-(3-Chlorophenyl)piperazine
MBZP	1-Methyl-4-benzylpiperazine
MEBP	<i>N</i> -(3-methylbenzyl)piperazine
MeOPP	1-(2-Methoxy-phenyl)piperazine
MeP	1-Methyl-3-phenylpiperazine
TMFPP	1-(3-Trifluoromethylphenyl)piperazine

Pharmacology

- BZP: inhibits serotonin reuptake; also a serotonin receptor agonist
- TMFPP: Release of endogenous stores of serotonin [like MDMA]
- Sold as pills containing multiple chemicals
- 75-150 mg
- Onset >2 hours after dose, so multiple doses often taken

Clinical Effects

- Often indistinguishable from amphetamines
- 1/10 as potent
- Stimulant at lower doses; hallucinogenic at higher doses
- BZP + TMFPP = MDMA like effect
- Palpitations, anxiety, headaches, vomiting
- Seizures 30 min=8 hours post ingestion
- 32% had QT prolongation

Detection/Management

- Often false positives for amphetamine
- GC/MS screens available [but not readily]
- Cardiac monitoring
- IV fluids, cooling, benzos
- Monitor closely

KROKODIL

desomorphine

- Synthetic morphine analog
- Manufactured in the US in 1930
- 10x more potent than morphine
- Fast onset; brief duration of action

Krokodil

- Russia about a decade ago
- Cheap alternative to heroin [1/3 of the cost]
- Made from cooking down desomorphine with gasoline, paint thinner, alcohol, iodine, red phosphorous (match heads), etc.
- Why Russia- no methadone, no clean needles, poverty, high cost of heroin

Krokodil

- Injected
- Destroys tissue
- Turns skin scaly and green, like a crocodile
- Blood poisoning, abscesses, open sores
- Thrombophlebitis/gangrene/amputations/death
- Staph infections/MRSA
- Recent cases in Phoenix

“MOLLY”

- Originally pure powdered form of MDMA
- Now highly adulterated
- Often little MDMA, and more caffeine, meth, methyline etc.
- Popular at concerts; sold for \$25-50 a dose
- Frequently seen in ER
- teeth grinding, dehydration, anxiety, insomnia, loss of appetite and fever
- uncontrollable seizures, high blood pressure, elevated body temperature and depression
- 2 deaths at a music festival in 2013

Conclusions

- The prevalence of synthetic drugs of abuse is rising
- New substances are becoming available at a rapid rate
- Providers know relatively little about short and long term consequences of these substances
- Better ways of detection, and management are needed