

Clinical Implications of Synthetic Cannabinoid and Synthetic Hallucinogen Abuse

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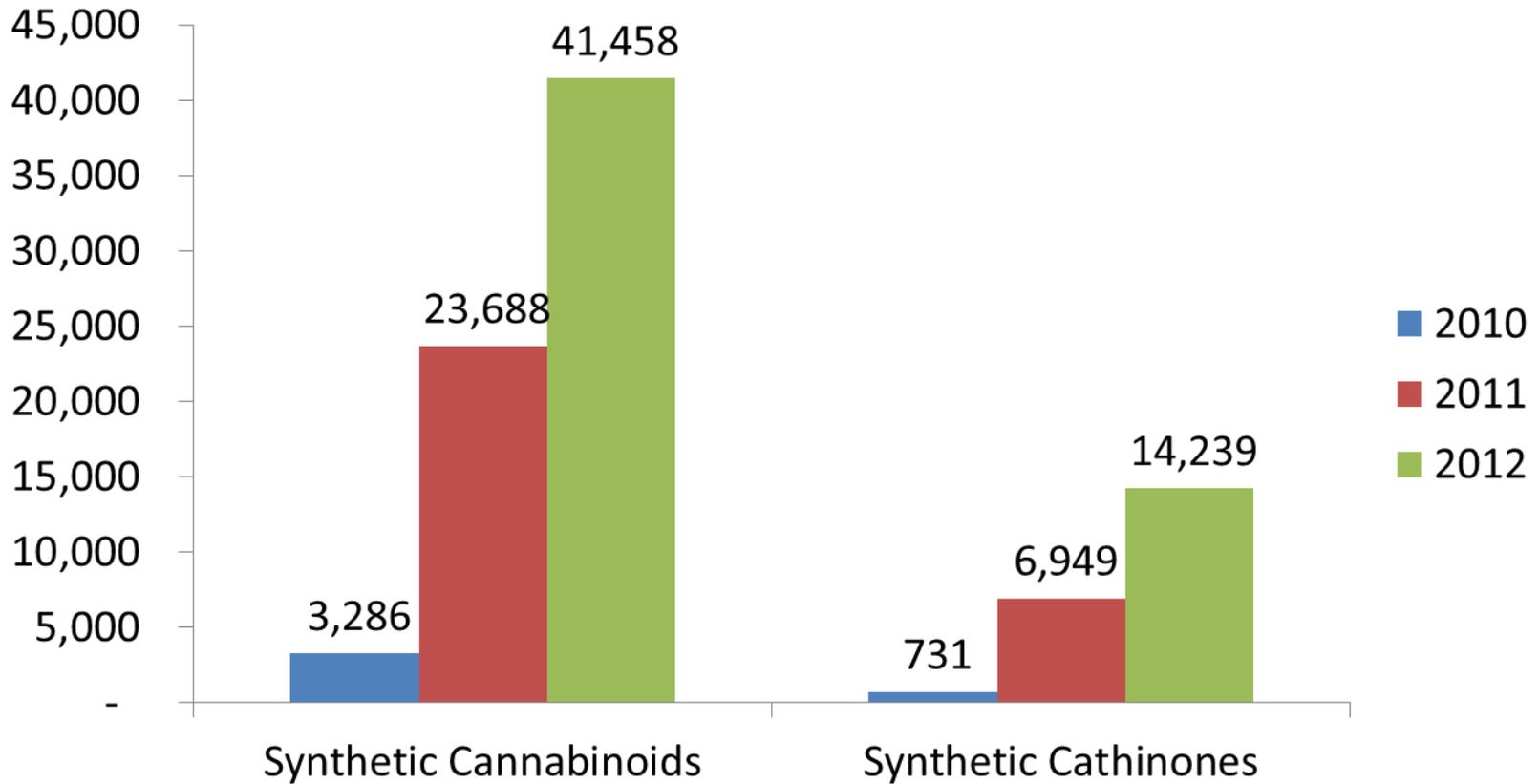
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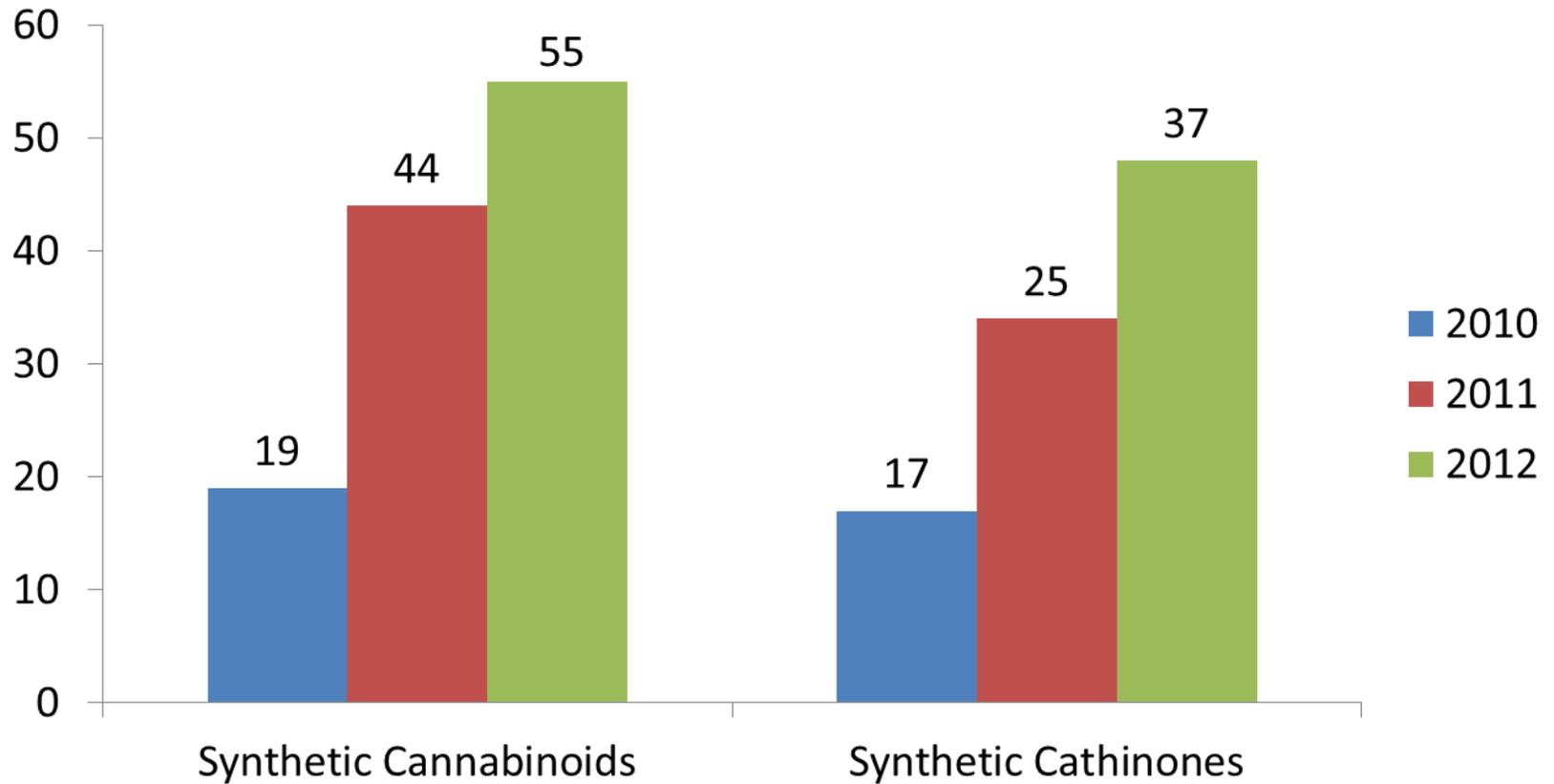
IHS Center for Tele-Behavioral Excellence

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

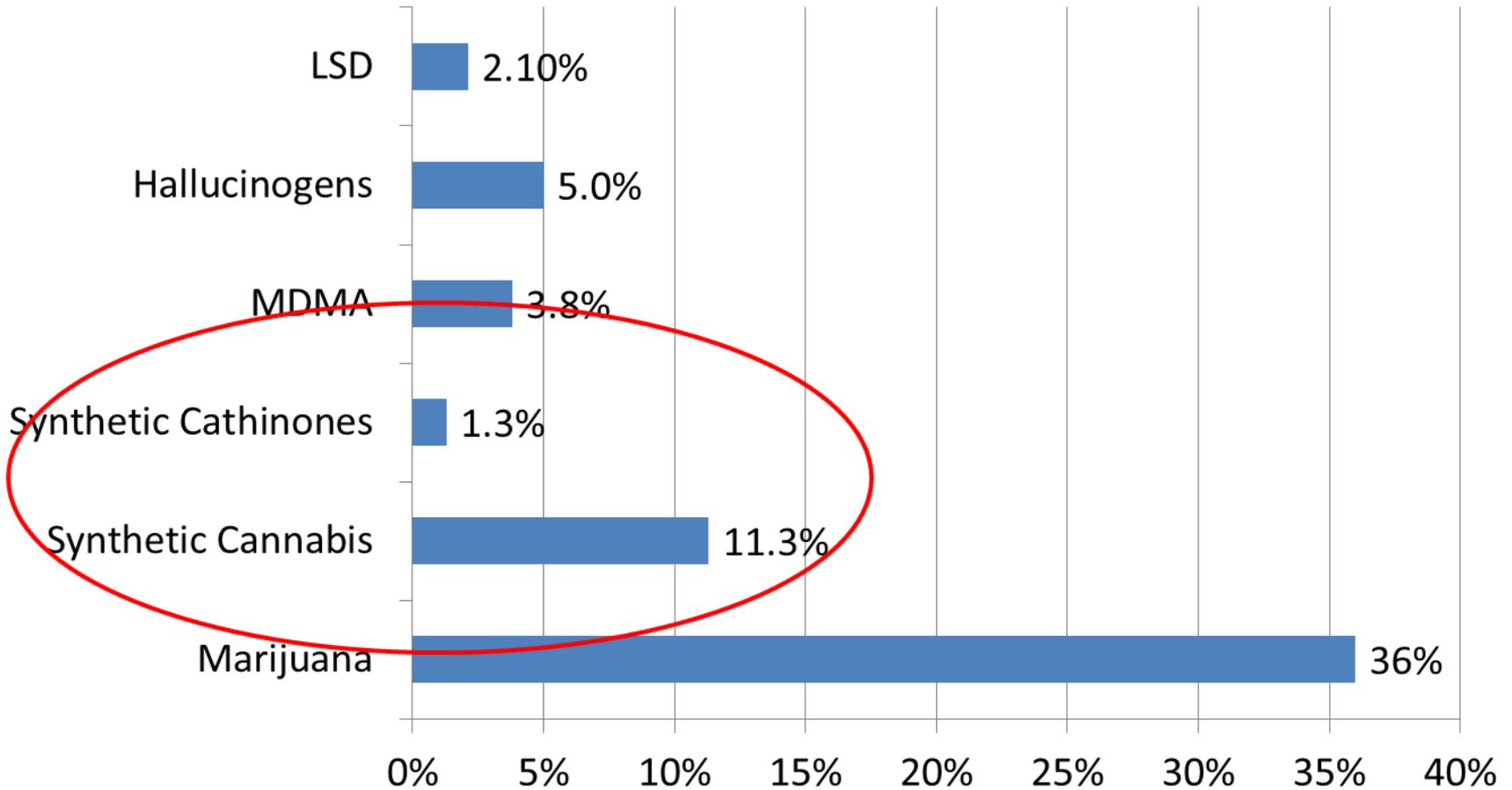
Emerging Drug Items Identified in U.S. NFLIS Forensic Labs: 2010-2012



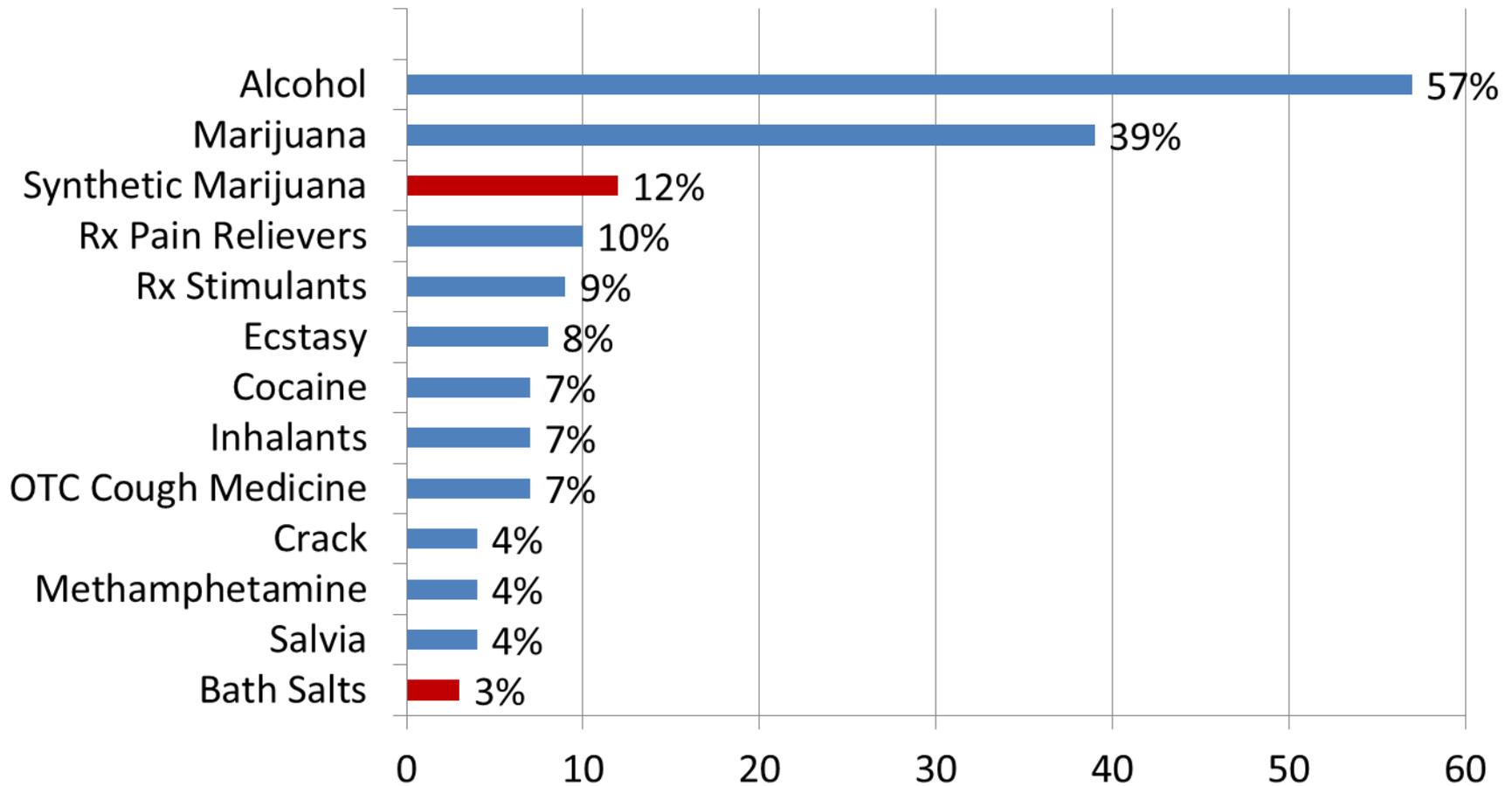
Number of Unique Types of Synthetic Drugs Identified Nationally: NFLIS (2010-2012)



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)

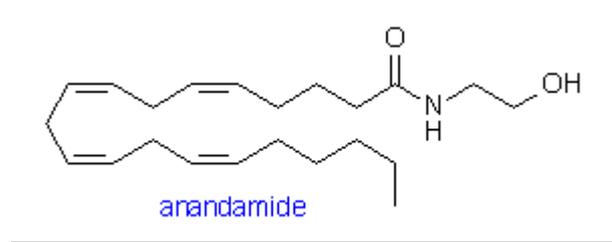


SOURCE: Adapted by CESAR from The Partnership for a Drug-Free America and the MetLife Foundation, *The Partnership Attitude Tracking Study (PATS): Teens and Parents, 2013*.

"SPICE" [SYNTHETIC CANNABINOIDS]

What is it? Is it safe?

Anandamide- Endogenous Cannabinoid



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”

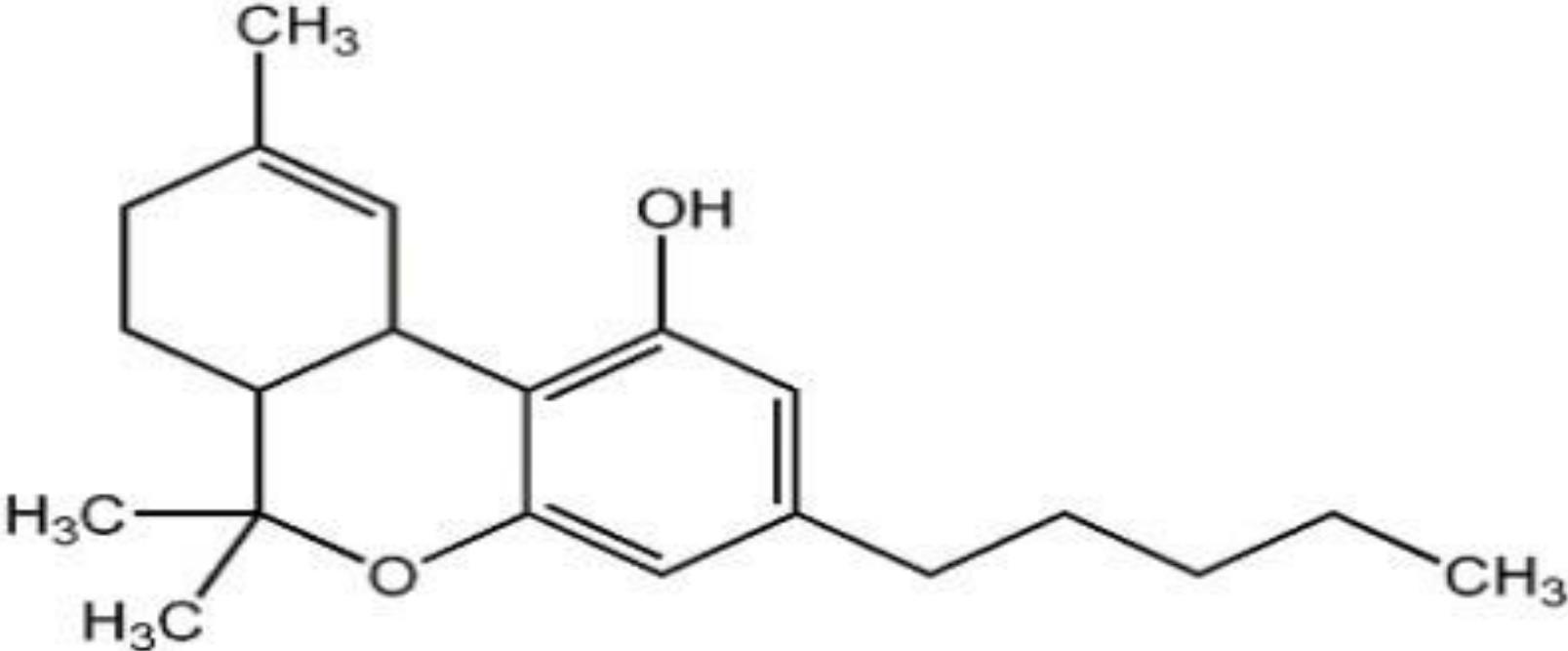
Endocannabinoids are important!

- 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

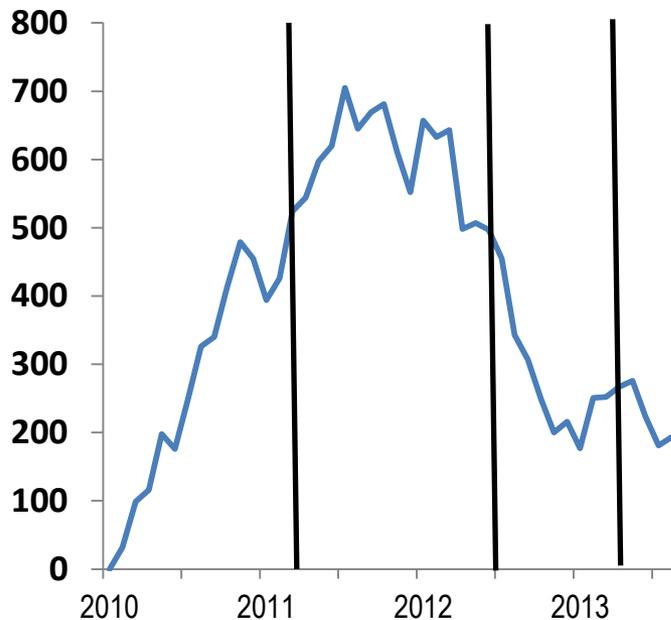
- NONE detected in standard urine tests
- GC/MS can detect up to 17 common ones
- LC-MS/MS can pick up several more
- Commercial blood tests can detect several
- Window: 48-72 hours
- Check with your local labs!

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.

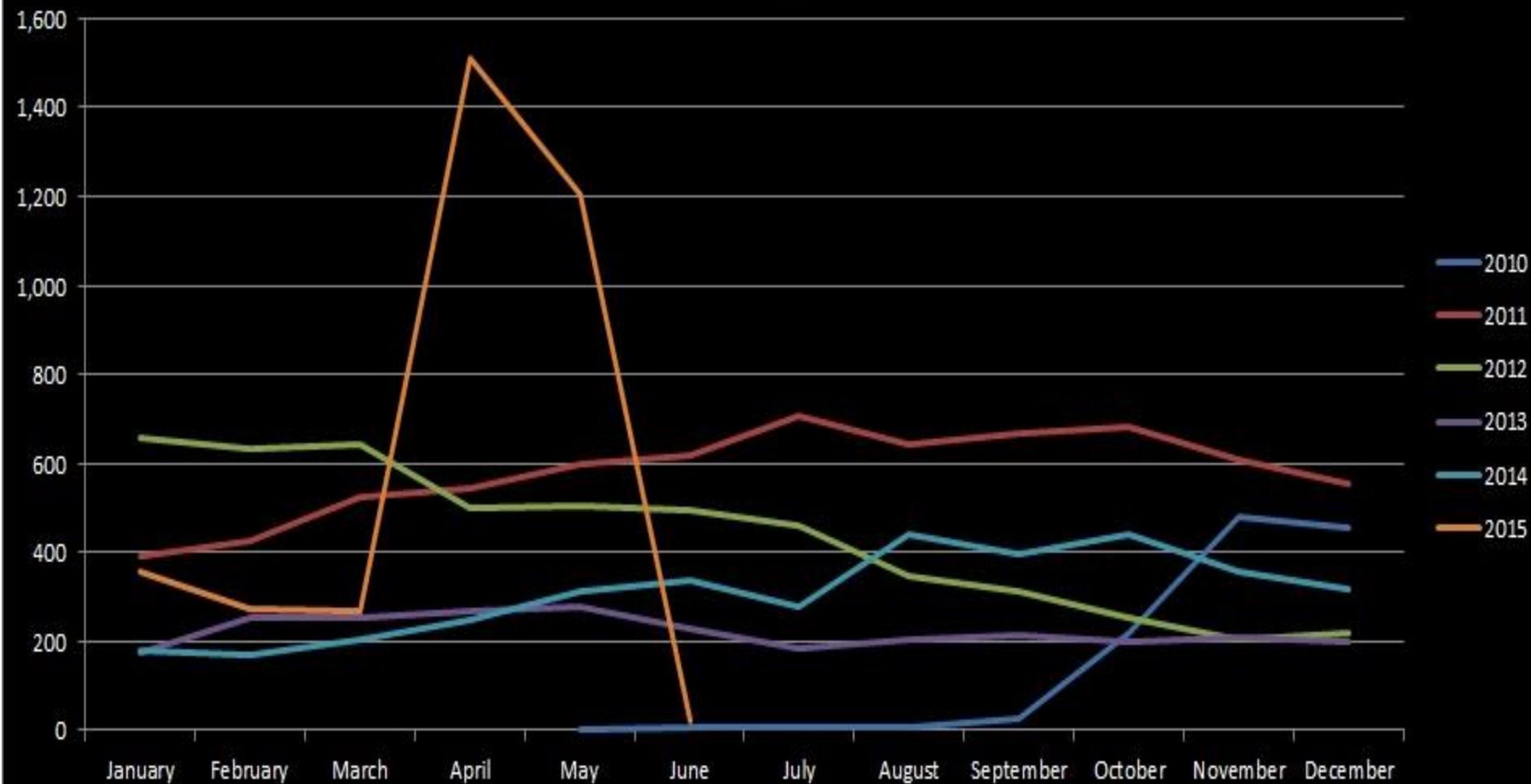
Recent News

- Surge in synthetic cannabinoid exposures and poison control calls in April and May 2015
- Northeastern states and Southern states particularly effected
- NY: over 160 hospitalized following synthetic cannabinoid use in 2 weeks in April, 2015

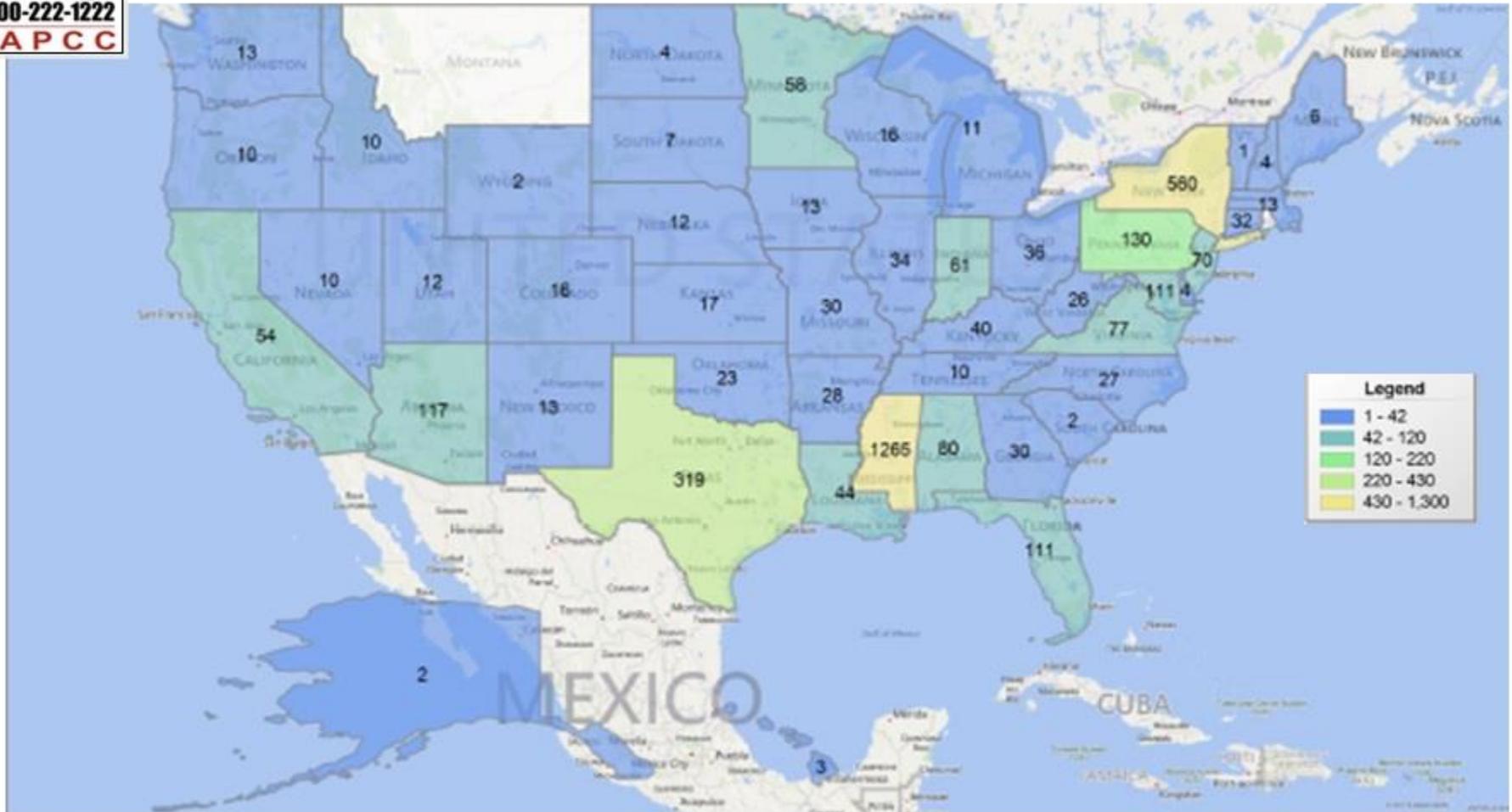
Recent news: Poison control center calls

- 2013: 2668
- 2014: 3680
- 2015 through June 1: 3641
- New compounds: AB-Chimnaca, Fubinaca
- New street names: Blonde, Summit, Standard, Blaze, Red Dawn x, Citron, Green giant, Smacked, Wicked X, AK-47, Geeked Up, Ninja, Caution, Red Giant, Keisha Cole

AAPCC Poison Center Synthetic Marijuana Exposure Calls (2010 -2015)



Synthetic Cannabinoid Calls to U.S. Poison Centers (1/1/15-5/31/15)



PLEASE NOTE:

- These data are only representative of calls received by the poison centers and may not reflect the actual severity of the problem in the U.S. or any specific geographic location.
- As there is no mandatory reporting, there may be emergency room presentations and hospital admissions of which poison centers are unaware.
- Subject to the above bullets, these numbers are largely reflective of those users/abusers who have experienced adverse effects from the use of these products significant enough to warrant poison center or other health professional intervention; not all individuals who use/abuse such products call poison centers or visit emergency rooms..
- Nevertheless, the data are a good surrogate marker for rising use/abuse patterns and patterns of adverse medical outcomes associated with their use.
- For more information about the American Association of Poison Control Centers (AAPCC) data, please visit: <http://www.aapcc.org/data-system/>

Demystifying HALLUCINOGENS

Nomenclature

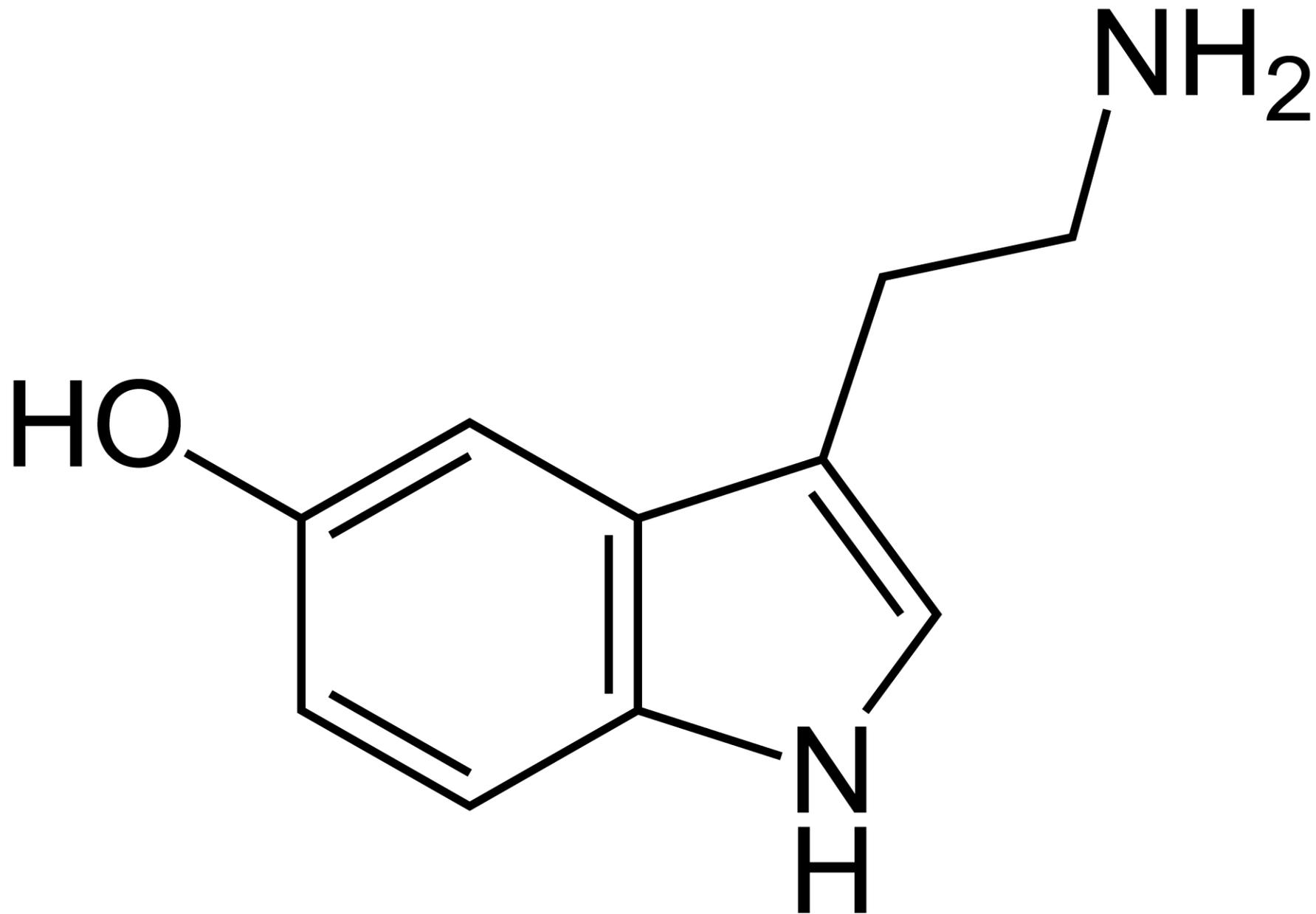
- Hallucinogen
- Psychedelic [makes manifest the hidden realities of the mind]
- Psychotomimetic
- Entheogen [Generates the God within]

Hollister's Criteria

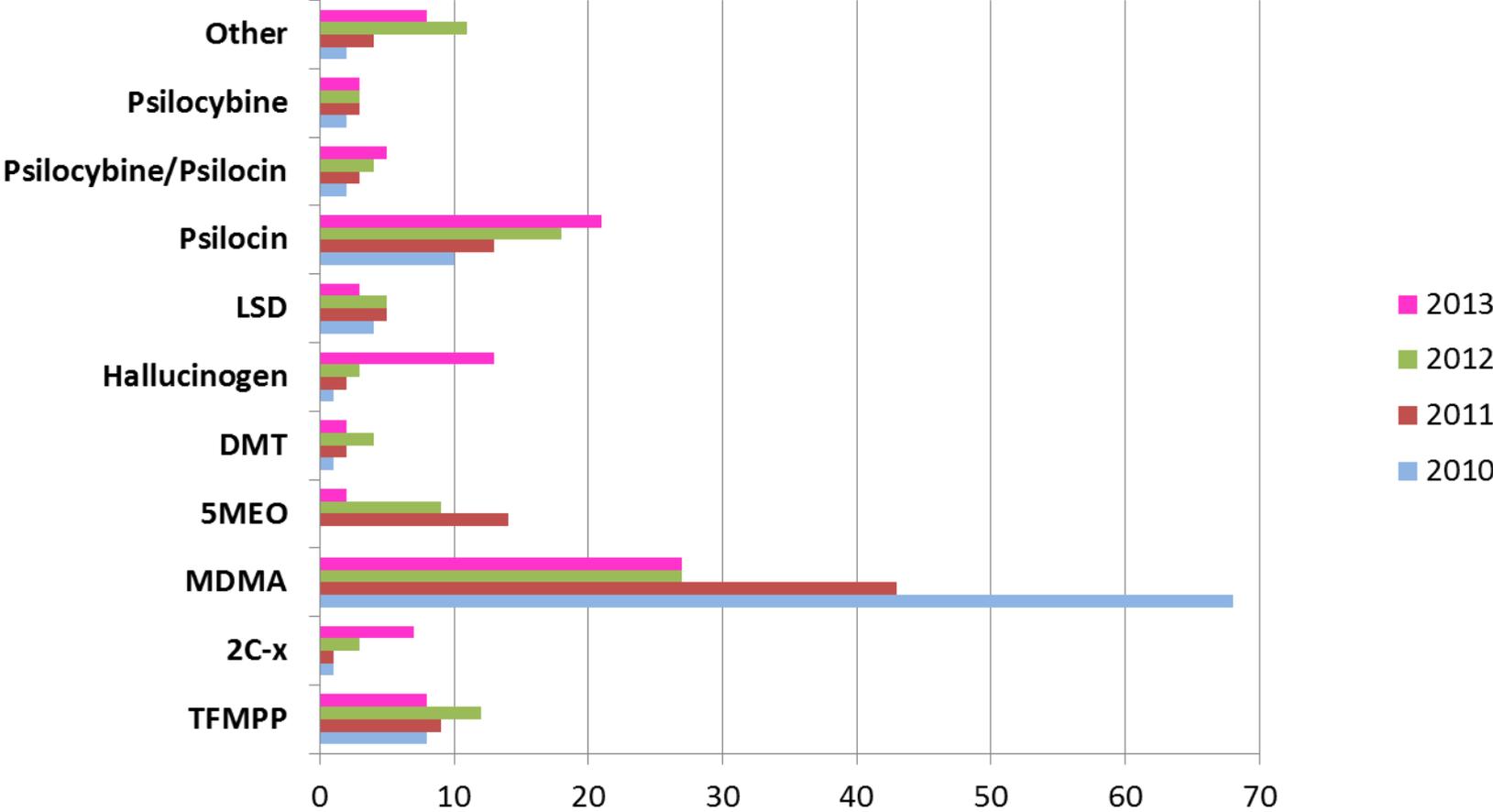
- Changes in thought, perception, and mood predominate
- Intellectual and memory impairments minimal
- Stupor, narcosis, or excessive stimulation NOT integral effects
- Minimal autonomic nervous system side effects
- Addictive craving **absent**

Classic hallucinogens

- Hollister's criteria **PLUS**
 1. Bind at 5-HT₂ serotonin receptors
 2. are recognized by animals trained to discriminate 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from vehicle.



Prevalence



Prevalence

- Lifetime: 14.8%
- Past year: 1.8%
- Age 12-17: 4.1% lifetime/3.0% past year
- Males: 18.5%/2.3%
- Females: 11.3%/1.3%
- Caucasian: 17.8/1.9
- Black/African American: 6.6%/1.4%
- AI/AN: 28.3%/6.6%
- Asian: 5.5%/0.8%
- Hispanic/Latino: 9.5%/1.7%

Effects of hallucinogens- Somatic

- Dizziness
- Weakness
- Tremors
- Parasthesias
- Drowsiness
- Nausea
- Blurred vision

Effects of hallucinogens- perceptual

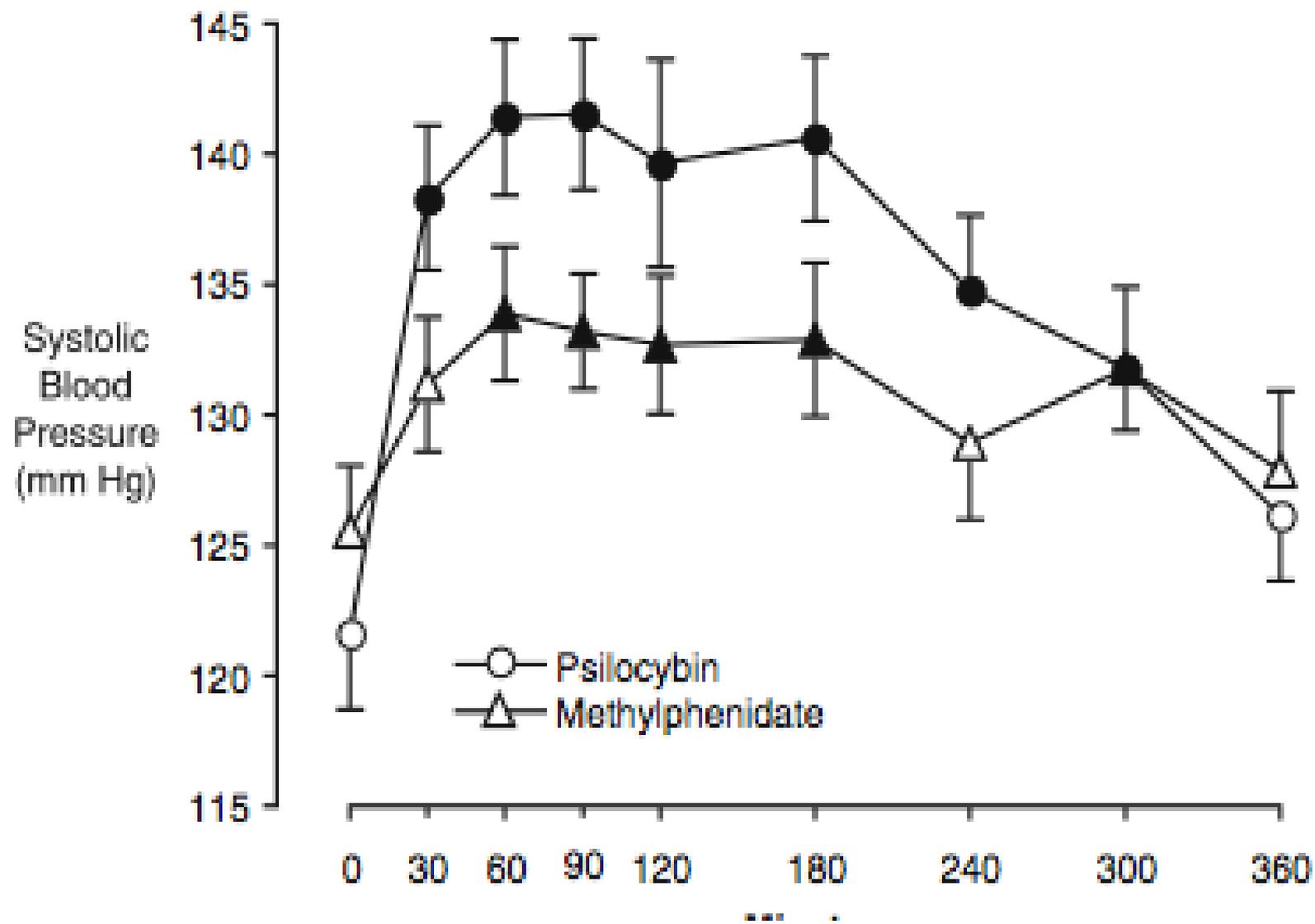
- Altered shapes and colors
- Difficulty focusing on objects
- Heightened sense of hearing
- Synesthesia- tasting colors, seeing music etc.
- Illusions
- True hallucinations- less common
- Altered sense of time

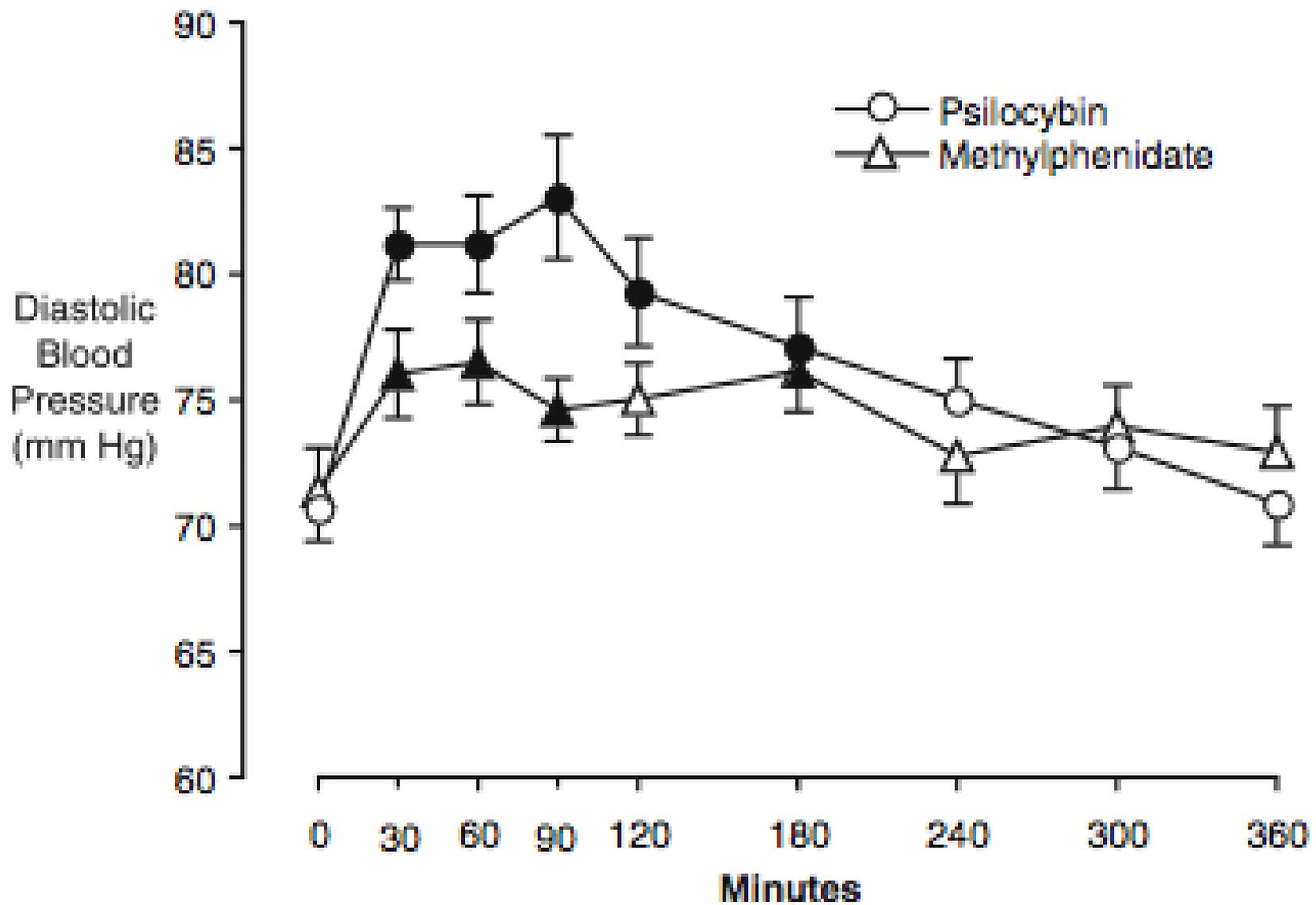
Other notable effects of hallucinogens

- Affective component- alterations in mood
- Anxiety/tension
- Depersonalization
- Dream-like state
- Difficulty expressing thoughts

Four stages of hallucinogenic experience

- Perceptual
- Biographical
- Symbolic
- Spiritual





“Bad trips”

- Challenging experiences
- Affective, perceptual
- Highly dependent on “set” and “setting”
- Use grounding techniques [deep breathing]
- Usually amenable to “talking down”
- May use benzodiazepines or antipsychotics for more difficult experiences

Classification

- Two subtypes of arylalkylamines
 1. Indolelalkylamines- Bind to 5-HT_{2A}, 2B, 2C, 1A
 2. Phenylalkylamines- selective for 5-HT_{2A}

Note: Arylalkylamines can also be stimulants or empathogens based on their molecular structures

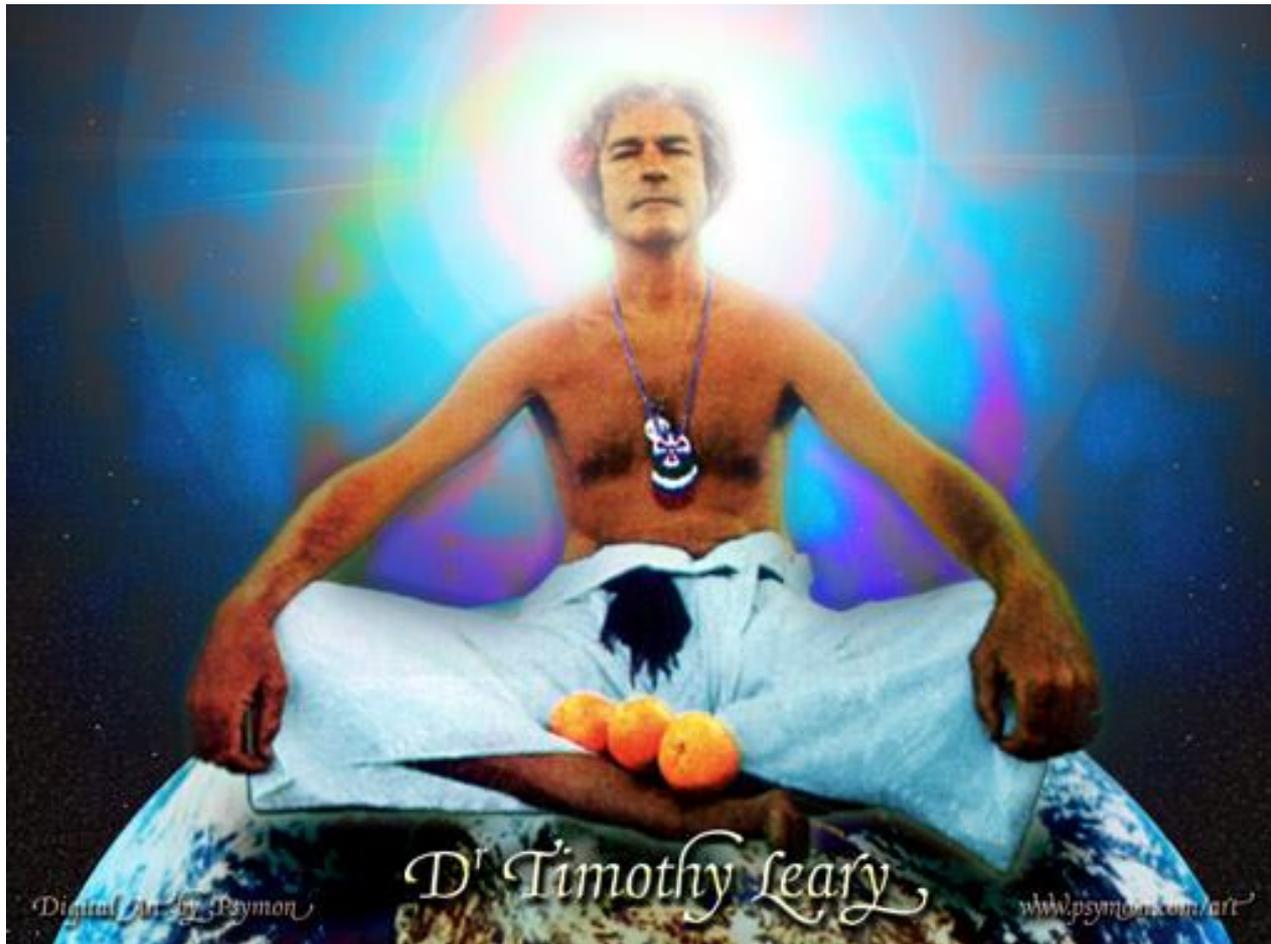
Indolealkylamines: substituted tryptamines

- DMT [N,N- Dimethyltryptamine]
- Ayahuasca
- Psilocybin/Psilocin
- Lysergamides [LSD]
- Beta-carbolines [harmaline]

Indolealylamines-lysergamides



Indolealylamines-lysergamides



Indolealylamines-lysergamides



**turn on
tune in
drop out**

PHENYLALKYLAMINES

Phenylalkylamines

- Largest group of classic hallucinogens
- Mescaline [peyote, San Pedro]
- 2-CB [“nexus”]
- DOM, DOB, DMA, MDA, many others

Peyote

- Sacramental use within Native American Church
- Grows within a 50 mile distance of Rio Grande along US-Mexico border, and in hills north of Mexico City
- Buttons harvested from top of peyote cactus
- Onset 30-60 min: nausea, increased respiration rate, minor perceptual changes
- Next several hours [5-10]: classic hallucinogen effects

DOM

- Very potent
- Results from structural modification of mescaline-like substances
- Used as model hallucinogen in drug discrimination studies

MDA

- Stimulant + hallucinogenic effects
- Modified to form MDMA [“ecstasy”]- stimulant + empathogenic effects

Endless combinations are possible

- By changing the molecular structure, you can get hallucinogen, empathogen, stimulant, or a combination of these three!

Alexander “Sasha” Shulgin

- Discovered, synthesized, and personally tested over 200 psychoactive substances for their psychedelic properties
- Authored PIHKAL, TIHKAL [Phenethylamines and Tryptamines I Have Known and Loved]
- Popular creations include the DOx creations [DOB, DOM], and 2C series [2CB, 2CI]

“Magical half dozen”

- DOM
- 2-CB
- 2-CE
- 2C-T-2
- 2C-T-7
- [mescaline]

2C-phenylethylamines

- A broad range of compounds that share a common phenylethan-2-amine structure.
- 2 C-X can be snorted or dissolved into a liquid and placed on blotter paper under the tongue.
- May last 6-10 hours; onset takes 15 min- 2 hours

2C-phenylethylamines

- Almost all of the 2C-phenethylamines are produced in Asia, principally China, but some small labs in the U.S. are capable of producing 2C (usually 2C-B).
- In 2011, DEA offices throughout the country began noting the increasing availability and abuse of 2C at raves and in nightclubs, particularly by teenagers and young adults.
- NFLIS labs nationwide identified 253 reports of phenylethylamines in 2010, 336 in 2011, 828 in 2012, and 230 through May 2013.

2C-B [“Nexus”]

- Used by underground therapists in 1970s
- Create a warm atmosphere, ego weakening, therapeutic rapport
- `My body was flooded with orgasms - practically from just breathing. The love-making was phenomenal, passionate, ecstatic, lyric, animal, loving, tender, sublime....I am aware of every muscle and nerve in my body, unbelievably erotic, quiet and exquisite, almost unbearable..'
- Sold over the counter as a sexual enhancer worldwide until 1993
- Popular at raves; banned by DEA

2C-B [“Nexus”]

- ‘When I take Nexus, I merge with the music, become one with the crowd, and fuse with the whole of Planet Earth. This isn't a drug, it's a trance-dance sacrament.’
- ‘a cross between the warm, lovey-dovey feeling produced by Ecstasy and the visual patterning you get when you take magic mushrooms’
- ‘I tried it once and all that happened was that I felt jittery, disorientated and strung out for the entire evening.’

2C-I

- Became popular between 2001-2005
- Strong stimulant component, with associated hallucinogen and empathogen components
- Often delayed effect [users taking multiple doses as a result]
- Users report virtually no nausea, vomiting or muscle cramps [as opposed to 2C-T-2 and 2C-T-7]
- ‘deeper, more purely psychedelic and less sensory’ compared to 2C-B

2C-C-NBOMe, 2C-I-NBOMe, 25-I-NBOMe, Mescaline-NBOMe

- New class of 2C drugs
- NO history of human consumption prior to 2010
- Linked to several hospitalizations and deaths
- Usually result of people taking upto 10x the recommended doses
- “N-Bomb”, “Smiles”

2C-C-NBOMe, 2C-I-NBOMe, 25-I-NBOMe, Mescaline-NBOMe

- Strongly active at the **sub-milligram dose (a Super Potent drug)**
- Most 25I and 25C is sold as **pure powder**
 - Weighing and handling pure high-potency chemicals such as LSD or 25I-NBOMe should be performed wearing eye protection, gloves, and a filter mask
- Perhaps the greatest risk of the wide availability of pure NBOMe powders is **confusing one white powder for another**, or simply **misunderstanding the difference** between one psychedelic or stimulant drug and another
- In 2011, 10 items of the NBOMe family were seized and identified in NFLIS forensic laboratories, as compared to 447 in 2012.

2C-C-NBOMe, 2C-I-NBOMe, 25-I-NBOMe, Mescaline-NBOMe

- Effective November 15, 2013, the United States Drug Enforcement Administration (DEA) made the synthetic phenethylamines 25I-NBOMe, 25C-NBOMe, and 25B-NBOMe Schedule I, illegal drugs under the Controlled Substances Act (CSA) for the next two years.
- Plan to make them permanently illegal

Hallucinogen Persisting Perception Disorder (HPPD)

- Re-experiencing of perceptual symptoms experienced while intoxicated following cessation of use = flashbacks
- Unrelated to dose or number of exposures
- Usually resolves within 1-2 years of last use
- Can be triggered by other substance use

Conclusions

- Synthetic substances of abuse are evolving at a very rapid rate
- This has made it difficult for clinicians and law enforcement agencies to keep up
- It is imperative for us to understand these substances in order to better serve our communities