Part 2: Hallucinogens

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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.
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)

- **Alcohol**: 57%
- **Marijuana**: 39%
- **Synthetic Marijuana**: 12%
- **Rx Pain Relievers**: 10%
- **Rx Stimulants**: 9%
- **Ecstasy**: 8%
- **Cocaine**: 7%
- **Inhalants**: 7%
- **OTC Cough Medicine**: 7%
- **Crack**: 4%
- **Methamphetamine**: 4%
- **Salvia**: 4%
- **Bath Salts**: 3%

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. Indolelakylamines- Bind to 5-HT2A, 2B, 2C, 1A
  2. Phenylalkylamines- selective for 5-HT2A

Note: Arylalkylamines can also be stimulants or empathogens based on their molecular structures
INDOLEALKYLAMINES: SUBSTITUTED TRYPTAMINES
DMT [N,N- Dimethyltryptamine]
DMT [N,N- Dimethyltryptamine]

• Prototypical of this subtype
• Naturally occurring [Sonoran desert toads, Mimosa hostillis, phallaris grass etc.]
• Rapid onset of action [5 minutes, or less]
• Brief duration of action [30 minutes]
• Characteristic odor
• Smoked or injected
• Not orally stable
• Released by pineal glands during times of stress
• Dream states; near death experiences
Ayahuasca

• DMT + harmaline [MAOI]
• Psychotria viridis + Banisteriopsis caapi
• Ceremonial uses among indigenous populations in the Amazon
• Ceremonial uses among the mestizo religions [uniao de vegetal, santa]
Psilocybin and Psilocin

- Tryptamines that naturally occur in certain types of mushrooms
- “shrooms”
- Cross-Tolerance with LSD
- Rapid tolerance build up
- Onset within 30 minutes
- 4-6 hours duration of effects
- Psilocybin metabolized to psilocin, the psychoactive alkyloid
- Nausea, panic attacks, anxiety are common adverse effects
- Mild BP elevation usually observed
Psilocybin

Psilocin
Indolealylamines-lysergamides
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Indolealylamines-lysergamides

• LSD [lysergic acid diethylamide]
• Does not occur naturally
• Synthesized by Albert Hoffman [1938]
• “... affected by a remarkable restlessness, combined with a slight dizziness. At home I lay down and sank into a not unpleasant intoxicated[-]like condition, characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After some two hours this condition faded away.”
Indolealylamines-lysergamides

• Highly potent
• Water soluble, clear while odorless crystals
• Sheets of thin blotter paper with dried solution of LSD [most common]
• Sugar cubes [“Dropping acid”]
• Pills [“microdots”], or thin gelatin squares [“windowpanes”]
Indolealylamines-lysergamides

• Onset 30-60 minutes
• Peak 2-4 hours
• Duration 8-12 hours
Indolealkylamines- Beta-carbolines

- Harmaline, harmine
- Bind to, but do not activate 5-HT2A
- Not psychedelic
- Act as MAOI
- Component of ayahuasca and “pharmahuasca”
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 [“ecstacy”] - 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 [Phenylethylamines 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.

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
POSSIBLE THERAPEUTIC USES
Psilocybin and Mystical Experiences

• Double blind study done at Johns Hopkins University
• At 14 month follow up:
  – 58% rated the psilocybin-occasioned experience as being among the five most personally meaningful experiences
  – 67%- five most spiritually significant experiences of their lives
  – 64% indicated that the experience increased well-being or life satisfaction
Among the Top 5 Personally Meaningful Experiences of Lifetime

- Methp 2 mo. (n=29)
- Psil 2 mo. (n=29)
- Psil 14 mo. (N=36)
Among the Top 5 Spiritually Significant Experiences of Lifetime

- Methp 2 mo. (n=29)
- Psil 2 mo. (n=29)
- Psil 14 mo. (N=36)
Increased Current Personal Well-Being or Life Satisfaction

Percentage of Participants

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (n)</th>
</tr>
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<tbody>
<tr>
<td>Methp 2 mo.</td>
<td>25% (n=29)</td>
</tr>
<tr>
<td>Psil 2 mo.</td>
<td>75% (n=29)</td>
</tr>
<tr>
<td>Psil 14 mo.</td>
<td>75% (N=36)</td>
</tr>
</tbody>
</table>
Other Notable investigations

- Large double blind, placebo controlled trial of psilocybin and cancer related anxiety at Johns Hopkins, New York University, and Harbor-UCLA
- Small study of Psilocybin and OCD at University of Arizona
Psychedelics and Addiction Treatment

• Over one hundred years ago William James described the phenomenon of sudden transformative change of a religious or spiritual nature, which was often accompanied by changes in behavior such as the abrupt onset of sobriety in alcoholics.

• More recently, William R. Miller and others have elucidated the nature of what has been termed “quantum change”
Psychedelics and Addiction Treatment

- Over 30 studies evaluating LSD for treatment of alcoholism between 1950-1970
- Most studies plagued with methodology
- However, some of the best-designed studies (e.g. (Hollister, Shelton, & Krieger, 1969; Ludwig, Levine, Stark, & Lazar, 1969) appear to show an effect on drinking of 1-3 months duration following a single dose of LSD in a supportive environment
- Recent meta-analysis: NNT of 6 [slightly less than naltrexone!!]
Psychedelics and Addiction Treatment

• hallucinogenic drug experiences, undergone in a relatively structured supportive setting, may provide a useful model of quantum change
• Such carefully tailored and purposeful experiences (as opposed to misuse or “recreational” use) may be associated with reduced use of other substances
Psychedelics and Addiction Treatment

- Ibogaine for heroin and alcohol dependence
- Ketamine for heroin and alcohol dependence
- Cross-sectional studies consistently show reduced rates of alcohol dependence among
  - Native American Church [Peyote]
  - US and Brazilian religions using ayahuasca
Psychedelics and Addiction Treatment

• University of New Mexico psilocybin for treatment of alcohol dependence [PI: Michael Bogenschutz]
• Safety and feasibility study completed
• Double blind placebo controlled study with N=180 under way, with NYU as a second research site
• https://www.youtube.com/watch?v=uX5MrmR86mk
Conclusions

• Classic hallucinogens exert their actions through agonism at the 5-HT2 serotonin receptor
• Classic hallucinogens have a major effect on thought, perception and mood
• Classic hallucinogens do not induce addictive craving
• There are many new and emerging hallucinogens whose actions and effects are poorly understood, and may pose a risk to public safety
• There are potential therapeutic applications of classic hallucinogens