Background

What qualifies as hallucinogenic?
1. Single effective dose
2. Produce noticeable changes in thought, mood, and perception without memory loss
3. Produce neither narcosis nor excessive stimulation
4. Produce no severe autonomic side effects
5. Are non-addictive


Unlike other psychoactive drugs, like stimulants and opioids [see Morphinans, DJJ], these drugs do not merely amplify familiar states of mind, but rather induce experiences that are qualitatively different from those of ordinary consciousness:
- trance
- meditation
- dreams
- insanity
- religious ecstasy
- near-death experiences

Typically broken into three categories: **psilocybin, dissociatives, and deliriants**

**Psychedelics** alter cognition & perception, and typically fall into three classes:
- tryptamines, phenethylamines, and lysergamides

**Dissociatives** distort perception and produce feelings of detachment from environment and self.

**Deliriants** induce (you guessed it) delirium, as opposed to the more lucid states of the other two classes.

**Psychedelics**

Often referred to as serotonergic or classical hallucinogens

- Project MKULTRA
- Problem solving/creativity
- Psychotomimetic
- Adjunct to therapy
- Terminal illness
- Alcoholism
- Antipsychotic drugs

"Naturally occurring hallucinogenic drugs played a significant role in the development of philosophy and religious thought in many earlier cultures... How many Neolithic hunters, one might wonder, eking out an existence in the wild, were likely to sit before the fire at night contemplating the nature of man and the meaning of life?"


"I consider LSD to be a powerful unspecified amplifier or catalyst of biochemical and physiological processes in the brain." Grof, S. *Observations from LSD Research* 1975, New York: Viking Press.

Psilocybin ("magic" mushrooms), mescaline (peyote cactus), and dimethyltryptamine (various sources) have been used medicinally and spiritually since before recorded history.

The discovery of LSD by Albert Hofmann in 1943 (and likely the popularity of hallucinogens in the ensuing decades) sparked research into the usefulness of these compounds.

-Synthetic THC is used to treat nausea and vomiting brought on by chemotherapy, as well as an appetite stimulant.

-CBD is generally believed to have a wider scope of medical applications, and is "less mind-altering".

CB1 antagonist Rimonabant was explored as an obesity treatment and appetite suppressant. "One European clinical study... found that a daily dose of 20 mg coupled with a reduced calorie diet led to an average sustained weight loss of 7 kg vs. an average sustained weight loss of 2 kg in the placebo group, treated with diet alone." Since, rimonabant has been removed from the market due to risk of severe depression and suicidal thoughts.

Therapeutic Hallucinogens


Delirants

Delirants induce delirium, and generally refer to anticholinergic drugs, which block the neurotransmitter acetylcholine in both the CNS and PNS. Some examples include uncured tobacco (in high enough doses), the tropane alkaloids found in Mandrake & Jimson Weed, and OTC drugs like benadryl and dramamine.


Cannabinoids

Δ9-tetrahydrocannabinol

Cannabidiol

anandamide

2-arachidonoylglycerol
Therapeutic Hallucinogens

Dissociatives - KOR agonists

- Nonselective - 5HT, KOR, D, M, A, N
- Used to treat fatigue, hunger, and thirst
- Opiate addicts reported they lost the desire to use
- Studies in cocaine self-administering rats corroborate

Ibogaine
R = OMe

Ibogamine
R = H

N

H

R

N

- Nonselective - 5HT, KOR, D, M, A, N
- Used to treat fatigue, hunger, and thirst
- Opiate addicts reported they lost the desire to use
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Salvinorin A
- Salvia divinorum
- Religious sacrament
- Analgesia & addiction treatment

Serotonin Releasers

- Empathogen
- Neither a psychedelic nor a stimulant
- Empathy, love, and closeness to others

"In a double-blind placebo controlled pilot study investigating the efficacy of MDMA in the treatment of PTSD, 20 individuals diagnosed with PTSD took part in 2 drug administration sessions and 11 psychotherapy sessions. The MDMA group showed 83% clinical response to treatment compared to 25% in the placebo control group at two month follow-up."

Mesembrine is found in the herb kanna, used by South African hunter-gatherers as a mood-altering, empathogenic substance. It is generally believed to be a selective serotonin reuptake inhibitor. Kanna has been used to decrease anxiety and treat depression.

Dissociatives

Dissociatives produce a feeling of detachment from the environment and self. They block signals to the conscious mind from other parts of the brain, and often cause sensory deprivation. Some may induce euphoria, and they are generally associated with depressant effects. Two classes are NMDA (N-methyl-D-aspartate) antagonists and κ-opioid receptor agonists.

Syntheses of Lysergic Acid

1. H₂, Pd/C
2. BzCl (58%)

1. Ac₂O, Δ
2. AlCl₃ (60%, sole diast.)

Br \rightarrow \text{CO}_2\text{Et}
Zn, THF

1. MeI, NaH
2. HBr, DCM
3. Et₃OBF₄; H₂O (44%, 3 steps)


General Tryptamine Synthesis

1. KH, nBuLi,
B(OBu)₃ (88%)
2. Pd(PPh₃)₄,
Na₂CO₃ (aq)
EtOH (91%)

1. NaBH₄,
CaCl₂ (85%)
2. MnO₂ (92%)

NaOH,
MeOH,
(91%)

“Mescaline... produces symptoms almost identical with schizophrenia.”

Lisuride, an antiparkinson agent available in several EU countries and China is nonhallucinogenic in humans. It is also used to treat migraines in low doses.

General Phenethylamine Synthesis

1. KH, nBuLi,
B(OBu)₃ (88%)
2. Pd(PPh₃)₄,
Na₂CO₃ (aq)
EtOH (91%)

1. NaBH₄, TFA
2. Mel, DCM
3. NaBH₄, MeOH
4. NaOH, EtOH

Syntheses of Lysergic Acid

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\begin{align*}
\text{Kornfeld, E.C.; Fornefeld, E.J.; Kline, G.B.; Mann, M.J.; Morrison, D.E.;} \\
\text{Jones, R.G.; Woodward, R.B.} & \text{ J. Am. Chem. Soc. 1956, 78, 3087.}
\end{align*}
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