Non-Hallucinogenic Psychedelic Analogs to Mitigate Anxiety, Depression, and Addiction

TTI/Vanguard's Resilience Conference

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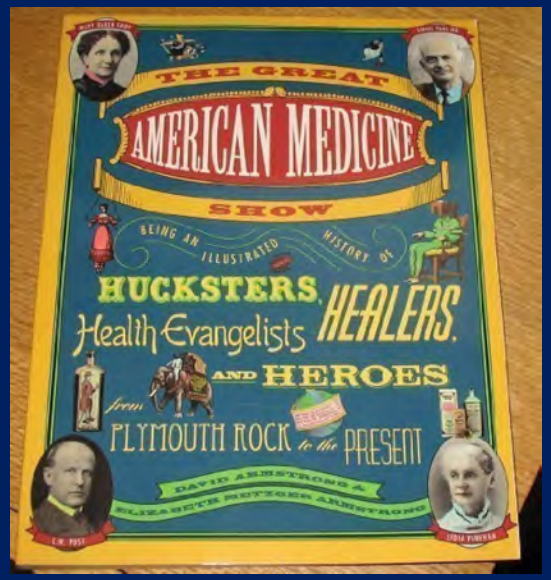
Wonder Drugs That Help Reduce or Eliminate

- Anxiety
- Depression
- Posttraumatic stress disorder
- Substance use disorder (tobacco and ethanol addition)
- Obsessive-compulsive disorder
- Baldness


THE GREAT
AMERICAN MEDICINE
SHOW
BEING AN ILLUSTRATED HISTORY OF
HUCKSTERS, HEALERS,
Health Evangelists
AND HEROES
from
PLYMOUTH ROCK to the PRESENT
DAVID ARMSTRONG &
ELIZABETH PETTEGREE ARMSTRONG


THE ICE WATER STORE
ICE FOR SALE
DR. FEELGOOD
WALL DRUG

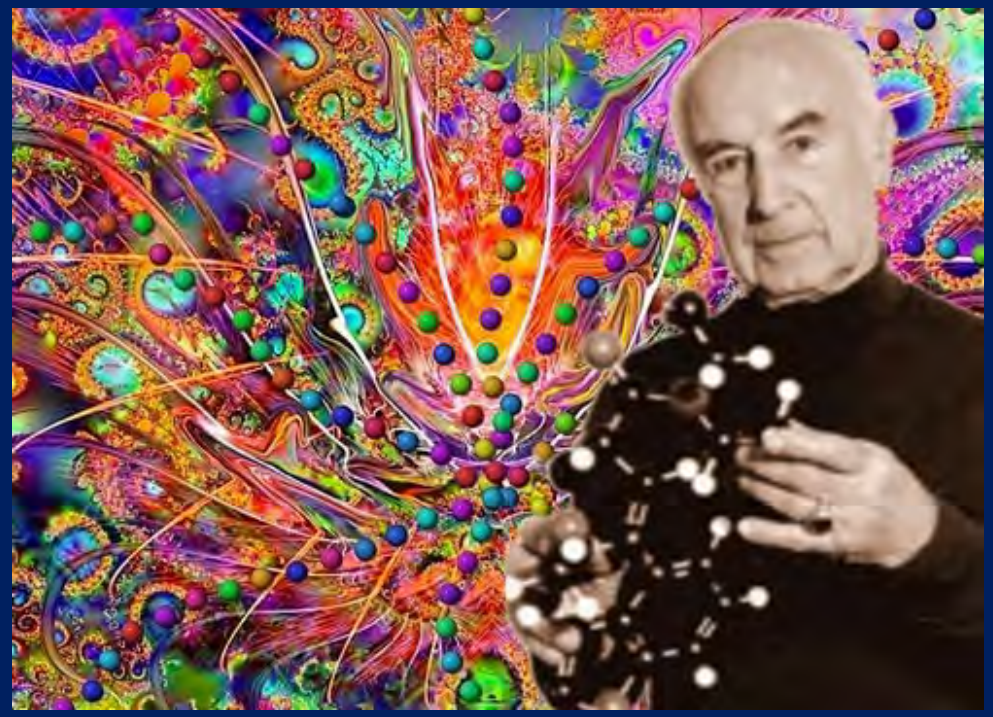
These “Wonder Drugs” Are Psychedelics, So What Are They?

Psilocybin

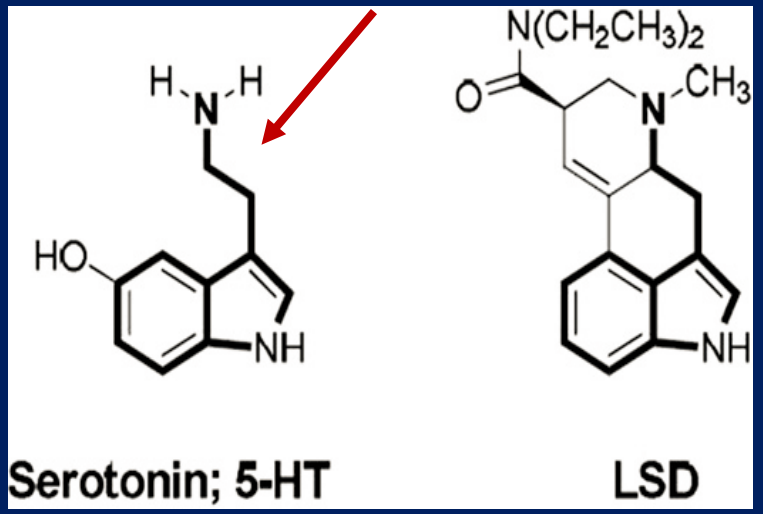
Mescaline

Ayahuasca
(Dimethyltryptamine)

Discovery of LSD
LSD Chemical Structure Similar to Neurotransmitter Serotonin (5-HT)



http://www.acidprogram.com/albert/psychedelic-albert-hoffman-with-molecule.jpg



Nichols, *Pharm Rev* 2016

Psychedelics Have Been Used for Millenia

- Psychotropic plant use dates to 5700 years in the northeastern region of Mexico
- Buttons of peyote cacti and red beans containing mescaline found in caves used for human habitation
- Mescaline still used by members of the Native American Church in ceremonies
- Psilocybin was used at least ~1,000 BC in Europe
- Ayahuasca (dimethyltryptamine or DMT) still used in Amazon for healing and spiritual ceremonies
- Lysergic acid – fungal infection of grain in Medieval Ages, produced hallucinations
- LSD-25 - first synthesized in 1938 by Hoffman
- 1943 – Hoffman accidentally poisoned himself – psychedelic effects
- Delysid (LSD) marketed by Sandoz in 1947

Effects of LSD and Early Therapeutic Uses of Psychedelics

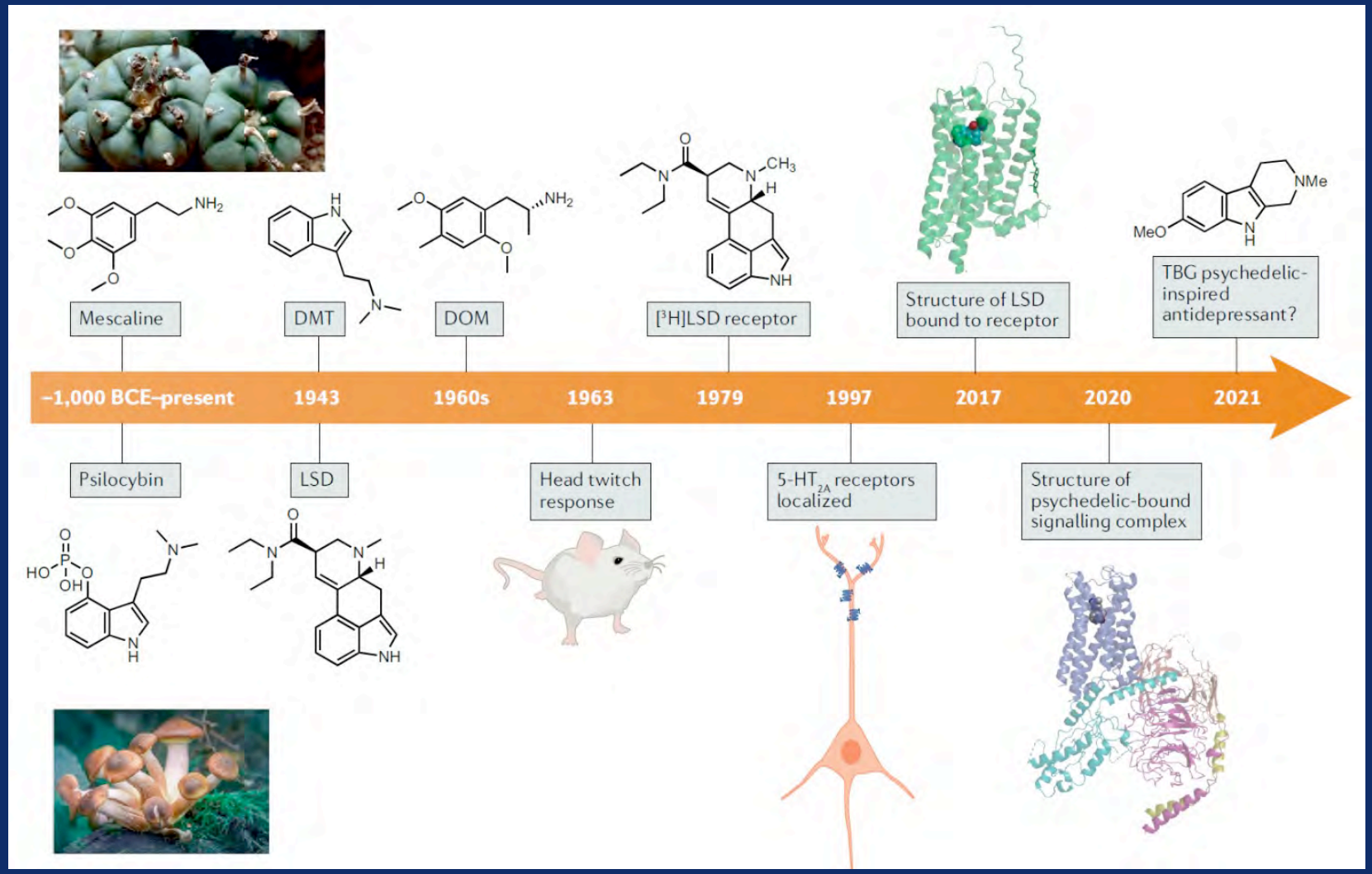
- Acute LSD intoxication mimics some symptoms of acute psychosis
  - Ego-dissolution
  - Thought disorder and visual misperceptions
  - Increased emotional connection to repressed memories
  - Spiritual awakening

  - LSD used by psychiatrists to understand acute psychosis in patients
- In the 1950's and 1960's small clinical trials with LSD, psilocybin, and mescaline
  - Depression
  - Anxiety
  - Obsessive-compulsive disorder
  - Drug abuse
- Psychedelics are not toxic
- Effects of psychedelics are long-lasting

Availability of Psychedelics Restricted

- Wide use of psychedelics in late 60's
- Hallucinogen Persisting Perceptual Disorder
- 1967 Psychedelics listed as Schedule I DEA drugs – considered to have no therapeutic potential
- Psychedelics were no longer available for basic or clinical research

Psychedelic Use and Discoveries About Them



DMT = *N,N*-dimethyltryptamine
LSD = lysergic acid diethylamide
DOM = 2,5-dimethoxy-4-amphetamine
TBG = tabernanthalog

McClure-Begley & Roth, *Nat Rev, Drug Discov* 2022

Recent Reports of Positive Therapeutic Effects of Psychedelics

- Small Clinical Studies
- Case Reports
- Reported Observations – indigenous peoples, individuals

Registered Clinical Trials

- More than 200 clinical trials with psilocybin, LSD, and dimethyltryptamine
  - Depression, Suicide, Bipolar Type II Disorder
  - Anxiety
  - Posttraumatic Stress Disorder
  - Obsessive-Compulsive Disorder
  - Anorexia Nervosa
  - Binge Eating
  - Body Dysmorphic Disorder
  - Autism
  - Cognitive Impairment
  - Substance Use Disorder (opioids, Δ^9 THC, psychostimulants, ethanol, tobacco)
  - Chronic Pain, Headache
  - Consciousness
  - Irritable Bowel Syndrome

How Do Psychedelics Work?

- Actions at serotonin, norepinephrine, dopamine, and other receptors
- Particular interest in the 5-HT_{2A} serotonin receptor
  - 5-HT_{2A} antagonists block psychedelic-induced hallucinations
  - Beneficial psychedelic effects attributed to 5-HT_{2A} stimulated activity
    - This has never been tested with psychiatric patients
    - Psychedelic actions could be due to combinations of actions at receptors

Big Problems with Psychedelics as Therapeutics

Genetic Engineering and Biotechnology News

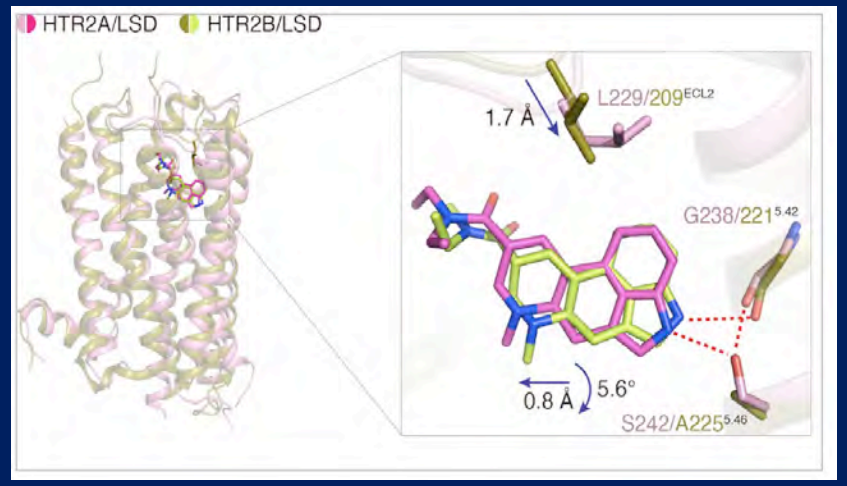
- **HALLUCINATIONS**
  - Nurse has to be constantly with patient
  - Some patients have “bad trips”
  - Some patients have “flashbacks”

How to avoid hallucinations, but have beneficial effects?

- Microdosing
  - Administer dose of psychedelic that doesn’t produce hallucinations
  - Results mixed – some reports positive, others no effects
  - Could produce cardiac abnormalities if used often due to 5-HT_{2B} activation

How to Have Beneficial Effects Without the Hallucinations?

5-HT_{2A} and 5-HT_{2B} Receptors Bound to LSD



Kim et al., *Cell* 2020

G protein signaling

β-arrestin signaling

- LSD's hallucinogenic effects are through β-arrestin activity
- Let's make a drug that stimulates the 5-HT_{2A} receptor to activate G protein signaling

Development of a Drug Without Hallucinagenic-Like Activity

de la Fuente Revenga et al.,
ACS Chemical Neuroscience 2022

5-HT_{2A} serotonin receptor biased agonist

- No hallucinogenic-like activity
- No abuse potential
- Had long-lasting anti-depressant-like actions
- Had long-lasting anxiolytic-like actions

Newer Compounds

- More specific for the 5-HT_{2A} serotonin receptor
- No 5-HT_{2B} serotonin receptor activity
- No toxicity
- Biased in G protein signaling
- Very long-lasting antidepressant-like actions

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