

# Treating Mental Health Disorders with Ketamine, MDMA and the Hallucinogens

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# Major Depressive Disorder

- Accounts date back to 2<sup>nd</sup> millennium, BCE
- Described by Greeks, Romans and Persians
- Suffered by:
  - Abraham Lincoln
  - Winston Churchill
  - Georgia O'Keefe
  - Edvard Munch
  - General William Tecumseh Sherman
  - Ernest Hemingway
  - Franz Kafka
  - Mark Twain

# Major Depressive Disorder

- Suffered by:
  - Leo Tolstoy
  - William James
  - Sigmund Freud
- Described in DSM-V

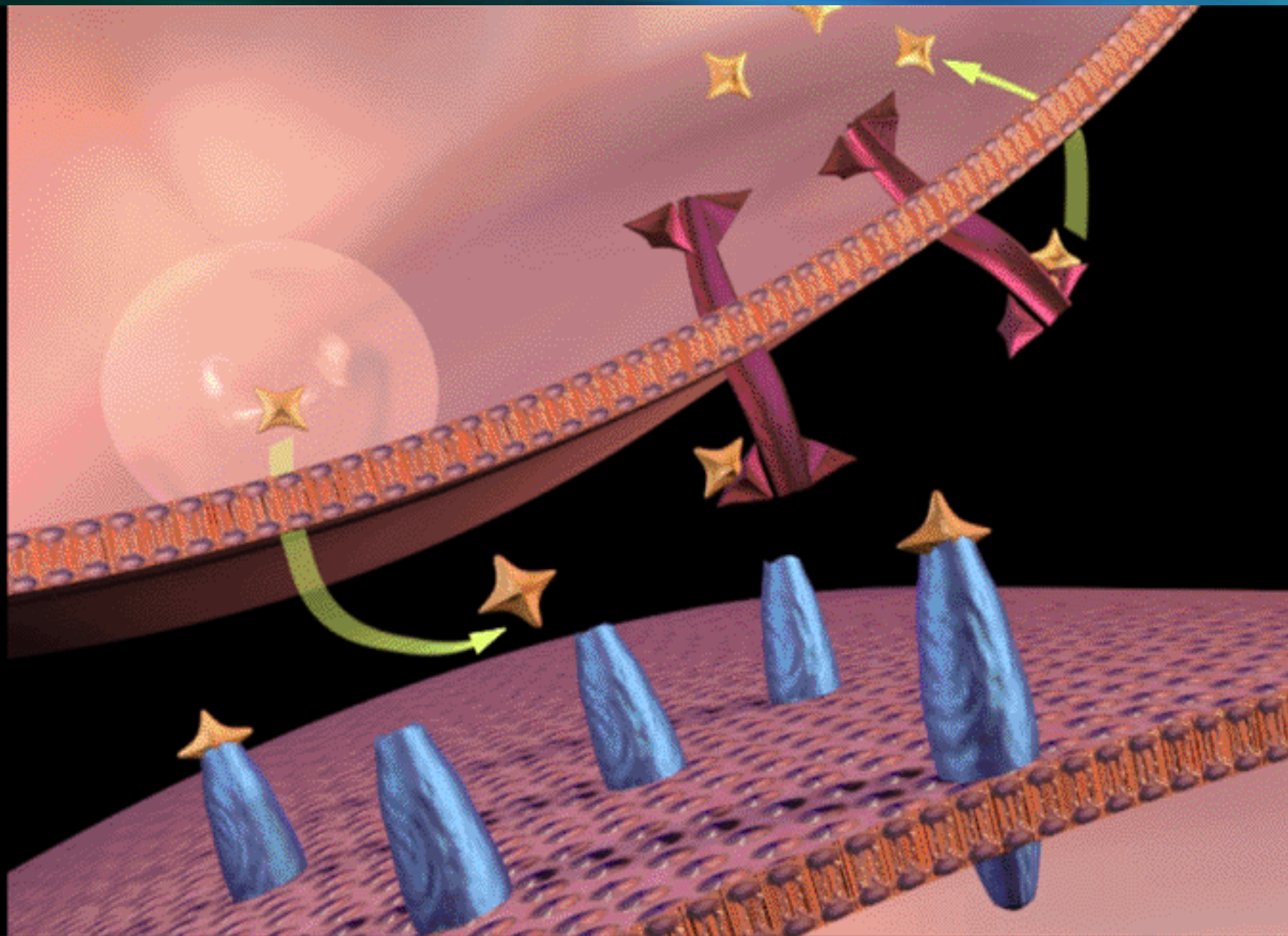


# Neurotransmitters

- Serotonin (5-HT)
- Norepinephrine (NE)
- Dopamine (DA)
- Acetylcholine (Ach)
- Glutamate (GLU)
- Gamma amino butyric acid (GABA)
- N-methyl-D-aspartate (NMDA)







# Early Antidepressants

- Tricyclics
- MAO-Inhibitors
- Primarily worked on adrenergic neurotransmitters
- Not everyone was helped



# SSRIs

- Selective serotonin reuptake inhibitors
  - Prozac
  - Paxil
  - Zoloft
  - Lexapro
  - Celexa



# SSRI Side Effects

- Insomnia
- Drowsiness
- Rash
- Headache
- Agitation or nervousness
- Dry mouth
- Dizziness

# Selective Serotonin/Norepinephrine Reuptake Inhibitors (SSNRIs)

- Cymbalta
- Effexor
- Pristiq



# SSNRI Side effects

- Nausea
- Dry mouth
- Tiredness
- Constipation
- Insomnia
- Changes in sexual function
- Loss of appetite

SOME PEOPLE ARE NOT HELPED BY THE  
TRADITIONAL ANTIDEPRESSANTS

Treatment-resistant?



# Ketamine

- Noncompetitive glutamate N-methyl-D-aspartate (NMDA) receptor antagonist
- Similar to PCP, but less risky/toxic
- Intravenous anesthetic
- Sometimes used with opioids for pain relief
- “Special K”, “Vitamin K”
- Extreme experience = “K-hole”

# Ketamine and BDNF

- Ketamine increases levels of brain-derived neurotrophic factor (BDNF)
- Thought to specifically increase nerve connectivity
- One basis for antidepressant activity.



# Ketamine for substance use disorders

- Has been found to decrease craving in both cocaine and alcohol dependent individuals

# TREATMENT OF SUD WITH KETAMINE

Grabski, et. al. (2022)

- Ketamine weekly x 3 weeks + psychotherapy
- Ketamine weekly x 3 weeks + alcohol education
- Saline weekly x 3 weeks + psychotherapy
- Saline weeks x 3 weeks + alcohol education

# Psychotherapeutic Use of Ketamine

- Most commonly intravenous
- Can be administered intramuscular, subcutaneous and intranasal
- Lower doses may involve therapist-patient interaction
- High doses do not include therapist in ketamine experience
- 40-60 minute session/2-3 hours of post-intervention observation
- Studies now looking at “at home” ketamine



# Psychotherapeutic Use of Ketamine

- Antidepressant effects can be seen within one day, or sometimes within hours and last 1-2 weeks
- Post-ketamine CBT has been found to increase lengths of depression remission

# Walsh, et. al. (2022)

- Reviewed:
  - 33 systematic reviews
  - 29 randomized control trials
  - 21 observational studies
- A primary problem was that in double-blind studies, subjects could tell if they had been given a psychoactive drug
- *Systematic reviews and meta-analyses provide support for robust, rapid and transient antidepressant and anti-suicidal effects of ketamine.*

# Undesired effects of ketamine treatment

- Worsening mood
- Anxiety
- Emotional blunting
- Psychosis
- Thought disorders
- Dissociation
- Depersonalization
- Hallucinations
- Increased blood pressure



# Side effects of ketamine treatment

- Increased heart rate
- Decreased blood pressure
- Decreased heart rate
- Heart palpitations/arrhythmia
- Chest pain
- Headaches
- Dizziness
- Unsteadiness
- Confusion

# Side effects of ketamine treatment

- Memory loss
- Cognitive impairment
- Blurred vision
- Insomnia
- Nausea
- Fatigue
- Crying/tearfulness
- Suicidal thoughts (one suicide attempt reported)

# Walsh, et. al. (2022)

- Research questions:
  - How to minimize side effects
  - How to screen for appropriate patients
  - Optimal dose
  - Route of administration
  - Number of doses of ketamine
  - Added and interactive benefit of psychotherapy alongside ketamine treatment



# Ketamine Vs. Traditional Antidepressants

## Ketamine

- Expensive
- Must be administered frequently
- Works immediately
- Has misuse potential

## Traditional Antidepressants

- Relatively inexpensive
- Daily use required
- Takes 7-14 days to work
- No misuse potential

# DRUG FACILITATED THERAPY: HALLUCINOGENS

# Hallucinogens (Lower risk)

- Addiction potential low
- Tolerance develops rapidly
- Short- and long-term physical toxicity potential low
- Psychiatric impairment low to moderate
- Neurochemical mechanism of action:
  - Stimulation of serotonin subreceptors (5HT<sub>2A</sub>)
  - Decreased GABA activity
  - Increase in glutamate



# LSD Vs Psilocybin

- Psilocybin rarer on the street, but this is changing
- Psilocybin decriminalized in Oregon and other states
- Psilocybin duration shorter than LSD (4-6 hours Vs 8-12)
- Psilocybin granted “Breakthrough therapy” status in 2019

# Hallucinogens (Lower risk)

- Effects (desired):
  - Hallucinations
  - Perceptual distortions
  - “Morphing”
  - Synesthesia
  - Altered body image
  - Altered experience of time and space
  - Consciousness expansion
  - Mystical experiences

# Hallucinogens (Lower risk)

- Effects (side)
  - Slight increase in body temperature
  - Nausea (rare)
  - Blurred vision (rare)
  - Slightly increased/decreased blood pressure
  - Slight elevation of pulse
  - Dilated pupils



# Hallucinogens (Lower risk)

- Effects (Undesired/Bad Trip)
  - Panic
  - Fear of insanity
  - Paranoia
  - Frightening hallucinations
  - Depersonalization
  - Derealization

# Therapeutic Use of Psilocybin

## Nutt & Carhart-Harris (2021)

- Hallucinogen research common until late 60s
- Promising results (LSD) with terminal cancer patients and persons with alcohol use disorder
- Virtually no LSD research since then
- Psilocybin current focus

# Therapeutic Use of Psilocybin

## Nutt & Carhart-Harris (2021)

- Psilocybin psychotherapy
- Four phases:
  - Assessment
  - Preparation
  - Experience
  - Integration
- Two sessions over 2-3 weeks



# Therapeutic Use of Psilocybin

## Nutt & Carhart-Harris (2021)

- Hypothesized method of action:
  - Effect on 5-HT (serotonin) receptors
  - Works best on internalizing disorders with negative “self-talk” and thinking
  - Psilocybin disrupts the brain systems that encode negative, repetitive thinking
  - Interruption of this encoding allows brain to challenge thinking patterns

# Psilocybin Vs. Lexapro

- Group 1: Two psilocybin sessions 3 weeks apart + daily placebo tablet
- Group 2: Two very low doses of psilocybin 3 weeks apart + daily Lexapro
- At six weeks, both groups had improved depression scores
- Psilocybin effects persisted beyond test period
- Lexapro effects disappeared when medication discontinued

# Psilocybin and AUD

- Bogenschutz (2022):
  - Psilocybin Vs. placebo
  - Higher abstinence rate and fewer drinks per day in psilocybin group
  - Effect persisted for seven months



# PTSD

- Descriptions exist beginning in BCE period
- Based on the concept of external trauma
- Previous names:
  - Shell shock
  - Combat fatigue
  - War neurosis
  - Railway spine

# PTSD

- Before the establishment of PTSD as a disorder, many people refused to admit to symptoms
- Was often not treated
- Received new attention during Viet Nam period
- Added to DSM-III in 1980

# DRUG FACILITATED PSYCHOTHERAPY: MDMA



# MDMA

- 3,4-methylenedioxymethamphetamine
- “Ecstasy” / “molly”
- Sometimes known as an “empathogen”
- Granted “Breakthrough Therapy” designation” in 2017

# PTSD

- Most patients had PTSD associated with combat or childhood trauma
- Often “treatment resistant”

# MDMA Treatment for PTSD

- Intended to allow clients to revisit traumatic memories while staying emotionally engaged
- Higher level of trust in therapist



# Mithoefer, et. al. (2019)

- Rational for phase 3 trials
- Examined six phase 2 clinical trials
- Experimental (MDMA) Vs placebo
- Both received manualized psychotherapy in two 8-hour sessions one month apart
- Three 90-minute sessions before drug/placebo
- 2-3 afterwards

# Post-MDMA Survey (Smith, et. al.[2021])

- Of subjects who had their MDMA experience 12 months ago:
  - 86%: Substantial benefits
  - 84%: Reported improved feelings of well-being
  - 71% had fewer nightmares
  - 69% had less anxiety
  - 66% had improved sleep.

# Post-MDMA Survey (Smith, et. al.[2021])

- Most common side effects:
  - Increase in pulse and BP
  - Bruxism
  - Anxiety
  - Jitteriness
  - Headache
  - Nausea



# Contraindications for MDMA Therapy

- Personal or family history of psychosis
- History of heart problems or high blood pressure

# Ketamine Treatment for PTSD

## Feder, et. al. 2021

- Ketamine Vs. midazolam
  - Single infusion
  - Ketamine: 67% had at least a 30% reduction in symptoms
  - Midazolam: 20% had at least a 30% reduction in symptoms

# Characteristics of a good hallucinogen/MDMA therapist

- Experienced therapist
- Understanding of the drug and its role
- Knowledge of when to speak and when to remain quiet
- Ability to intervene in bad drug reactions
- Patience
- Specialized training (e.g., MAPS\* Therapy Training Program)

\* Multidisciplinary Association for Psychedelic Studies



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