Treating Mental Health Disorders with Ketamine, MDMA and the Hallucinogens

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Major Depressive Disorder

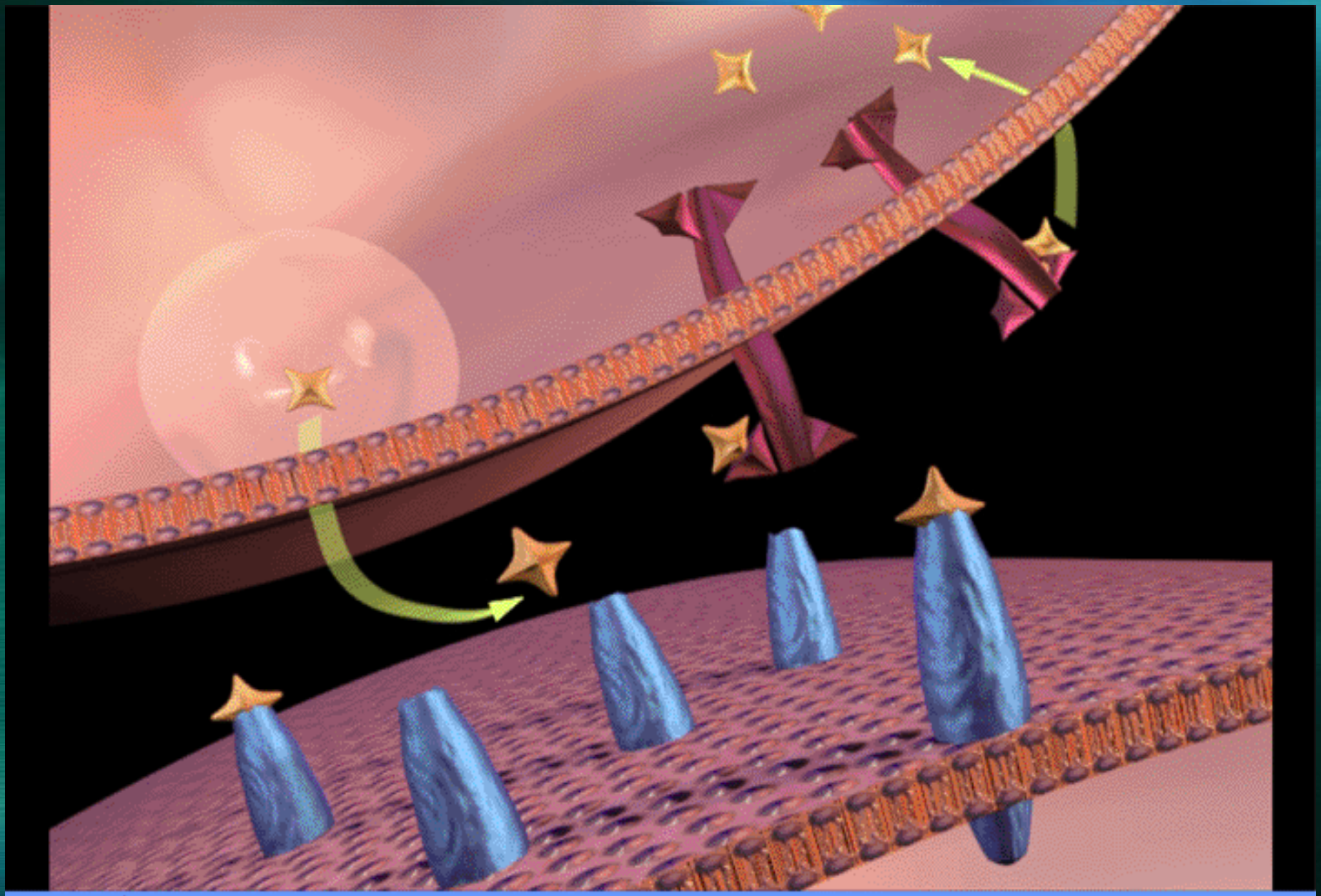
- Accounts date back to 2nd millennium, BCE
- Described by Greeks, Romans and Persians
- Suffered by:
  - Abraham Lincoln
  - Winston Churchill
  - Georgia O'Keefe
  - Edvard Munch
  - General William Tecumseh Sherman
  - Ernest Hemingway
  - Franz Kafka
  - Mark Twain

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)



NIDA NATIONAL INSTITUTE ON DRUG ABUSE

www.drugabuse.gov

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?

Instruments used to measure MDD symptoms

- Structured Clinical Interview for DSM-V
- GRID-Hamilton Depression Rating Scale

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 for substance use disorders

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

TREATMENT OF AUD 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
- Measure: Days abstinent after 6 months

Psychotherapeutic Use of Ketamine

- Most commonly intravenous
- Can be administered intranasally
- Subanesthetic dose
- 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

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
- *Systematic reviews and meta-analyses provide support for robust, rapid and transient antidepressant and anti-suicidal effects of ketamine.*
- A primary problem was that in double-blind studies, subjects could tell that they had been give a psychoactive drug

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 FACILIATED THERAPY: HALLUCINOGENS

Hallucinogens (LSD, Psilocybin)

- 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 ($5HT_{2A}$)
  - Decreased GABA activity
  - Increase in glutamate

LSD Vs Psilocybin

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

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

Assessment

- Diagnosis of MDD
- No history of psychosis or bipolar disorder personally or in family
- Desire to experience psilocybin as treatment, not recreation
- Intent to follow through with post-psilocybin sessions

Preparation

- Establishment of therapeutic alliance
- Understanding and acceptance of what the drug will do
- Description of the session, who will be there, visual deprivation, headphones
- Length of session
- Identification and processing of fear or anxiety regarding the experience

Experience

- Initially low dose, then higher doses for subsequent session
- Prone position, eye blinder/sleep mask
- Selected music broadcast through headphones
- At least one therapist (team of two) present at all times
- Therapist encourages the patient to reflect inwardly
- Therapist non-directive

Experience

- Avoid discussion of spiritual dimension unless the patient brings it up
- Patient and therapist discuss what is happening
- Therapist intervenes if patient becomes distressed

Integration

- Post-session discussion
- Therapist investigates what the patient experienced and how the experience affected him/her
- Application to real life discussed

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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 to Treat MDD (Davis, et. al., 2021)

- Two psilocybin sessions
  - 20 mg/70 kg
  - 30 mg/70 kg
- GRID scores at beginning averaged 22.8
- GRID scores at week 1: 8.0
- GRID scores at week 8: 8.5

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

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
- A Schedule I drug
- “Ecstasy”/”molly”
- Sometimes known as an “empathogen”
- Valued for its “prosocial effects”
  - Friendliness
  - Love
  - Strong connection to others
- Granted “Breakthrough Therapy” designation in 2017

MDMA: Psychopharmacology

- Effects on serotonin increase appreciation of sensory stimuli
- Increases in NE and dopamine enhance mood
- (Less clear): Increase in oxytocin may be responsible for prosocial effects

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

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

PTSD

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

Contraindications for MDMA Therapy

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

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 receive 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 PTSD 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 Treatment

I spent over a decade pushing people away and making life harder on myself and not loving myself. So, as far as the combat part of my PTSD, we were successful in that, but I still think I can be a better person. I still think there's room to grow.

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

THANK YOU FOR YOUR ATTENTION!
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