



Ketamine: Applications in Psychiatric Illness

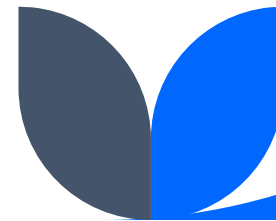
Lisa Schock, MD





Objectives

1. Understand ketamine's proposed mechanism in treating psychiatric illness
2. Identify evidence-based applications of ketamine therapy in psychiatric illness
3. Outline the potential problems with ketamine therapy



The Scope of the Problem

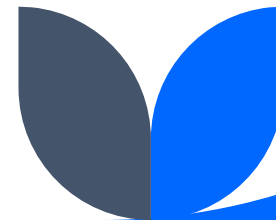
Treatment Resistance in
Psychiatric Illness





Our Best Isn't Good Enough

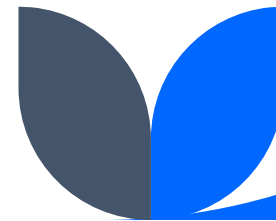
- Treatment goal for MDD → remission
- Treatment resistant depression is common and debilitating
- First line antidepressant
 - 1/3 remission, 1/3 response, 1/3 no response
- Switch to second antidepressant
 - 1/3 remission, 1/3 response, 1/3 no response



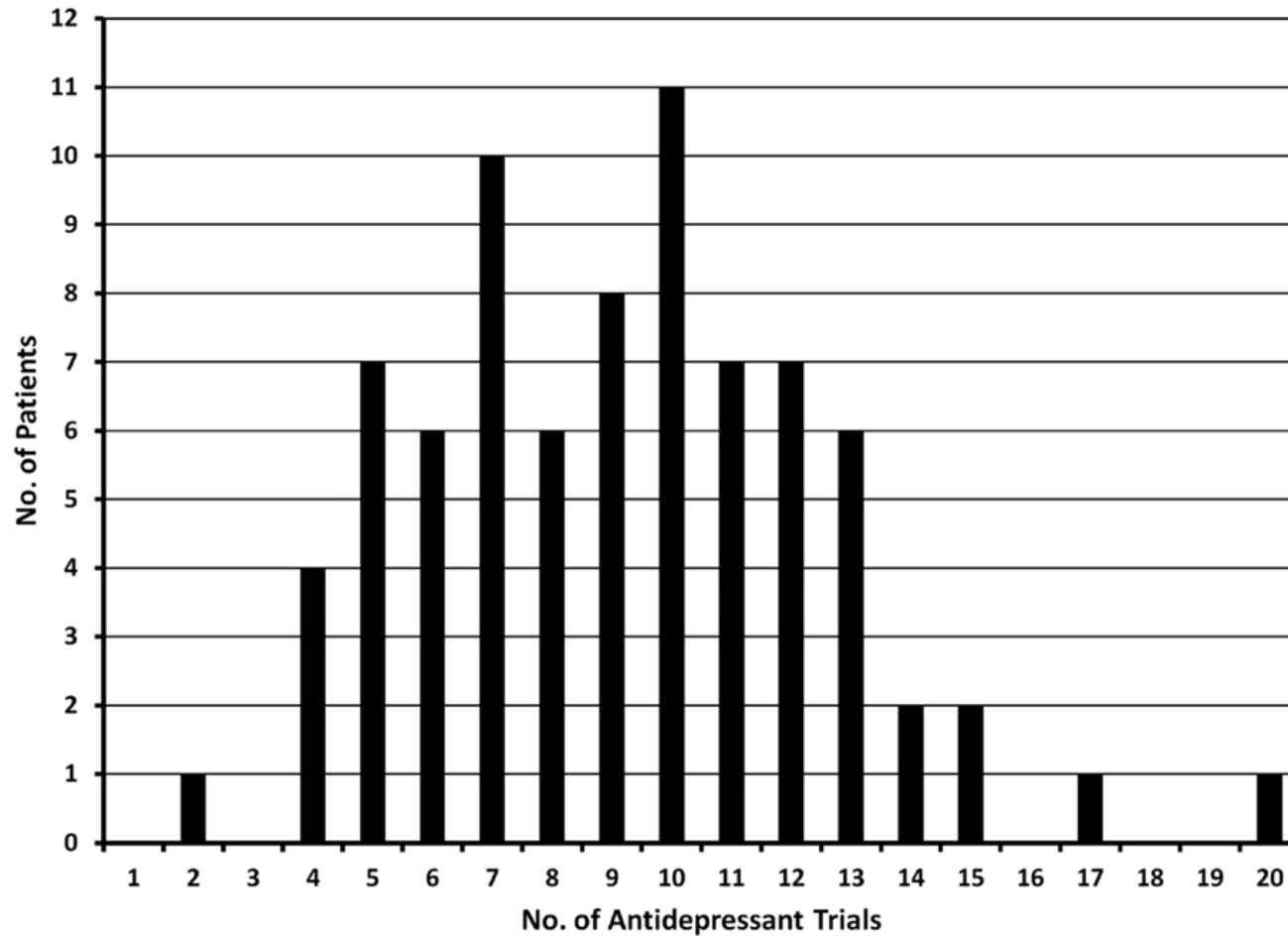


Our Best Isn't Good Enough

- After 2 medication trials, 20% of patients with MDD have no response to an antidepressant
- After 2 failed medication trials, the likelihood of reaching remission with another antidepressant (switch or augmentation) trial around 10%



Treatment Resistant Depression





Treatment Resistant Depression

- Medication trials take 4-6 weeks
- Untreated and sub-optimally treated depression becomes harder to treat the longer it persists
- Risk of future depressive episodes increases with each MDD episode
 - 50% after 1 episode, 80% after 2nd episode, >90% after 3rd episode
- Adherence to medication regimen decreases when it's ineffective, has side effects, or is complicated





Bipolar Depression

- Tends to be the more debilitating and difficult to treat mood state
- Poor response to antidepressants
- Polypharmacy common
- Average # of medication->4





Other Psychiatric Illnesses

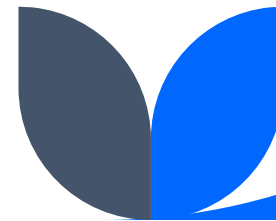
- PTSD can be chronic, evidence-based therapies require exposure and emotional distress tolerance
- 1/3 of patients with treatment-resistant schizophrenia on clozapine continue to have positive symptoms
- Negative symptoms of schizophrenia respond poorly to current treatment
- Anxiety disorders tend to wax and wane in severity over time





The Need for Better Treatment

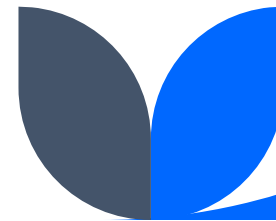
- Goal → get more people better, faster
- Neuromodulation (ECT, TMS) has been effective in treating depression
 - Rapid neuroplastic changes leads to structural and functional alterations
 - Facilitate adaptive neuroplastic changes (ie, increased hippocampal volume post ECT)



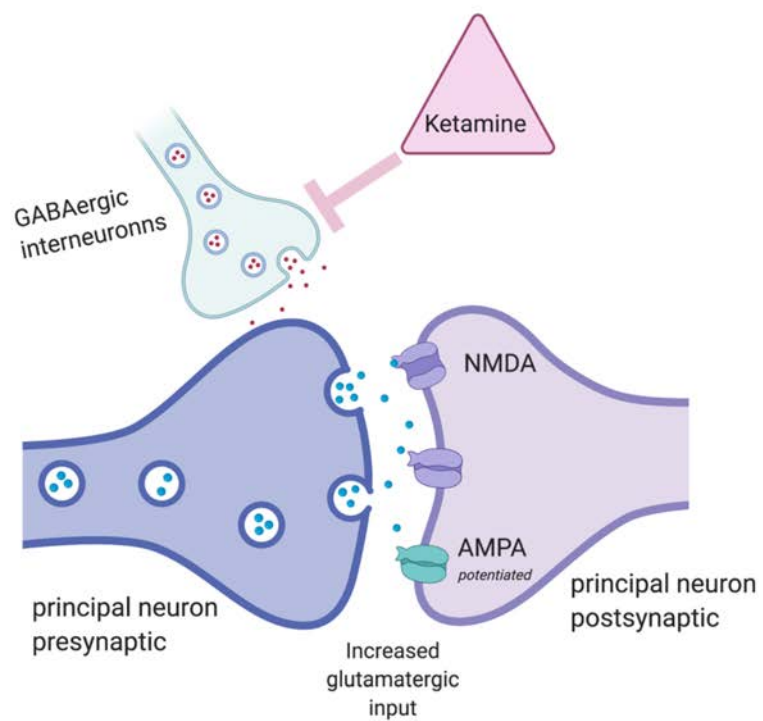


The Need for Better Treatment

- Although ECT is highly effective for MDD:
 - Limited access depending on location
 - Patient preference/acceptability
 - Use of general anesthesia
 - Can be disruptive to daily function during treatment
- TMS:
 - Greater patient acceptability, fewer side effects
 - Slower response times
 - Accessibility/time constraints

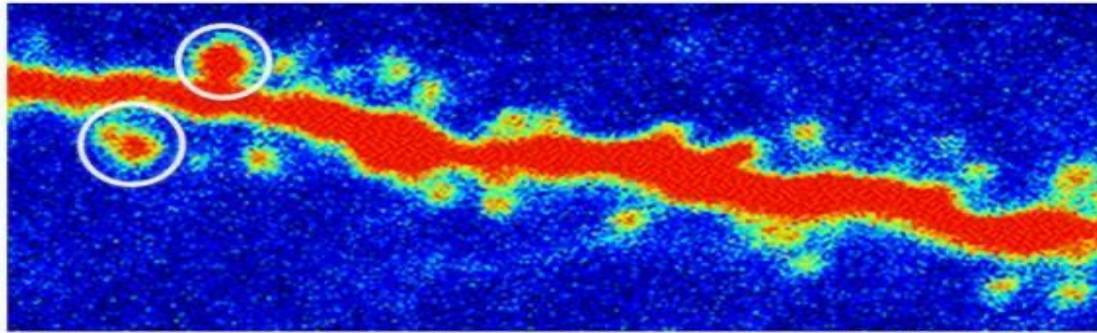


Ketamine

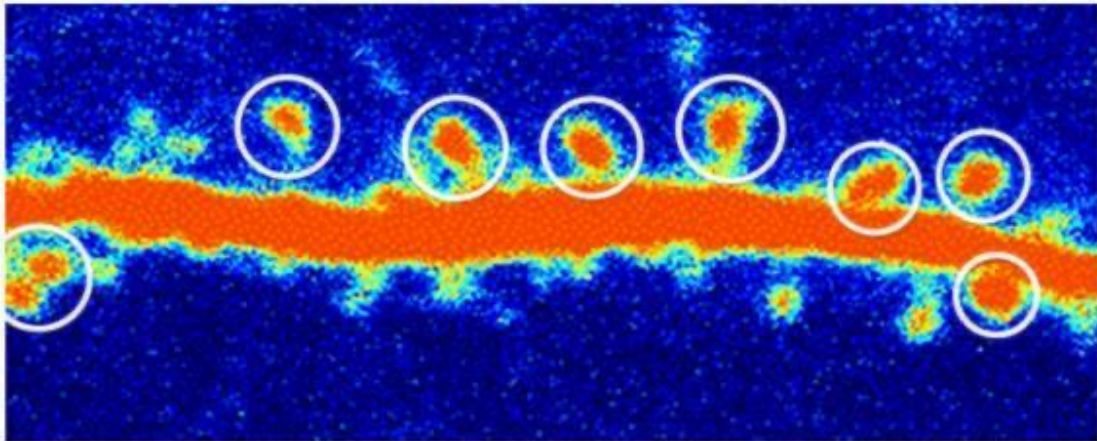


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Ketamine



Ronald Duman/Yale University



Ronald Duman/Yale University

Evidence-Based Ketamine Treatment





Initial Studies

- First RCT 2000
- Subanesthetic infusions of ketamine given over a single, 40 minute infusion
- Rapid resolution (2 hours) of depressive symptoms, suicidality
- Effect short-lived, with many patients maintaining response for 7 days
- Meta-analysis of 9 RTCs demonstrated similar results





Evolution of the Protocol

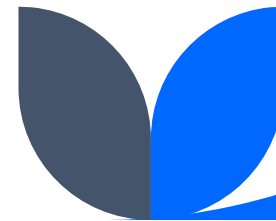
- 2016 RTC on repeated dosing (2-3 days per week over 4 weeks)
- Extended effect out to 15 days
- Small studies on bipolar depression follow similar trend
- Ongoing studies to determine long-term risk and benefit of maintenance treatment





Esketamine

- FDA approved 2019 for treatment resistant depression in adults
- S-entantiomer of racemic ketamine → 3-4X higher affinity for NDMA receptors
- RCTs showing rapid reduction in depression rating scales vs placebo, both treatment groups experienced rapid reduction in Severity of Suicidality score





Esketamine

- 2021 meta-analysis of 10 studies
- Mixed results on difference between esketamine plus antidepressant versus esketamine versus placebo on depression symptoms
- Delayed relapse in esketamine vs placebo





Too Good to Be True?

-2018 study combining ketamine with naltrexone appeared to interfere with ketamine's antidepressant effect

- Concern for addiction/abuse

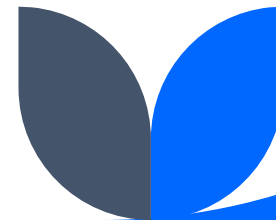
- May be the result of mu-opioid receptor blockade attenuating downstream mediators of ketamine targets





Too Good to Be True?

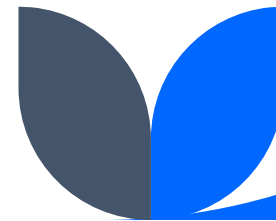
- 2023 Stanford study
- 40 participants with moderate-severe depression undergoing general anesthesia for routine surgery
- Ketamine infusions given during procedure to blind dissociative effect
- Treatment revealed two weeks later- both groups had significant improvement in symptoms equal to effects in other ketamine studies
- Most patients were unable to correctly guess their intervention





Ketamine vs Esketamine

- 2023 study comparing efficacy and tolerability of IV ketamine versus esketamine
- Drugs about equal in efficacy and side effects
- Ketamine often more economical in overall treatment costs
- Further questions of bioavailability vs binding




Pitfalls and Precautions





Side Effects

- Effects of repeated infusions long-term are unknown
 - High blood pressure
 - Bladder irritation/GU problems
 - Dissociation
 - Nausea
 - Abuse/addiction (tolerance)
 - Potential to induce mania/psychosis
- 



Identifying the Right Patient

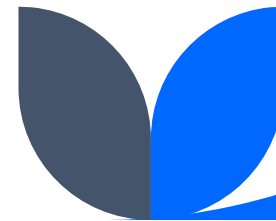
- Variability in diagnostic accuracy
- Psychiatric symptoms present across many conditions
- Comorbidities are common
- Inaccuracies in treatment history
- Setting expectations





Logistics of Treatment

- Availability
- Need for transportation
- Cost
- Time commitment





Lack of Regulation

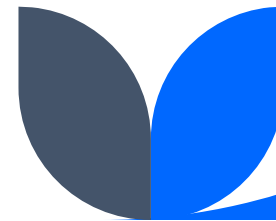
- Many clinics offering ketamine do not involve a psychiatrist
- Providers giving ketamine infusion may have no psychiatric training
- Variability in evidence-base to treatment protocols (dosing, routes of administration)
- Lack of standardization in treatment guidelines, education/training





The Future

- Expansion of ketamine and psychedelic assisted treatments and psychotherapies
- Novel treatment mechanisms for rapidly treating severe and chronic mental illness
- Early treatment of illness to reduce chronicity and treatment resistance





The Future

- Impact of psychosocial factors on psychiatric illness
- Psychiatric research has problems with treatment study design (placebo, novelty effects, etc)
- Will clinical practice outpace the evidence?
- Sometimes we need to do our best with what we have
- The concept of "psychiatric dialysis"
- The power of belief and hope

