Ketamine in Psychiatry
Pharmacology and potential applications

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Disclosures

Cristina Cusin 2017-2021:

- **Speaking/CME/Consulting**: Janssen, Takeda, Boehringer, Lundbeck, Alkermes, Perception, Clexio
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  Acryliccurbit[N]uril type molecular containers to treat intoxication and substance abuse
  - Springer (book on TRD)
OUTLINE

• Ketamine
• Mechanisms of action
• Efficacy
  – MDD
  – PTSD
  – OCD, SUD

• Ketamine clinic at MGH
• Side effects
• Right patients
• Clinical outcomes
• Predictors
What is ketamine?
Ketamine facts

• **Ketamine** is an **old anesthetic and analgesic**, FDA-approved in 1970, widely used in the ED, OR, ECT, pain clinics, battlefield, veterinary medicine

• “**Indications:** trauma patients with moderate to severe pain and whose vital signs are potentially unstable, excited delirium, rapid sequence airway management, and for the maintenance of sedation.”

• **Use:** pre-anesthesia, procedures, children, does not suppress breathing and allows lower use of opiates for post-surgical pain

• It is also a drug of abuse “party drug” or “special K”

  – **For depression ketamine is still OFF LABEL**
What is S-ketamine?

50% $S$-ketamine + 50% $R$-ketamine = ketamine

S- ketamine
(Spravato® by Janssen)
FDA approved for TRD
Mechanism of action
How does ketamine work? - II

• The antidepressant effect **peaks at 24 hrs, after the drug has cleared from the body**
• Downstream effects from NMDA action are critical in generating and sustaining the response
• Enhancement of spine-remodeling and synaptoplasticity are necessary in the antidepressant effects in rodents
• Activation of the mammalian target of rapamycin complex1 (mTORC1) signaling pathway, synaptic protein synthesis
• Rapid eEF2- and BDNF-dependent potentiation mediated through increased surface expression of AMPA receptors
Ketamine Mechanism of Action

Dwyer and Duman, Biological Psychiatry, 2013
How does ketamine work? - III

• Other putative mechanisms:
  necessary a transient increase in glutamate transmission through the postsynaptic a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR)

• the co-administration of AMPAR antagonists can block the antidepressant effect of ketamine in animal models

(More hype)

• Is ketamine acting though opioid system?

• Small pilot study on 12 patients, pretreatment with naltrexone partially blocked the effect of ketamine, Published x2

• Lot of publicity in the media, fear of ketamine being and opiate-like drug, highly addictive, leading to tolerance and dependence
How does ketamine work? - IV

(More hype)

• Is ketamine acting through opioid system?
• Small pilot study on 12 patients, pretreatment with naltrexone partially blocked the effect of ketamine
• Published x2 in high impact journals
• Lot of publicity in the media, fear of ketamine being an opiate-like drug, highly addictive, leading to tolerance and dependence
No, really...How does it work?

a) NMDA block on GABA inhibitory neurons
b) Dishinibition excitatory neurons
c) And d)direct effect on postsynaptic NMDA receptors
e) Inhibition burst on habenula
Efficacy

Jan 2021 – review
24 trials, 1877 participants

Racemic ketamine vs esketamine demonstrated greater overall response (RR = 3.01 vs. RR = 1.38) remission rates (RR = 3.70 vs. RR = 1.47) lower dropouts (RR = 0.76 vs. RR = 1.37).

Most esketamine-treated patients - more rigorous definition of TRD
One trial of older adults receiving esketamine – negative
Functional unblinding in research
Does S-ketamine work?

- In March 2019 the FDA approved Intranasal Esketamine (Spravato) for treatment-resistant depression, in conjunction with a standard antidepressant.
- 2 pivotal Phase-3 trials were positive in adults (18-65).
- Trial in elderly pts >65 was stopped early – not statistically significant.
- One randomized blinded discontinuation study also showed that continuing Esketamine decreased the risk for relapse.
Some balanced views

Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation

Roger S. McIntyre, M.D., Joshua D. Rosenblat, M.D., M.Sc., Charles B. Nemeroff, M.D., Ph.D., Gerard Sanacora, M.D., Ph.D., James W. Murrough, M.D., Ph.D., Michael Berk, Ph.D., M.B.B.Ch., Elisa Brietzke, M.D., Ph.D., Seetai Dodd, Ph.D., Philip Gorwood, M.D., Ph.D., Roger Ho, M.D., M.B.B.S., Dan V. Iosifescu, M.D., ...

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Abstract

Replicated international studies have underscored the human and societal costs associated with major depressive disorder. Despite the proven efficacy of monoamine-based antidepressants in major depression, the majority of treated individuals fail to achieve full syndromal and functional recovery with the index and subsequent pharmacological treatments. Ketamine and esketamine represent pharmacologically novel treatment avenues for adults with treatment-resistant depression. In addition to providing hope to affected persons, these agents represent the first non-monoaminergic agents with proven rapid-onset efficacy in major depressive disorder. Nevertheless, concerns remain about the safety and tolerability of ketamine and esketamine in mood disorders. Moreover, there is uncertainty about the appropriate position of these agents in treatment algorithms, their comparative effectiveness, and the appropriate setting, infrastructure, and personnel required for their competent and safe implementation. In this article, an international group of mood disorder experts provides a synthesis of the literature with respect to the efficacy, safety, and tolerability of
And the perennial skeptics...

Small improvement
Esketamine has more side eff than placebo!!
Pts relapse when they stop it

Esketamine for treatment resistant depression: a trick of smoke and mirrors?

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Abstract
In March 2019, the US Food and Drug Administration (FDA) approved a nasal spray formulation of esketamine for the treatment of resistant depression in adults. Esketamine is the S-enantiomer of ketamine, an FDA-approved anaesthetic, known to cause dissociation and, occasionally, hallucinations. While ketamine has not been approved for depression in the USA or in any other country, it has been used off-label in cases of severe depression (Daly and Singh, 2018; Popova et al., 2019; Zhang and Hashimoto, 2019). However, ketamine is used for recreational purposes because it produces desired mental and behavioural changes, such as euphoria, and perceptual changes, such as dissociation and, occasionally, hallucinations (Caddy et al., 2015). These effects,
Ketamine and PTSD

41 pts
0.5 mg/kg

Changes in Posttraumatic Stress Disorder and Depressive Symptom Levels During the First Period

Figure Legend:

Changes in Posttraumatic Stress Disorder and Depressive Symptom Levels During the First Period

Change in the Impact of Event Scale–Revised (IES-R) total score, the IES-R mean subscale scores, and the Montgomery-Asberg Depression Rating Scale (MADRS) score over 1 week for the first period (n = 41). Error bars represent standard errors. For this study, the IES-R was modified to inquire about symptoms over the previous 24 hours (instead of the previous 7 days).
A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder

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Objective: Posttraumatic stress disorder (PTSD) is a chronic and disabling disorder, for which available pharmacotherapies have limited efficacy. The authors’ previous proof-of-concept randomized controlled trial of single-dose intravenous ketamine infusion in individuals with PTSD showed significant and rapid PTSD symptom reduction 24 hours postinfusion. The present study is the first randomized controlled trial to test the efficacy and safety of repeated intravenous ketamine infusions for the treatment of chronic PTSD.

Methods: Individuals with chronic PTSD (N=30) were randomly assigned (1:1) to receive six infusions of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) (psychoactive placebo control) over 2 consecutive weeks. Clinician-rated and self-report assessments were administered 24 hours after the first infusion and at weekly visits. The primary outcome measure was change in PTSD symptom severity, as assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), from baseline to 2 weeks (after completion of all infusions). Secondary outcome measures included the Impact of Event Scale—Revised, the Montgomery-Åsberg Depression Rating Scale (MADRS), and side effect measures.

Results: The ketamine group showed a significantly greater improvement in CAPS-5 and MADRS total scores than the midazolam group from baseline to week 2. At week 2, the mean CAPS-5 total score was 11.88 points (SE=3.96) lower in the ketamine group than in the midazolam group (d=1.13, 95% CI=0.36, 1.91). Sixty-seven percent of participants in the ketamine group were treatment responders, compared with 20% in the midazolam group. Among ketamine responders, the median time to loss of response was 27.5 days following the 2-week course of infusions. Ketamine infusions were well tolerated overall, without serious adverse events.

Conclusions: This randomized controlled trial provides the first evidence of efficacy of repeated ketamine infusions in reducing symptom severity in individuals with chronic PTSD. Further studies are warranted to understand ketamine’s full potential as a treatment for chronic PTSD.


Posttraumatic stress disorder (PTSD) is a chronic and disabling psychiatric disorder, with a lifetime prevalence in the United States of approximately 6% (1). Rates vary by trauma category, with combat veterans and those who have experienced a natural disaster having the highest rates. PTSD is characterized by reexperiencing traumatic events, avoidance of trauma cues, negative changes in cognitions and mood, and hyperarousal. Exposures to combat and natural disasters are the two most common trauma types associated with PTSD, with both types being associated with a high risk of co-occurring anxiety and depressive disorders (2). Current treatments for PTSD, including cognitive behavioral therapy and several classes of antidepressants, are limited in their effectiveness. Selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine—are approved by the U.S. Food and Drug Administration (FDA) for PTSD treatment, and only four medications have shown at least moderate efficacy in randomized controlled trials. After these four medications, only limited efficacy has been documented in patients with PTSD. The study of new targeted treatments is critical to maximize the chances of effective PTSD treatment.
Ketamine and PTSD

FIGURE 3. Effect of treatment with ketamine compared with midazolam on depressive symptom severity in patients with chronic PTSD. 
Ketamine and OCD, SUD

• Several glutamate modulators, including memantine, topiramate and lamotrigine, have been evaluated in OCD
• Handful of studies with IV and IN ketamine in treatment-resistant OCD
• Ketamine and motivational enhancement therapy in AUD
• phase II, multi-site, RCT I is ongoing to investigate the effectiveness of IV ketamine in reducing relapse rates in recently detoxified alcohol-dependent individuals with depressive sx
Ketamine and OCD, SUD

- RCT ketamine vs midazolam (N=18) showed significantly greater reductions in cocaine use, relapse rate and cravings with infusions of ketamine
- Reduction of cravings associated with mystical-type effects
- N=55 cocaine-dependent individuals RCT IV ketamine vs midazolam +5-week course of mindfulness-based relapse prevention
- 50% abstinent at 2 wks ketamine arm vs 10% on midazolam
Why a ketamine clinic at MGH?

- Tertiary care center, extremely treatment-refractory patients, experts in psychopharmacology who have tried every other option
- Patients have failed multiple interventions including medications, psychotherapies, TMS, ECT
- Frequent in this population is a history of ‘tachyphylaxis’ or loss of response to antidepressants
- For those patients we do not have clear guidelines
- Patients seeking ‘experimental’ treatments participated to research trials with ketamine and had benefit
Side effects in the clinic

- >2500 intravenous (IV) ketamine infusions at the MGH ketamine clinic since October 2018
- 8 infusions were discontinued due to Aes - rare
- 1 instance of BP increase requiring labetalol 5mg (elderly pt with poorly controlled BP)
- Approximately 2% of patients drop out after one infusion, disliking the experience
- Nausea is common (35%) – treated with ondansetron
- During the infusion: dizziness, sedation, dissociation
- 1 day Post infusion: headache, nausea, insomnia, fatigue
- No cases of persistent side effects beyond day 1, no urinary problems, no new onset of psychotic sx, 1 case severe dissociation in patients with PTSD (improved over time)
Driving the day after

-26 volunteers
-Driving simulator
-Esketamine (84 mg) vs placebo vs oral mirtazapine (30 mg)
significantly impaired
-on road driving performance

No significant difference in driving performance was observed at 8 hrs
Who are the right patients? (IV)

• AT MGH: Must be referred by treating psychiatrist*

• Any of the following
  – Severe MDD, with significant functional consequences
  – ECT is being considered, has failed, or lead to intolerable side effects
  – Suicide risk in MDD or BP
  – Significant mood or suicide-related symptoms in setting of other Axis I psychiatric disorders
  – Symptoms known to be responsive to antidepressants in other psychiatric conditions; symptoms that severely interfere with life or confer suicide risk
  – Maintenance of antidepressant response in patients who had good therapeutic response from an acute course of ketamine treatment
  – No major acute medical issues **
Who are the right patients? (IV Ketamine)

Exclusions:

• substance use disorders (sobriety for how long? *),
• Psychosis
• Unstable medical illness (?).
• Psychiatrist not involved, patients self-referred
• No escort available for transportation – MGH mandates an escort, no exceptions (no matter how low the dose)
• Patient not providing access to medical records, Urine tox screen, release to talk to psychiatrist
• Not failed enough*? Ethical dilemma of when it is “enough” and need for guidelines
  – Balancing acute need for relief (i.e. suicidal, about to drop out of college) vs rigid rule about # past treatments
  – Pts who refuse standard ADs?
• What about patients with advanced cancer and depression?
• What about MCI and depression?
• What about mixed state/rapid cycling?
How long is the treatment?

• No rigorous long-term data beside registry on Esketamine, case series from MGH, Yale and Emory
• Similar to other chronic medical conditions
• Young patients with intermittent disease and long intervals between episodes may have a relatively short course (?)
• Patients who have been chronically ill for >5 ys (the majority of patients in the clinic) **do relapse** when they stop ketamine
Informed consent: what are my chances of responding to ketamine?

• From literature 65-70%
• In extremely treatment refractory patients, at our site lower
• On average 50%
• Post ECT failure still 45-50%
• Informed consent is a long process
• NEED TO ABSOLUTELY HAVE A PLAN B ready from the evaluation visit, especially for patients with extremely treatment refractory MDD and SI
• They don’t take a NO very well...
IV Ketamine Clinic opened in 2018

- Self-pay (until October 2020), 2 insurers since then
- MDD/BP depression, multiple comorbidities
- Generally healthy, well controlled medical issues
- Failed >4 antidepressants
- Referred by primary provider, in treatment
  - No SUD current, no psychosis
- Flexible ketamine dose (based on tolerability, efficacy)
What are our Outcomes?

- Over 80% of patients complete the initial series of 6
- 20% drop out – tolerability, insufficient improvement and costs
- Mean dose of ketamine 0.60-0.9 mg/kg

- Slightly less than 20% achieved response defined as 50% improvement, and 1/3 improve 35% or more (on QIDS-16 score)
- YET approximately 50% decides to continue with maintenance infusions – self-pay
- Patients report marked improvement in concentration, motivation, and social functioning
Comparable to?

- In (STAR*D) Level 4 trial, response rates after up to 14 weeks of MAOI and combination treatment (VEN+MIR) were **12.1%** and **23.5%**, respectively (McGrath et al., 2006)
- Vagal Nerve Stimulation (VNS), the cumulative response rate of TAU at 3 months was **less than 10%** for those who had on average 7.3 failed treatments for depression (Aaronson et al., 2017)
## Predictors of response?

<table>
<thead>
<tr>
<th>Predictor</th>
<th>F</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.68</td>
<td>0.01*</td>
</tr>
<tr>
<td>Sex</td>
<td>2.06</td>
<td>0.16</td>
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<tr>
<td>Marriage</td>
<td>2.78</td>
<td>0.07</td>
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<tr>
<td>Employment</td>
<td>0.95</td>
<td>0.42</td>
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<tr>
<td>Primary diagnosis</td>
<td>0.07</td>
<td>0.79</td>
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<tr>
<td>Psychiatric comorbidity</td>
<td>0.29</td>
<td>0.59</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1.90</td>
<td>0.17</td>
</tr>
<tr>
<td>Duration of current episode</td>
<td>0.67</td>
<td>0.41</td>
</tr>
<tr>
<td>Prior suicide attempt</td>
<td>1.49</td>
<td>0.23</td>
</tr>
<tr>
<td>History of neuromodulation</td>
<td>5.12</td>
<td>0.03*</td>
</tr>
<tr>
<td>Number of failed antidepressant trials</td>
<td>0.18</td>
<td>0.68</td>
</tr>
<tr>
<td>Prior tachyphylaxis</td>
<td>0.04</td>
<td>0.84</td>
</tr>
<tr>
<td>QIDS-SR$_{16}$ at baseline</td>
<td>0.82</td>
<td>0.37</td>
</tr>
</tbody>
</table>
Informed consent: long-term side effects?

• At present unknown – case series
• Data from Esketamine trials, presented to FDA are reassuring in short and medium-term (5 years)
• Concerns for neurotoxicity and addiction over long term? Olney’s lesions?
• Fear of some yet unknown long-term possible side effect
• Anecdotal tolerance for high dose IN, possibly one case developing partial tolerance to IV
Ketamine in the ED? In the inpatient unit?

Logistic becomes even more complicated..

- Who approves a patient? Ketamine clinic staff available 24/7?
- Who pays for ketamine/esketamine? Getting pre-auth- BCBS can take 2 weeks. If insurance denies it?
- How to ensure there is slot in the ketamine clinic to continue tx? First opening is 2 months from now
- Who is responsible for the patient’s safety between ED discharge and first clinic opening?
- Finding a team for patients not connected with care?
Symptomatic improvement vs Functional Recovery

- 40-50% of patients felt better with ketamine for the first time in years
- Short duration of effect (↑ treatment resistance -> ↓ duration of effect, often only 1-2 days)
- Then they can become again severely depressed and suicidal
- Often improvement of depression can make pts more suicidal
- In chronically ill patients symptom improvement does not translate in functional recovery!
- Need good CBT team, vocational rehab
- Logistical challenges in implementing ketamine-assisted psychotherapy
Questions?

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