AIP Clinical Pearl: Ketamine for Depression

Review of Depression

- Pathophysiology of depression is multifactorial in which there is dysregulation of monoamines in the body. Originally depression was theorized to occur from an imbalance of serotonin in the body, but this theory has evolved to include imbalances of norepinephrine, and dopamine.
- First line therapies for the treatment of depression include selective serotonin receptor antagonist (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Adjunct treatments and ECT are options for patients are have refractory depression.
- However, the challenge to adequately treating depression lies in the slow onset of effects, and increased remission rates. All the while, more options are being investigated for patients that still are refractory to their treatments.

Review of Ketamine

- Ketamine was developed back in the 60's and became popular as a battlefield anesthetic.
  - In the 1908's; however, ketamine gained interest as a recreational drug.
  - Today, ketamine is still used for anesthesia, as well as pain.
- Role in depression
  - Increase in glutamate=greater excitatory effects
  - BDNF Functionality
- Mechanism of Action: Main action is NMDA antagonism. In which, the excitatory neurotransmitter, glutamate, is increased.

Onset	Duration	Metabolism	Elimination
30 seconds	10-15 minutes	N-dealkylation to Norketamine	Renal, $T_{1/2}$=1-2 hours
Adverse effects: Emergence phenomena, sympathomimetic effect			
Absolute contraindications: Patients with schizophrenia due to an increase in positive symptoms, children younger than 3 months old			
Relative contraindications: Hypertensive patients, pulmonary compromise			
Formulations: IV only			

The first RCT

- Berman published the first randomized-controlled trial that assessed the use of ketamine in depressed patients[1]
  - Patients received either saline or ketamine infusions (dose of 0.5mg/kg infused over 40 minutes)
  - Authors found that in this small group (n=8) there was a significant decrease in depressive symptoms after administration.
  - As noted, ketamine has a short half-life of 1-2 hours but noted in this study the antidepressant effects appeared to last for 3 days on average.

Meta-Analysis

Title	Newport, D. Jeffrey, et al. "Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression." *American Journal of Psychiatry* 172.10 (2015): 950-966.
Primary Outcomes	• Treatment response rate (decrease in 50% on the depression rating scale) • Rate of remission of symptoms • Change in depression severity (utilizing the Montogomery-Asberg Depression rating scale (MADRS) or the Hamilton Depression Rating scale (HAM-D)

Studies Included	• Only double-blind placebo controlled trials were included in this meta-analysis (12 studies were included)
	• Patients had either major depressive disorder or bipolar disorder
	  • Ketamine was never studied in treatment-naïve patients
	  • Most studies enrolled patients that did not have any other comorbidities except anxiety.

Treatment	• The majority of studies administered a dose of ketamine-0.5mg/kg over 40-60 minutes • The amount of doses received was variable between the studies (i.e., 1-6 doses)
Statistics	• Odds ratios for treatment response • Hedges adjustment for small samples

Results	• Antidepressant effects (6 studies)[2]
	  • A single infusion of ketamine, produced significant reductions in depression scores within 1 hours of administration[2]
	  • Significant antidepressant reductions were also noted at 24 hours post-infusion.
	  • Another study depicted how patients responded to ketamine over a course of 72-hours[3]. Patients reported a decrease in depression scores within the 3-4 hours but then in most cases these effects wore off.

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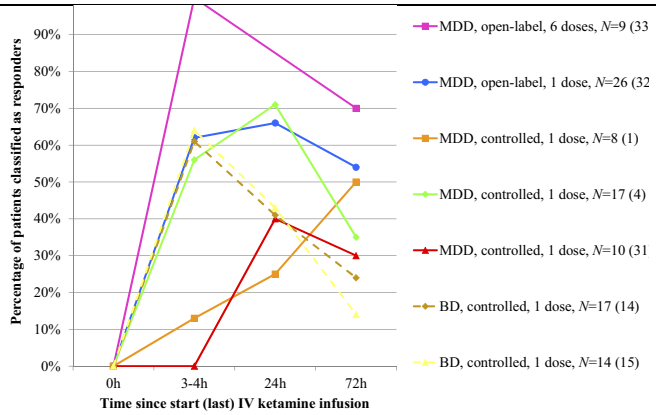
<tr><td></td><td></td><td> 

However, in 6 of the RCTs, they reported antidepressant effects were still present at 7 days post-ketamine infusion. However, this was not statistically significant.[2]
Adverse effects included transient blood pressure increases. In two of the studies, mean systolic pressures increased by 7 mmHg. These effects returned to baseline after 4 hours post-infusion.[2]
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<tr><td></td><td>Conclusions</td><td>
IV infusion of subanesthetic doses produces a rapid antidepressant effect
Low doses can also potentiate psychomimetic side effects
Significant therapeutic effects do not last long
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<tr><td></td><td>Limitations</td><td>
Patients were all randomized to saline vs. ketamine for treatment could mean unblinding of participants
Small study populations
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<tr><td>Other Avenues</td><td colspan="2">
Decreased suicidality[4]
Augmentation of ECT[5]
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<tr><td>Conclusions</td><td colspan="2">
Initial studies have demonstrated a potential treatment option for refractory depression.
Why not other NMDA antagonists (e.g., memantidine, lanicemine)?
Failed to match the effects of ketamine in RCTs[2]
Not recommended, quite yet…

There are a limited numbers of patients studied
The long term effects of ketamine infusions are unknown

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<tr><td>Place in therapy</td><td colspan="2">
Last-line treatment

More studies are needed to determine long term effects
The potential for medication abuse

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<tr><td>Pharmacy operations</td><td colspan="2">Restrictions

Currently at JHH, ketamine is restricted for the use of procedural sedation and for pain management.
Last month, the P&T committee approved a policy for ketamine infusion in the outpatient setting for pain

Administration

Nurses may only administer ketamine under specific written protocols

Protocol for ketamine for depression

None currently
No specified monitoring parameters
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<tr><td>References</td><td colspan="2">1. Berman, Robert M., et al. "Antidepressant effects of ketamine in depressed patients." Biological psychiatry 47.4 (2000): 351-354
2. Newport, D. Jeffrey, et al. "Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression." American Journal of Psychiatry 172.10 (2015): 950-966.
3. Aan Het Rot, Marije, et al. "Ketamine for depression: where do we go from here?." Biological psychiatry 72.7 (2012): 537-547.
4. Reinstatler, L., & Youssef, N. A. (2015). Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature. Drugs in R&D, 15(1), 37-43.
5. Okamoto, Nagahisa, et al. "Rapid antidepressant effect of ketamine anesthesia during electroconvulsive therapy of treatment-resistant depression: comparing ketamine and propofol anesthesia." The journal of ECT 26.3 (2010): 223-227.</td></tr>
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