Ketamine Update: What Should Clinicians Know

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Disclosures

• Grant Support
  • Medibio- research time support
  • Mayo Clinic

• Mayo Clinic has financial interest in AssureRX and OneOme

• Off-Label Product Use
Objectives

1. Describe the background of Ketamine
2. Review key studies - Single dose and serial infusions intravenous racemic ketamine
3. Review Ketamine use in the US
4. Review Esketamine data, FDA approval, limitations
Pharmacotherapy Over the Past 6 Decades

- Limited success in developing medications with radically novel mechanisms of action
- Current treatments: slow onset and limited effectiveness
- However, there is a resurgence of interest with the discovery of ketamine’s effects
Phencyclidine (PCP)

- CI-395; Sernyl (synthesized in 1956) – Park Davis
- Anesthetic for surgery – prolonged post-surgery delirium
- Luby et al – Model for Schizophrenia (SCZ) – SCZ like symptoms in healthy subjects
- Not used as an anesthetic agent in humans

CI-581 (Ketamine)

- Short acting derivatives of PCP – 1962
- 1970 – introduced as a short-acting anesthetic
- Psychomimetic effects and dissociation
- Visual hallucinations, out-of-body experiences
- Recreational drug worldwide
- Ulcerative cystitis in ketamine users (abuse)

Shahani et al. Urology. 2007; 69 (5): 810-812
Ketamine

• FDA approved - General Anesthesia & Procedural Sedation

• Schedule III substance

• Noncompetitive antagonist at NMDA receptor
  • also AMPA, sigma-1, mu-opioid receptors

• Single IV infusion, at a subanaesthetic dose, can produce rapid antidepressant effect
  • **No FDA approval** “..is outpacing scientific scrutiny”
  • abuse liability, cognitive impairment, cystitis

• Antidepressant MOA an active area of study

Rasmussen et al., Psychopharmacology 2013, Vande Voort et al., J Afffective Disorders 2015, Bobo et al., Depression Anxiety 2014
Proposed Mechanism of Action

1. GABA and NMDA receptors are blocked by Ketamine.

2. Glutamate release is increased.

3. AMPA activation is increased.

4. BDNF release is increased.

5. Increase protein synthesis and synapse number & function.

Sanacora and Schatzberg. Neuropsychopharmacology. 2015
Ketamine For Depression – Early Studies

- 4 placebo-controlled single infusion studies (total n=56 BP/UP)
  - Randomized placebo-controlled (saline)
  - 0.5 mg/kg over 40 min or ~0.75 mg/kg/hour
  - Rapid, non sustained antidepressant response

- 8 open studies (total n ~ 100 BP/UP)
  - Open single infusion (same rate) similar response

  - TRD patients with baseline SI (n=167)
  - Rapid (within 1 day & up to 1 week) reduced SI, both clinician-administered and self-report
Response Rate for Treatment-Resistant Unipolar Depression (N=18)

Response Rate:
71% Ketamine
0% Placebo

Remission Rate:
29% Ketamine
0% Placebo

• Randomized, placebo-controlled, double-blind cross over study
• Saline vs Ketamine (0.5 mg/kg infused over 40 minutes)

Reduction in MADRS score 24 hours after infusion significantly greater for the ketamine group than for the midazolam group ($p \leq 0.002$).
Response Rates in Patients With TRD Given a Single Infusion of Ketamine or Midazolam

Modified intention-to-treat group.
Response = 50% reduction Montgomery-Åsberg Depression Rating Scale.

Murrough et al., 2013. Am J Psychiatry
Intravenous Ketamine Or Placebo For Treatment-resistant Bipolar Depression

N=18 (Lithium = 10, Valproate = 8)
2 test days 2 weeks
Response Rates: 71% Ketamine 6% Placebo

*D < .001, †P < .01, ‡P < .05.*

*D < .05, †P < .01, ‡P < .001*
Effects Of Ketamine On Suicidal Ideation

MADRS: Suicidal Thoughts

### A) 1 day after initiation of ketamine (heterogeneity: $\chi^2=4.27$, df=4, $p=0.51$, $I^2=0\%$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
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</thead>
<tbody>
<tr>
<td>Diazgranados et al. (85)</td>
<td>26.053</td>
<td>1.359</td>
<td>499.339</td>
<td>2.164</td>
<td>0.030</td>
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<tr>
<td>Lapidus et al. (84)</td>
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<td>149.455</td>
<td>2.134</td>
<td>0.033</td>
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<td>Murrough et al. (87)</td>
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<td>1.578</td>
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<td>Sos et al. (91)</td>
<td>15.294</td>
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<td>Zarate et al. (88)</td>
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<td>Zarate et al. (86)</td>
<td>22.176</td>
<td>1.133</td>
<td>434.158</td>
<td>2.042</td>
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</table>

### B) 1 week after initiation of ketamine (heterogeneity: $\chi^2=1.14$, df=5, $p=0.95$, $I^2=0\%$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio</th>
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<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
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</thead>
<tbody>
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<td>0.426</td>
<td>58.636</td>
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<tr>
<td>Lapidus et al. (84)</td>
<td>3.171</td>
<td>0.179</td>
<td>56.222</td>
<td>0.787</td>
<td>0.431</td>
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<tr>
<td>Murrough et al. (87)</td>
<td>3.937</td>
<td>1.149</td>
<td>13.492</td>
<td>2.181</td>
<td>0.029</td>
</tr>
<tr>
<td>Sos et al. (91)</td>
<td>4.706</td>
<td>0.950</td>
<td>23.302</td>
<td>1.898</td>
<td>0.058</td>
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<tr>
<td>Zarate et al. (88)</td>
<td>19.783</td>
<td>1.060</td>
<td>369.109</td>
<td>1.999</td>
<td>0.046</td>
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<tr>
<td>Zarate et al. (86)</td>
<td>3.222</td>
<td>0.176</td>
<td>58.849</td>
<td>0.789</td>
<td>0.430</td>
</tr>
</tbody>
</table>

Newport et al., 2015 Am J Psychiatry
Ketamine Clinics For Depression – Early Studies

- Do serial infusions provide better response / remission rates than single infusions while maintaining safety?
  - Shiroma 2013 (n=14): 6 Txs, 92%/66%
  - Murrough 2013 (n=24, off AD): 6 Txs, 71% response
  - Rasmussen 2013 (n=10): 4Txs, 80%/50% F/U 4 wks

- Is 0.5 mg / kg over 40 minutes the best dosing strategy?
  - Rates ≥ 0.3 mg/kg at Mayo require anesthesia monitoring
  - Can you reduce side effect burden with slower infusion?

- Given NMDA receptor & glutamate/GABA receptors, are there medications to be excluded to optimize response?
  - Benzodiazepines
If the antidepressant benefits of ketamine are limited to 3-7 days, should we provide repeat administration?
Safety and Efficacy of Repeated-Dose Intravenous Ketamine

• Repeated doses (six infusions over the course of several weeks) have shown promise from an efficacy and safety standpoint

  • Even when dose is escalated

  • No advantage in efficacy in sustaining the initial antidepressant effects for two times vs three times a week intravenous ketamine in patients (n=67)

Serial Infusions of Ketamine for Unipolar Depression

- N=24
- Open label
- Up to 6 IV infusions (3 per week)
  - Monday-Wednesday-Friday schedule
- 0.5 mg/kg over 40 minutes
- Overall responder status determined after 6th infusion or last observation for non-completers.
- 21 completed all 6 infusions

Results: Serial Infusions of Ketamine

- Overall response rate at study end was 70.8%.
  (17 responders and 7 non-responders)
Results: Serial Infusions and Risk of Relapse

- Median time to relapse was 18 days.
- 4 subjects did not relapse in 83 days.

N=17 responders after 6 infusions

Serial infusions of low-dose ketamine for major depression

Keith G Rasmussen¹, Timothy W Lineberry¹, Christine W Galardy¹, Simon Kung¹, Maria I Lapid¹, Brian A Palmer¹, Matthew J Ritter², Kathryn M Schak¹, Christopher L Sola¹, Allison J Hanson¹ and Mark A Frye¹

Abstract

Background: Single infusions of ketamine have been used successfully to achieve improvement in depressed patients. Side effects during the infusions have been common. It is not known whether serial infusions or lower infusion rates result in greater efficacy.

Methods: Ten depressed patients were treated with twice weekly ketamine infusions of ketamine 0.5 mg/kg administered over 100 min until either remission was achieved or four infusions were given. Side effects were assessed with the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale (BPRS). Patients were followed naturalistically at weekly intervals for four weeks after completion of the infusions.

Results: Five of 10 patients achieved remission status. There were no significant increases on the BPRS or YMRS. Two of the remitting patients sustained their improvement throughout the four week follow-up period.

Conclusions: Ketamine infusions at a lower rate than previously reported have demonstrated similar efficacy and excellent tolerability and may be more practically available for routine clinical care. Serial ketamine infusions appear to be more effective than a single infusion. Further research to test relapse prevention strategies with continuation ketamine infusions is indicated.
Mayo Serial Infusion Trial: Results

• N=10 (5 female, 5 male)
• Mean age 47.2 ± 15 SD (range 19-61)
• IRB approval to infuse at 0.5 mg/kg over 100 minutes (not 40 minutes)
• Twice weekly infusions, up to 4 infusions or until remission was achieved

• MADRS
  • Baseline 33.3 ± 6.5
  • Endpoint 16.7 ± 13.2

Mayo Serial Infusion Trial: Results

• At end of infusions
  • Response rate 80%
  • Remission rate 50%
  • Only one patient remitted after first infusion
  • Usually more than one infusion needed

• At end of one month follow-up
  • 40% (2/5) maintained remission
  • In other words, 60% relapsed

## Mayo Serial Infusion Trial: Side Effects

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Dizziness</td>
</tr>
<tr>
<td>3</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>1</td>
<td>Visual hallucinations</td>
</tr>
<tr>
<td>1</td>
<td>Vertigo</td>
</tr>
<tr>
<td>1</td>
<td>Dysmegalopsia</td>
</tr>
<tr>
<td>1</td>
<td>Diplopia</td>
</tr>
<tr>
<td>1</td>
<td>Anxiety</td>
</tr>
</tbody>
</table>
Benzodiazepine Attenuates Ketamine Response

Mean Dose Lorazepam

P = 0.026 *

0.75 mg ± 0.29  
Response  
n=4

3.0 mg± 1.4  
Non-Response  
n=2

Frye et al. 2015 J CI Psychopharmacology
Continuation phase intravenous ketamine in adults with treatment-resistant depression


ARTICLE INFO

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Received 5 August 2016
Received in revised form 7 September 2016
Accepted 9 September 2016
Available online 12 September 2016

ABSTRACT

Background: Little is known about the antidepressive effects of repeated intravenous ketamine infusions beyond the acute phase of treatment in patients with refractory depression.

Methods: Twelve subjects with treatment-resistant non-psychotic unipolar or bipolar major depression and suicidal ideation were given repeated (up to 6) thrice-weekly acute-phase intravenous infusions of ketamine (0.5 mg/kg, administered over 100 min). Those who remitted during acute-phase treatment met criteria for continuation phase ketamine treatment. Ketamine was given thrice-weekly for up to 6 weeks.

Results: Eight of 12 subjects met criteria for remission during acute-phase treatment. Six subjects continued with ketamine for up to 6 weeks. Of these, five met criteria for remission during the continuation phase.

Conclusions: Continuation phase intravenous ketamine administration appears to be a safe and effective way to achieve remission in a subset of treatment-resistant major depressive disorder patients.

Financial disclosures: No financial disclosures for any author.
Mayo continuation trial: Results -- patients

- N=12 (11 female)
- Mean age 45.8 ± 8 SD
- MADRS Baseline 29.4 ± 7.5
- 9/12 (75%) Major depression, 2 with bipolar II, 1 with bipolar I
- All subjects failed at least 3 treatments during current depressive episode
- Four subjects did not respond to ECT
Mayo Clinical Ketamine Trials

![Graph showing MADRS total score changes across different phases of the trial.](image)

**5 Min Insulin (10 μg/ml) Stimulation**

Percent change in pmTOR/mTOR in PBMC following 5 minutes of exposure to insulin (ex-vivo) was significantly different in those subjects that remitted to ketamine during the acute phase of our recent ketamine trial.

Single, Repeated, and Maintenance Ketamine Infusions for TRD: A RCT

Phase 1
Randomized double-blind crossover
- Ketamine
- Midazolam

Phase 2
Six thrice-weekly open-label ketamine infusions
1 2 3 4 5 6

Phase 3
Four once-weekly open-label ketamine infusions
1 2 3 4

Baseline
Post-phase 2
Post-phase 3

Estimated Marginal Mean MADRS Total Score
A. Total Sample (N=41)
B. Single Ketamine Infusion Responders (N=11)
C. Single Ketamine Infusion Nonresponders (N=30)

Single, Repeated, and Maintenance Ketamine Infusions for TRD: A RCT

LONG-TERM DATA
Figure 2. Longer-Term (2-year) Outcomes of Patients Who Received Continuation/Maintenance Ketamine Treatment for Treatment-Resistant Depression (n = 14)\textsuperscript{a}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Longer-Term (2-year) Outcomes of Patients Who Received Continuation/Maintenance Ketamine Treatment for Treatment-Resistant Depression (n = 14)\textsuperscript{a}}
\end{figure}

\textsuperscript{a}The sample size decreases over time, reflecting that patients are at different stages of continuation/maintenance therapy and not reflecting patient dropout. Data for 1 of the patients were previously published in a case report.\textsuperscript{27}

Abbreviation: QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report.

Williams et al. 2018. Acute and Longer-Term Outcomes Using Ketamine as a Clinical Treatment at the Yale Psychiatric Hospital
Safety

- Two patients who received treatment later committed suicide

- Patient 1. Significant clinical improvement after 4 treatments. Received 1 maintenance treatment 2 months following the acute course of treatments but no further ketamine treatments following this. Committed suicide by hanging 4 months after her last dose of ketamine.

- Patient 2. Partial improvement from the ketamine following 4 treatments (35.6% improvement). Committed suicide by hanging approximately 10 months after receiving his final ketamine treatment. He had been seen in psychiatric follow-up the week of his death and had been in a heated argument with an ex-spouse the day of his suicide.
• “These cases highlight the critical need for consideration of longer-term strategies prior to treatment initiation, especially given the lack of long-term data on ketamine use.”
Ketamine and Glutamate

- Healthy Controls
  - Increase anterior cingulate GLU, but not GLX or subcortical GABA

- MDD patients
  - Baseline MRS GLX/GLU in DM/DA PFC (-) correlated with improvement

- MDD patients
  - Peripheral glutamate decrease (baseline to 4 days post-infusion) associated with ketamine response

- MDD patients remitted with ketamine single infusion
  - 6 MRS scans (each 13 minutes: pre, during, post)
  - mPFC GLX and GABA peaked (38% both) in ~ 26 minutes.
  - Mean AUC for GLX and GABA correlated (0.79, p=0.18).
  - Improvement correlated 90 minute norketamine (r=-0.78 p=0.023)

Rotroff et al., 2016, Salvadore et al., 2012, Taylor 2012, Stone et al., 2012, Milak et al., 2016
Ketamine – Promising Path or False Prophecy?

- Ketamine Abuse Liability via Mu Opioid Receptor
  - Dissociation
  - Psychosis
  - Potential for abuse
  - Pain management?

- Unregulated “ketamine clinics“ increasing in US

- “…an intravenously agent that is a street drug of abuse, works rapidly and whose enantiomers are being studied by industry for intranasal use – we should be anxious”

- Biomarkers, safety, predictors of response (suicidality) adverse event (dissociative symptoms) need further study

- Additional NMDA antagonists under development
Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism

Ketamine induced reductions in depressive symptoms were significantly attenuated (mean difference= -16.7, SD=6.7; p< 0.001)

Ketamine + Placebo

- Improvement in depression
  - Mean= -22.3, SD=3.2; p < 0.001

Ketamine + Naltrexone

- Minimal change in depression scores
  - mean= - 5.6, SD=5.7; p=0.04

Williams et al; *Am J Psychiatry*, 2018 Dec 1;175(12):1205-1215
Physicians Initiating Practice of Off Label Ketamine

Wilkinson et al., 2017 Am J Psychiatry
Esketamine
Esketamine

• S-enantiomer of ketamine
• Higher affinity for the NMDA receptor than the R-enantiomer
• Bioavailability of intranasal ketamine: 25-50%
August 16, 2016: FDA action marks second Breakthrough Therapy Designation for intranasal esketamine, highlighting its potential as treatment for patients with major depressive disorder who are at imminent risk for suicide and for those with treatment-resistant depression.
Intranasal Esketamine Adjunctive to Oral Antidepressants

• N=67 with TRD

• Double blind, randomized, placebo controlled

• Period 1 (1 week):
  • Randomized (3:1:1:1) to:
    • Placebo (n=33)
    • Esketamine 28 mg (n=11)
    • Esketamine 56 mg (n=11)
    • Esketamine 84 mg (n=12)
  • Dosed twice weekly

Daly et al. JAMA Psychiatry. 2018.
Intranasal Esketamine Adjunctive to Oral Antidepressants

• Period 2 (1 week):
  • 28 placebo-treated subjects randomized (1:1:1:1) to 1 of the 4 treatment arms (placebo, esketamine 28, 56, 84 mg)

• Open-label phase:
  • Administration reduced from twice weekly then once weekly and then to once every 2 weeks.

• Follow-up phase (8 weeks): No esketamine given

• Existing antidepressant treatment was continued during the study

• Primary outcome: Change in MADRS

Daly et al. JAMA Psychiatry. 2018.
Efficacy of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in TRD

Period 1 (days 1-8) & Period 2 (days 8-15)

EJ Daly et al, JAMA Psychiatry 2018
Results: Intranasal Esketamine Adjunctive to Oral Antidepressants

“Esketamine Taper”

No Esketamine

Daly et al. JAMA Psychiatry. 2018.
## Comparison Of Esketamine Studies

### Results of Short-Term Studies of Esketamine.

<table>
<thead>
<tr>
<th>Study and Treatment Group</th>
<th>No. of Patients</th>
<th>Primary Efficacy Measure: MADRS Total Score</th>
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<tr>
<td></td>
<td></td>
<td>Baseline Score</td>
</tr>
<tr>
<td>3001</td>
<td></td>
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</tr>
<tr>
<td>ESK, 56 mg</td>
<td>115</td>
<td>37.4±4.8</td>
</tr>
<tr>
<td>ESK, 84 mg</td>
<td>114</td>
<td>37.8±5.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>113</td>
<td>37.5±6.2</td>
</tr>
<tr>
<td>3002</td>
<td></td>
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<tr>
<td>ESK, 56 or 84 mg</td>
<td>114</td>
<td>37.0±5.7</td>
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<tr>
<td>Placebo</td>
<td>109</td>
<td>37.3±5.7</td>
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<tr>
<td>3005</td>
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<td></td>
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<tr>
<td>ESK, 28, 56, or 84 mg</td>
<td>72</td>
<td>35.5±5.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>65</td>
<td>34.8±6.4</td>
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</table>

* In Study 3001, the lower dose could not be tested for statistical significance because the higher dose failed. CI denotes confidence interval, ESK esketamine, and MADRS Montgomery–Åsberg Depression Rating Scale (scores range from 0 to 60, with higher scores indicating more severe depression). Data are from the Food and Drug Administration. Plus–minus values are means ±SD.

† One-sided P values are compared with P = 0.025.
Adverse-events (≥ 5 %)

- Dizziness
- Dissociation
- Hypoesthesia
- Nausea/vomiting
- Headache
- Fatigue/lethargy
- Increased blood pressure
- Vertigo
- Feeling drunk
FDA approval: March 05, 2019

- Risk of sedation and dissociation – Monitor patients for at least 2 hours
- Potential for abuse and misuse of the drug - Monitor patients for signs and symptoms of abuse and misuse
- ONLY available through a restricted distribution system, under a Risk Evaluation and Mitigation Strategy (REMS)
- Dispensed and administered ONLY in a medically supervised health care setting
- Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants
CONTRAINdications

• Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation.

• Intracerebral hemorrhage.

WARNINGS AND PRECAUTIONS

• Increases in Blood Pressure
• Cognitive impairment
• Impaired Ability to Drive and Operate Machinery
• Embryo-fetal Toxicity
Nasal Spray Device

Indicator
One device contains 2 sprays.
(1 spray for each nostril)
- 2 green dots (0 mg delivered): Device full
- 1 green dot: One spray delivered
- No green dots: Two sprays (28 mg) delivered
- Device empty

Each device delivers two sprays containing a total of 28 mg of esketamine.

Step 1: Get ready

Before first device only:
Instruct patient to blow nose **before** first device only.
Confirm required number of devices.

56 mg = 2 devices
84 mg = 3 devices

$590
$885

Table 1: Recommended Dosage for SPRAVATO

<table>
<thead>
<tr>
<th>Phase</th>
<th>Period</th>
<th>Adults</th>
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<tbody>
<tr>
<td>Induction Phase</td>
<td><strong>Weeks 1 to 4:</strong></td>
<td>Day 1 starting dose: 56 mg or 84 mg</td>
</tr>
<tr>
<td></td>
<td>Administer twice per week</td>
<td>Subsequent doses: 56 mg or 84 mg</td>
</tr>
<tr>
<td>Maintenance Phase</td>
<td><strong>Weeks 5 to 8:</strong></td>
<td>56 mg or 84 mg</td>
</tr>
<tr>
<td></td>
<td>Administer once weekly</td>
<td>56 mg or 84 mg</td>
</tr>
<tr>
<td></td>
<td><strong>Week 9 and after:</strong></td>
<td>56 mg or 84 mg</td>
</tr>
<tr>
<td></td>
<td>Administer every 2 weeks or once weekly*</td>
<td>56 mg or 84 mg</td>
</tr>
</tbody>
</table>

* Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.
Unregulated Ketamine Use

- 52-year-old divorced man 30-year history of recurrent major depressive disorder
  - 1st episode / hospitalization / suicide attempt age 22
  - Remote history of outpatient chemical dependency treatment for alcohol use disorder as a young adult.
- Prospective course of illness
  - Annual admissions at our medical center 2012-2015
    - All for major depression with suicidal ideation
    - clear treatment-resistant depression
  - Limited capacity to address overall treatment plan.
Unregulated Ketamine Use II

• Admission # 1
  • misuse lorazepam 1 mg BID (taking 5 mg daily).
  • out-of-state single iv ketamine with benefit for 4-5 days
  • community MD in another state prescribing intranasal ketamine for depression with benefit.

• Admission # 2
  • out-of-state prescriber verified prescribing ketamine 150 mg/mL, 0.5-1 mL intranasal q 4 hours prn depression
  • 10-12 times a day: (+) benefit 2-3 hours with dissociative side effects lasting up to 20 minutes
  • Intranasal ketamine in his vehicle
Admission #3

Permission to speak to family, ketamine “ripping his life apart”

Ketamine dependence (i.e. increased use, driving under influence, loss of employment).

Out of-state ketamine prescriber agreed to cease prescribing.

Petition for civil commitment not supported by the court.

1 year later notified of his death from a single-car crash

- autopsy was positive for alcohol 0.133% (0.08% legal limit), tetrahydrocannabinol, and bupropion (prescribed)
- family indicated belief that death was a suicide
A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders

Gerard Sanacora, MD, PhD; Mark A. Frye, MD; William McDonald, MD; Sanjay J. Mathew, MD; Mason S. Turner, MD; Alan F. Schatzberg, MD; Paul Summergrad, MD; Charles B. Nemeroff, MD, PhD; for the American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments

IMPORTANCE Several studies now provide evidence of ketamine hydrochloride’s ability to produce rapid and robust antidepressant effects in patients with mood and anxiety disorders that were previously resistant to treatment. Despite the relatively small sample sizes, lack of longer-term data on efficacy, and limited data on safety provided by these studies, they have led to increased use of ketamine as an off-label treatment for mood and other psychiatric disorders.

OBSERVATIONS This review and consensus statement provides a general overview of the data on the use of ketamine for the treatment of mood disorders and highlights the limitations of the existing knowledge. While ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data and the potential risk associated with the drug when considering the treatment option.

CONCLUSIONS AND RELEVANCE The suggestions provided are intended to facilitate clinical decision making and encourage an evidence-based approach to using ketamine in the treatment of psychiatric disorders considering the limited information that is currently available. This article provides information on potentially important issues related to the off-label treatment approach that should be considered to help ensure patient safety.
Mayo Clinic Depression Center
Paul Croarkin, D.O., M.S. Director

Mood Clinic
Marin Veldic M.D.
Director

Mood Program
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Mayo Core Value: The Needs of the Patient Come First

Rapid, Effective, and Personalized Treatments
Eligibility criteria

• Valid informed consent
• 18 (not in HS) to 64 years of age
• MDD, BP-I, BP-II
• Treatment-resistant depression
• Pass a comprehension assessment
• Aftercare being provided by referring clinician
• Physical exam and medical / laboratory clearance
Informed consent

• Risks associated with IV ketamine for depression, including non-response

• Limitations of available information pertaining to potential benefits of IV ketamine for depression

• Off-label use of ketamine

• No long term safety data (i.e. dosing strategy, cognitive impairment, abuse liability, cystitis)

• Discussion of alternative treatment options

• Written consent only
Depression Center Ketamine Clinic
Service provided in afternoon in ECT suite

**Pharmacotherapy and Psychotherapy as Usual**

<table>
<thead>
<tr>
<th>Screening</th>
<th>Acute Phase Infusion</th>
<th>Cont. Phase Infusion</th>
<th>Optimization Phase</th>
<th>Maintenance Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg/kg, 40-100 min 3x/week, up to 6 infusions</td>
<td>0.5 mg/kg, 40-100 min</td>
<td>0.5 mg/kg, 40-100 min 1x/week for 4 weeks</td>
<td>0.5 mg/kg, 40-100 min Maint optimum frequency</td>
<td></td>
</tr>
</tbody>
</table>

Is Clinical Practice Outpacing Research?

Urgent need tx potential  A clinical dilemma  Large gaps in evidence base

- Ketamine is unique
  - Rapid-acting, antidepressant, antisuicidal properties
- Urgent need must be balanced by a measured response
- Long-term efficacy and safety are unknown
- Informed consent is critical

Bobo et al. Depress Anxiety. 2016.
Ketamine Update: What Should Clinicians Know and Expect

- Great potential to address unmet need of treatment resistant depression and suicidality
- Scientifically rigorous and ethically sound development programs moving forward
- Increased off-label use of intravenous Ketamine
  - Infrastructure critical
  - National registry or dataset has appeal
  - Ketamine Clinics modeled after ECT and/or outpatient chemotherapy infusion center
- Biomarkers for Treatment Response
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- All the patients

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