The Promise and Perils of Ketamine in Psychiatric Practice

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Outline

- Background on Ketamine
- The Promise
  - Single Infusion Therapy for TRD, Suicidal Ideation, PTSD
  - Continuation Therapy
- The Perils
- Ketamine in Clinical Practice: Towards Best Practice Patterns for Off-label Use

Case Study: Ms. B

- Age 31, first depressive episode age 24 in law school
- 2 episodes/year, with loss of function, marked anhedonia, and suicidal ideation
- Past adequate trials of antidepressants:
  - Sertraline (200 mg)
  - Venlafaxine XR (300 mg)
  - Bupropion XL (450 mg)
  - Vortioxetine (20 mg)
- Adjunctive lithium and aripiprazole not well tolerated
- ECT effective but suffered severe memory impairment

WOULD YOU CONSIDER A TRIAL OF KETAMINE?

Ketamine: History

- Synthesized in 1962 by Calvin Stevens, a Parke-Davis chemist seeking an alternative anesthetic to PCP
- FDA approved for human use since 1970 (Schedule III)
- Approved indications:
  - “...the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation.”
  - “...the induction of anesthesia prior to the administration of other general anesthetic agents.”
  - “...to supplement low-potency agents, such as nitrous oxide.”

Ketamine and NMDA Receptor

- Dissociative anesthetic (2–3 mg/kg — 2000–3000 ng/mL peak plasma concentrations)
- Uncompetitive high-affinity NMDAR antagonist
- Binds to PCP “angel dust” site within ion channel
- Membrane depolarization relieves Mg block, and with co-agonist binding, Ca2+ and Na+ enters cell

ECT = electroconvulsive therapy.

PCP = phencyclidine.

NMDA = N-methyl-D-aspartate.
Antidepressant Mechanism of Action of NMDA Receptor Modulators

Are the Antidepressant Actions of Ketamine Independent of NMDA Receptor Activity?

Metabolic Pathways of Ketamine

Single Ketamine Infusion (0.5 mg/kg over 30 minutes) Rapidly Effective in TRD: Replication Study (N = 17)

Single Ketamine Infusion is Superior to Psychoactive Control in TRD: Baylor/Mt Sinai Study (N = 72)

Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group (P ≤ .002).

Ketamine dose = 0.5 mg/kg
Single Infusion of Ketamine – Efficacy in TRD (N = 147)


At 1 day

Study | OR | 95% CI | Z | p-value | Effect Size 0.5 mg/kg

Add-on Trial of Ketamine in Treatment-Resistant Bipolar Depression

Dose: 0.5 mg/kg ketamine

Depressive symptoms significantly improved in participants receiving ketamine compared with placebo

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Effect of Ketamine on Suicidal Ideation: Individual Patient Meta-Analysis


Dose: 0.5 mg/kg ketamine

Midazolam 0.045 mg/kg

Ketamine 0.2 mg/kg

Ketamine 0.5 mg/kg

Ketamine 1.0 mg/kg

Ketamine 2.0 mg/kg

SCREEN
RANDOMIZE
DAY 0
DAY 3
DAY 30
PRIMARY ENDPOINT ASSESSMENTS
STUDY COMPLETION

Double-Blind, Placebo-Controlled, Dose-Ranging Trial of Intravenous Ketamine as Adjunctive Therapy in TRD


Ms. A: “I feel good, I want to get out and do things, like get a haircut. I haven’t felt like this in a year. I tried to think about (the assault) but couldn’t. That was strange… I feel more connected to others, less afraid.”

Mr. B: “I feel much better, the sirens outside on the street no longer bother me. I called several friends that I hadn’t spoken with in a while. I feel calm, not so jumpy.”

Ms. C: “I feel energetic, not stressed out or anxious, I feel good, refreshed. I enjoyed going outdoor briefly for a smoke. I haven’t dwelled on thoughts about (the trauma). I let it go. I feel happy, upbeat, my mind is clear. Interacting with others no longer takes so much effort, I don’t feel like I have to fake.”

Take-Home Message:
Dose-Response Trial of IV Ketamine in TRD
- Both low dose (0.1 mg/kg) and higher doses (0.5 mg/kg and 1 mg/kg) of IV ketamine superior to active placebo
- Limitations:
  - Lack of racial diversity in study sample
  - Unclear reasons for failure of 0.2 mg/kg dose arm
  - No assessment of response durability beyond 72 hours or speed of response at 4 hours

Continuation and Maintenance Therapy
- Repeated ketamine infusions
- Maintenance ketamine protocols in combination with drugs, ECT, or psychotherapy

Thrice-Weekly Ketamine Infusions in TRD:
- Mt Sinai Sample (N = 24)
- Thrice-weekly ketamine infusions:
  - Mean time to relapse = 16 days
  - 92% responded; 67% remitted
  - Dose = 0.5 mg/kg over 40 minutes

Thrice-Weekly Ketamine Infusions in TRD:
- Minneapolis VA Sample (N = 14)
- Thrice-weekly ketamine infusions:
  - Mean time to relapse = 16 days
  - 92% responded; 67% remitted
  - Dose = 0.5 mg/kg over 40 minutes
Repeated Ketamine Infusions in TRD: Mayo Clinic Sample (N = 12)


Dose = 0.5 mg/kg over 100 minutes

58% responded, 42% remitted

Thrice-weekly up to 6 infusions

12-Month Naturalistic Observation of 3 Patients Receiving Ketamine Infusions for TRD


Twice-Weekly Dosing as Effective as Thrice-Weekly Dosing in TRD


Ket: 69% responded, 38% remitted

PBO: 15% responded, 7.7% remitted

Twice: 54% responded; 23% remitted

PBO: 6% responded; 0% remitted

RCT of the NMDA Receptor Partial Agonist D-Cycloserine (1 g/day) Augmentation for TRD


Proportion of responders [≥ 50% improvement on 21-item HAMD] during 6 week adjuvant treatment with D-cycloserine (n = 13) and placebo (n = 13). *P = .039

47 Assessed for eligibility

Enrolment, randomization, withdrawals and completion of the study (N = 26). (CONSORT flow diagram.)

NRX-101 for the Treatment of Acute Suicidal Ideation and Behavior in Bipolar Depression

NRX-101: Fixed dose combination of DCS + lurasidone

Primary outcome of Phase 2b Trial:
- Time to relapse following IV ketamine infusion

Randomized Arms following single IV ketamine infusion:
- NRX-101 (DCS + lurasidone)
- Lurasidone + placebo

D-Cycloserine for Relapse Prevention Post-IV Ketamine in Treatment-Resistant Bipolar Depression

D-Cycloserine (DCS = DCS)

ClinicalTrials.gov Identifier: NCT02974010.
Randomized-Controlled Trial of Low-Dose Ketamine Adjunctive to ECT in TRD

- **No benefit** of 0.5 mg/kg ketamine bolus (n = 40) in conjunction with standard anesthetic agent during a course of bitemporal ECT compared with placebo (n = 39)

- Primary Outcome: Hopkins Verbal Learning Test, Delayed Verbal Recall

- No benefit vs placebo on any efficacy outcome, including time-to-response and response at endpoint

Leveraging Neuroplasticity Changes to Create Synergistic Interventions with Both Rapidity and Durability

- **Perils**
  - Short duration of effect
  - Dissociative and other psychological side effects
  - Impact on hemodynamics
    - Transient increases in systolic and diastolic BP
    - BPs > 180/100 mmHg or HR > 110 bpm in 30% of MDD patients
  - Nausea/vomiting
  - Impact on Cognition
  - “Ketamine Bladder”
  - Addiction/Ketamine Use Disorder

Dissociative Side Effects

- Dissociative properties
  - Things in slow motion
  - Things seem unreal
  - Disconnected from body
  - Sense of body changed

Dose Dependence of Dissociative Side Effects

- **ELEKT-D**
  - Electroconvulsive Therapy (ECT) vs Ketamine in Patients with Treatment Resistant Depression (TRD)

Perils

Price RB. NIMH R01 Grant.

- Introduction of a neurocognitive training intervention during this window of opportunity

Price RB. IMH R01 Grant.

- CADSS = Clinician Administered Dissociative States Scale


Comparison of Side Effects: 0.5 mg/kg vs 0.75 mg/kg

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Infusion 1–3 (0.5 mg/kg)</th>
<th>Infusion 4–6 (0.75 mg/kg)</th>
<th>Physical side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>4/14 (29%)</td>
<td>3/13 (23%)</td>
<td></td>
</tr>
<tr>
<td>Tiredness/sleepiness/sedation/spaciness</td>
<td>1/14 (7%)</td>
<td>3/13 (23%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness/lightheadedness</td>
<td>1/14 (7%)</td>
<td>3/13 (23%)</td>
<td></td>
</tr>
<tr>
<td>Cold/cough/sinus congestion</td>
<td>2/14 (14%)</td>
<td>1/13 (8%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1/14 (7%)</td>
<td>1/13 (8%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1/14 (7%)</td>
<td>1/13 (8%)</td>
<td></td>
</tr>
<tr>
<td>Weepiness/crying</td>
<td>1/14 (7%)</td>
<td>1/13 (8%)</td>
<td></td>
</tr>
<tr>
<td>Nosebleed</td>
<td>1/14 (7%)</td>
<td>1/13 (8%)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1/14 (7%)</td>
<td>1/13 (8%)</td>
<td></td>
</tr>
<tr>
<td>Panic</td>
<td>1/14 (7%)</td>
<td>0/13 (0%)</td>
<td></td>
</tr>
<tr>
<td>Transient palpitations</td>
<td>1/14 (7%)</td>
<td>0/13 (0%)</td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>0/14 (0%)</td>
<td>1/13 (8%)</td>
<td></td>
</tr>
<tr>
<td>Difficulty starting urination</td>
<td>1/14 (7%)</td>
<td>0/13 (0%)</td>
<td></td>
</tr>
<tr>
<td>Bursitis/tendinitis</td>
<td>1/14 (7%)</td>
<td>0/13 (0%)</td>
<td></td>
</tr>
<tr>
<td>Easy bruising</td>
<td>1/14 (7%)</td>
<td>0/13 (0%)</td>
<td></td>
</tr>
<tr>
<td>Dissociative side effects (CADSS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amnesia</td>
<td>5/14 (36%)</td>
<td>4/13 (31%)</td>
<td></td>
</tr>
<tr>
<td>Depersonalization</td>
<td>9/14 (64%)</td>
<td>4/13 (31%)</td>
<td></td>
</tr>
<tr>
<td>Derealization</td>
<td>10/14 (41%)</td>
<td>8/13 (62%)</td>
<td></td>
</tr>
</tbody>
</table>

Average blood pressure increase (mmHg)
- Systolic +13 +18
- Diastolic +9 +10

Baylor/Mt Sinai Study: Treatment during Ketamine Infusion

<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Max or Min BP (Systolic)</th>
<th>Max or Min BP (Diastolic)</th>
<th>Reason for Intervention</th>
<th>Course of Action</th>
<th>Infusion Discontinued?</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSM01</td>
<td>150</td>
<td>101</td>
<td>Hypertension</td>
<td>Nitroglycerin (50 mg x 3)</td>
<td>No</td>
</tr>
<tr>
<td>MSSM02</td>
<td>73</td>
<td>45</td>
<td>Hypertension</td>
<td>Onasemid 3 mg</td>
<td>No</td>
</tr>
<tr>
<td>BCM01</td>
<td>176</td>
<td>102</td>
<td>Hypertension</td>
<td>Esmolol x 2 (20 mg, 30 mg)</td>
<td>No</td>
</tr>
<tr>
<td>BCM05</td>
<td>181</td>
<td>104</td>
<td>Hypertension</td>
<td>Esmolol x 1 (30 mg), Nitroglycerin (50 mg)</td>
<td>No</td>
</tr>
<tr>
<td>BCM16</td>
<td>168</td>
<td>112</td>
<td>Hypertension</td>
<td>Esmolol x 4 (mg)</td>
<td>No</td>
</tr>
<tr>
<td>BCM06</td>
<td>175</td>
<td>111</td>
<td>Hypertension</td>
<td>Ondansetron 4 mg</td>
<td>No</td>
</tr>
<tr>
<td>BCM17</td>
<td>151</td>
<td>88</td>
<td>Hypertension</td>
<td>Esmolol x 2 (20 mg, 30 mg)</td>
<td>No</td>
</tr>
<tr>
<td>BCM22</td>
<td>175</td>
<td>111</td>
<td>Hypertension</td>
<td>Esmolol x 2 (20 mg, 30 mg)</td>
<td>No</td>
</tr>
</tbody>
</table>

*15% of participants at BCM, 12% of participants at MSSM required anesthesiologist intervention.

Ketamine Infusions (Weekly or Twice Weekly) Not Associated with Memory Impairments in TRD

ECT-MQ = ECT Memory Questionnaire.

“Ketamine Bladder”
- Hemorrhagic or ulcerative cystitis associated with chronic use
- Extremely painful and frequent urination
- Recreational abusers tend to use much higher doses (one study showed 12 g/week)
- No reports associated with intermittent subanesthetic dose
  - Urinary track symptoms no greater than placebo in meta-analysis


Rapid Growth in Ketamine Providers

Most common off-label indications—
MDD (72%), bipolar (15%), PTSD (6%)

Survey Responses of Providers Offering Off-label Ketamine (N = 57)

<table>
<thead>
<tr>
<th>Provider Specialty</th>
<th>Route of Administration</th>
<th>Monitoring at each 15 min during IV infusion</th>
<th>Frequency of maintenance treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatry (67%)</td>
<td>Intravenous (88%)</td>
<td>Heart rate (78%)</td>
<td>Monthly (30%)</td>
</tr>
<tr>
<td>Anesthesiology (23%)</td>
<td>Oral (21%)</td>
<td>Pulse oximetry (80%)</td>
<td>Once per 3 weeks (21%)</td>
</tr>
<tr>
<td>Emergency Medicine (3.5%)</td>
<td>Intranasal (19%)</td>
<td>Blood pressure (76%)</td>
<td>Once per 2 weeks (12%)</td>
</tr>
<tr>
<td>Family Medicine (3.5%)</td>
<td></td>
<td></td>
<td>Less than monthly (16%)</td>
</tr>
</tbody>
</table>

Provider Specialty: Psychiatry (67%), Anesthesiology (23%), Emergency Medicine (3.5%), Family Medicine (3.5%).

Monitoring at each 15 min during IV infusion: Heart rate (78%), Pulse oximetry (80%), Blood pressure (76%).

Frequency of maintenance treatments: Monthly (30%), Once per 3 weeks (21%), Less than monthly (16%).

Patient Selection

- Comprehensive diagnostic assessment
- Evaluate for Hx of psychosis and SUDs/AUDs
- Past medical and psychiatric records
- Medical contraindications and relative contraindications
  - Uncontrolled HTN, CAD, severe OSA, CVA, dementia, poor anesthesia candidate
- For MDD diagnosis:
  - Severity of depression (QIDS or PHQ9) and episode duration
  - Previous treatment history
  - ECT history (Cleveland Clinic example)
- For Obese patients (BMI > 30) consideration should be made to adjust dosing to ideal body weight

Informed Consent Process

- Limits of available information pertaining to the potential benefits of ketamine therapy
- Acknowledgement of Off-label use of ketamine
- Discussion of alternative treatment options
  - Lithium augmentation
  - IMOIs/TCaAs
  - ECT/TMS/VNS
  - Clozapine (refractory bipolar disorder)
- Essential to have written informed consent before initiating treatment

Clinician Experience and Training

- Clinical specialty not as important as ability to manage potential cardiovascular events should they occur
- Reasonable standard — Licensed clinician who can administer a DEA Schedule III medication with ACLS certification
- On-site clinician available to treat psychiatric emergencies

ACLS = Advanced Cardiovascular Life Support.
Treatment Delivery

- Assessment of Respiratory Status (oxygen saturation or end-tidal CO₂)
- Assessment of cardiovascular function (BP, HR) at regular intervals
- Assessment of level of consciousness (Modified Observer’s Assessment of Alertness/Sedation Scale)
- Criteria for stopping infusion
- Crash cart availability for hemodynamic instability

Post-Infusion Monitoring and Discharge

- IV line in place for approximately 1 hour following infusion
- Generally monitor for up to 2 hours after the end of infusion
- Documentation of return to baseline physiological and mental status by clinician on-site
- Ensure that a responsible individual is available to transport patient home

Oral Ketamine in a Large Health Care System: The Kaiser Experience

- Long wait times for IV ketamine prompted exploration of oral forms of ketamine
  - 31/44 patients with a 50% reduction in QIDS after 6 to 8 administrations; Average dose 100 mg (1 mg/kg)
- Side effects minimal
  - Systolic BP increase 10 mm/Hg; slightly less increase in diastolic BP; no changes in HR
  - Patient ready for discharge in 45 to 60 minutes

Case Study: Ms. B

- Reasonable consideration for severe TRD with functional disability
- Should also be presented with full range of approaches, including drug, neurostimulation, psychotherapy alternatives —
  - Drug: MAOI, TCA, Liothyronine
  - Cognitive-behavioral therapy
  - Neurostimulation: rTMS (including Deep TMS); VNS

Resources / Additional Reading