Ketamine: Provocative Party Drug or Creative Cure for the Blues?

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Objectives
1. Define treatment resistant depression.
2. Compare and contrast the mechanism of action of ketamine vs. conventional antidepressants.
3. Assess current evidence for using ketamine for treatment resistant depression.
4. Develop a conclusion about ketamine’s current place in therapy for treatment resistant depression.
TREATMENT RESISTANT DEPRESSION

I. Definitions
   a. Treatment resistant depression (TRD)
      i. Lack of consensus of criteria for TRD in regards to number of adequate trials and duration of each trial
      ii. Commonly considered a failure to respond to two or more adequate trials of antidepressants
   b. Criteria of treatment response
      i. Nonresponse: failure to achieve $\geq 50\%$ symptom reduction
      ii. Response: $\geq 50\%$ symptom reduction
      iii. Partial response: 25% to <50% symptom reduction

II. Epidemiology of TRD
   a. No consensus on prevalence
   b. Stage-dependent prevalence (12-month)
      i. Failure to respond to one antidepressant: $\sim 50\%$
      ii. Failure to respond to two antidepressants: $\sim 35\%$
   c. Setting-dependent prevalence
      i. Less common in primary care settings
      ii. More common in inpatient settings

III. Predictive factors of resistance to antidepressants
   a. Psychiatric comorbidities
      i. Anxiety disorders
      ii. Substance abuse disorders
      iii. Personality disorders
         1. Anxious-fearful cluster (cluster C)
         2. Dramatic-unstable cluster (cluster B)
   b. Medical comorbidities
   c. Female gender
   d. Family history of mood disorders
   e. Early or late age of onset
   f. Severe major depressive disorder (MDD)
   g. Chronic depression: a major depressive episode lasting longer than two years

CURRENT THERAPIES AND STRATEGIES

IV. Psychotherapy

V. Monoaminergic antidepressants
   a. Proposed mechanism of action
      i. Immediate increase in monoamine transmission, but gradual improvement in depressive symptom (2-3 weeks up to 12-16 weeks)
      ii. Hypothetical causes of delay of onset of action
         1. Brain derived neurotrophic factor (BDNF) synthesis associated with antidepressant response
         2. Down regulation of N-methyl-D-aspartate (NMDA) receptors
   b. Strategies: switching or augmentation (with subsequent treatment steps remission rates decrease: 33% $\rightarrow$ 30% $\rightarrow$ 14% $\rightarrow$ 13%)

VI. ECT
   a. Various proposed mechanisms of action
   b. Gold standard with high remission rates
      i. MDD: 70-90%
ii. TRD: 50%
c. Rapid effects
d. Risk of cognitive impairment due to anesthesia and procedure
e. Clinical factors
   i. Choice of outpatient or inpatient depends on severity of illness (e.g., active suicidal ideation), comorbid medical conditions, post-treatment care
   ii. Bilateral associated with greater efficacy and more rapid response but increased risk of cognitive impairment (retrograde amnesia)
   iii. Administered two to three times a week
   iv. Pre-ECT evaluations: electrocardiogram (ECG), labs (comprehensive metabolic panel, complete blood count), pseudocholinesterase
   v. Concurrent medication therapy
      1. Antidepressants augment ECT response and may decrease relapse rates
      2. Anticonvulsant doses decreased or discontinued
   vi. No oral intake for eight hours prior to ECT
   vii. General anesthesia
   viii. Monitoring: vital signs, ECG, electroencephalogram
f. Financial factors
g. ECT in Texas
   i. Only 6% of ECT treatments conducted in public hospitals
   ii. Texas Department of State Health Services collects data every 3 months (e.g., number of patients receiving ECT and type of equipment used) from facilities administering ECT
   iii. Maximum number of treatments: 24 per 12-month period; 15 in 8 consecutive weeks
   iv. Not permitted in ages <16 years old
   v. Patients >65 years old: physicians required to testify medical necessity of ECT
   vi. Requires registration of ECT devices

GLUTAMATERGIC THEORY AND NMDA ANTAGONISTS

VII. Glutamatergic theory
   a. Glutamate
      i. Binds to ionotropic glutamate receptors
         1. NMDA
         2. Alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA)
            a. Mediates desensitizing excitation
            b. Responsible for early response to glutamate in the synapse
      ii. NMDA and AMPA coexpressed in mature synapses
         1. Glutamate binds to AMPA causing sodium influx and neuronal membrane depolarization
         2. Charge difference leads to free the magnesium cation plug from the NMDA receptor ionic channel leading to calcium influx
         3. Calcium activates a cascade of signals that causes the synthesis and release of BDNF
         4. BDNF leads to synaptogenesis and antidepressant effects in the hippocampus

VIII. NMDA antagonist mechanism of action
   a. Blocks NMDA receptor
   b. Favors AMPA over NMDA receptors causing fast excitation and antidepressant response
   c. Also causes antidepressant effects via BDNF expression
Figure 1. Proposed mechanisms of action of glutamate, NMDA antagonists, conventional antidepressants

IX. NMDA antagonists studied in depression\(^{14-16}\)
   a. Amantadine
      i. Low affinity, noncompetitive, selective
      ii. Reduces NMDA receptor function at high doses by 50%
      iii. Limited potential as antidepressant due to dopamine agonism and related side effects
   b. Memantine
      i. Low affinity, noncompetitive, selective
      ii. RCT (Zarate et al.): 5-20 mg/day for eight weeks ineffective in MDD
   c. Ketamine
      i. High affinity, noncompetitive, nonselective
      ii. RCT (Berman et al.): Ketamine 0.5 mg/kg intravenous (IV) over 40 minutes rapidly and robustly effective in depression

<table>
<thead>
<tr>
<th>KETAMINE</th>
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<tbody>
<tr>
<td>X. Proposed mechanism of action(^{17-19})</td>
</tr>
<tr>
<td>a. Acts in two ways to increase glutamatergic transmission</td>
</tr>
<tr>
<td>i. Blocks PCP site within NMDA ion channel</td>
</tr>
<tr>
<td>ii. Disinhibits GABAergic inputs (\rightarrow) increases rate of firing of glutamatergic neuron (\rightarrow) increases presynaptic release of glutamate (\rightarrow) increased extracellular glutamate</td>
</tr>
<tr>
<td>b. More glutamate binds to AMPA because NMDA receptors are blocked by ketamine</td>
</tr>
<tr>
<td>c. Causes increased glutamatergic throughput of AMPA vs. NMDA and fast excitation</td>
</tr>
<tr>
<td>d. Activates BDNF and mammalian target of rapamycin (mTOR)</td>
</tr>
<tr>
<td>e. mTOR phosphorylation leads to synaptogenesis causing acute antidepressant effects</td>
</tr>
</tbody>
</table>

XI. Uses\(^{17}\)
   a. Anesthesia
   b. Analgesia

XII. Safety\(^6,17\)
a. Psychotomimetic effects
b. Cardiovascular or respiratory function
c. Dependence

XIII. Clinical question: Is ketamine safe and effective in adults with TRD

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**EVIDENCE**

**Study #1**

| Question | Is a single infusion of ketamine effective in patients with TRD and are these effects sustained? |
| Description | Double-blind randomized placebo-controlled crossover study |
| Patients | • **Inclusion**: adults 18-65 years, inpatients, MDD recurrent without psychotic features, 21-item Hamilton Depression Rating Scale (HDRS) score ≥18 (screening and start of infusions), failed ≥2 adequate antidepressant trials per Antidepressant Treatment History Form (ATHF)  
  • **Exclusion**: bipolar disorder, history of antidepressant or substance-induced hypomania or mania, comorbid substance abuse/dependence within 3 months prior to study, serious suicide risk  
  • Comorbid anxiety disorder permitted if current treatment not required |
| Intervention | After a 2-week drug-free period, IV ketamine 0.5 mg/kg or IV normal saline 1 week apart |
| Outcomes | • **Primary**: Hamilton Depression Rating Scale (HDRS) measured at t-60 minutes, t+40 minutes, t+80 minutes, t+110 minutes, t+230 minutes, t+1 day, t+2 days, t+3 days, t+7 days; t=time infusion administered  
  • **Secondary**: Beck Depression Inventory (BDI), visual analogs scale for depression, Brief Psychiatric Rating Scale positive symptoms subscale (BPRS+), and Young Mania Rating Scale (YMRS)  
  • Response: ≥50% decrease in HDRS from baseline; remission: HDRS ≤7 |
| Results | Enrollment  
  • Randomized 18 patients, 17 patients received ketamine and 14 patients received placebo  
  • Four patients from the phase 1 ketamine group did not cross over due to response maintenance x7 days  
  • One patient withdrew from the study for medical reasons after placebo infusion |

**Table 1. Baseline demographics (n=18)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>12 (67)</td>
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<tr>
<td>Lifetime comorbid anxiety diagnosis</td>
<td>11 (61)</td>
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<tr>
<td>Lifetime diagnosis of any substance abuse or dependence</td>
<td>7 (39)</td>
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<tr>
<td>Lifetime diagnosis of alcohol abuse or dependence</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Subjects who received ECT previously</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Failed antidepressant trial for current major depressive episode (MDE)</td>
<td>17 (94)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>46.7 ± 11.2</td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>23.7 ± 12.5</td>
</tr>
<tr>
<td>Duration of current MDE (mo)</td>
<td>33.6 ± 37.4</td>
</tr>
<tr>
<td>Lifetime MDEs (n)</td>
<td>6.6 ± 4.7</td>
</tr>
<tr>
<td>Lifetime antidepressant trials (n)</td>
<td>5.7 ± 3.4</td>
</tr>
</tbody>
</table>
Primary Outcome

Figure 2. Change in the 21-item HDRS scores over 1 week (n=17)

*P<.05; †, P<.01; ‡, P<.001

- Completers (n=17) analysis: significant improvement for ketamine vs. placebo at 110 minutes through 7 days with significant main effects for drug (P<.001) and time (P<.001), drug x time (P<.001)

Secondary Outcomes

- Carryover effects with intent-to-treat (ITT) sample (n=18)
  - Placebo (P=.86): Phase 1 (baseline): 24.4 ± 6.9; Phase 2 (baseline): 24.9 ± 6.8
  - Ketamine (P=.004): Phase 1 (baseline): 24.9 ± 6.9; Phase 2 (baseline): 17.2 ± 6.9
  - Significant main effect for drug (P=.02), interaction (P=.04), no main effect for order (P=0.23)

- Mean percentage change in HDRS\textsubscript{21} t+24h - ketamine: -56.2% ± 20.4; placebo: -9.8% ± 20.1
- Effect size for drug difference: t+24h: d=1.46 (95% CI, 0.91-2.01); t+7 days: d=0.68 (95% CI, 0.13-1.23)

- Phase 1 analysis (independent of carryover effects) similar to completers and ITT analysis
  - Significant main effect for drug (P=.005) and time (P<0.001), drug x time interaction (P<0.001)
  - 80 minutes through day 7, ketamine group scores lower vs. placebo group

- Individual HDRS symptoms
  - Depressed mood, guilt, work and interests, and psychic anxiety improved significantly in ketamine group; depressed mood and guilt with earliest improvements (40 minutes)
  - Depersonalization/derealization worse at 40-110 minutes
  - Motor retardation and gastrointestinal symptoms worse at 40 minutes; at day 1 motor retardation better for ketamine vs. placebo

- BDI (completers analysis): significant main effects for drug (P<.001) and time (P<.001), no significant drug x time interaction (P=.06)

- Responders and remitters (ITT sample)
  - t+1 day: responders – ketamine, 71% (12/17) vs. placebo, 0% (0/14); remitters – ketamine, 29% (5/17) vs. placebo, 0% (0/14)
  - At t+7 days 35% (6/17) maintained ketamine response; 33% (2/6) maintained response ≥2 weeks
• BPRS+/YMRS
  o BPRS+ worse for ketamine vs. placebo only at 40 minutes (drug, \(P=0.04\); time, \(P<0.001\); drug x time, \(P<0.001\))
  o Trend between the percentage change in HDRS at day 1 and the peak percentage change in BPRS+ \((r=-0.46; P=0.06)\)
  o YMRS worse for ketamine vs. placebo at 40 minutes, significantly better from day 1 to 2 (drug, \(P=0.08\); time, \(P<0.001\); drug x time, \(P<0.001\))

Adverse effects
• More common in ketamine vs. placebo: perceptual disturbances, confusion, elevations in blood pressure, euphoria, dizziness, increased libido
• Majority of adverse effects stopped within t+80 minutes
• Euphoria or derealization/depersonalization for ketamine lasted until t+110 minutes
• No serious adverse events

Authors’ conclusion
Directly targeting the NMDA receptor complex brings about rapid and sustained antidepressant effects.

Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>RCT, multi-centered, multiple analyses, self-rated scale as secondary outcome, large effect sizes, funded by federal agencies, inclusion of patients with comorbid anxiety disorders, utilized YMRS to evaluate for euphoric effects, studied individual HDRS items</td>
<td>small sample size, short follow-up period, study blind may not have been preserved due to ketamine’s psychotomimetic effects, generalizability, did not study hemodynamic effects</td>
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Study #2

<table>
<thead>
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<tbody>
<tr>
<td>Question</td>
<td>How effective and safe is repeated ketamine dosing in preventing relapse of TRD?</td>
</tr>
<tr>
<td>Description</td>
<td>Open label with naturalistic follow-up ≥4 weeks or until relapse</td>
</tr>
</tbody>
</table>

Patients
• Previous responders (≥50% reduction in depression severity for ≥24 hours) of an open label, single dose IV ketamine study whom ultimately relapsed (average duration between single-dose and repeated-dose study: 311 days ± 116)\(^{22}\)
• Inclusion: chronic or recurrent MDD, failed ≥2 adequate antidepressant trials in the current MDE per ATHF, score ≥32 on the Inventory of Depressive Symptomatology-Clinician Administered (IDS-C\(_{30}\)) at screening and 24 hours before infusion #1
• Exclusion: lifetime history of psychotic symptoms or (hypo)mania, comorbid substance abuse or dependence within 3 months prior to study, active serious suicidal ideation (deemed to cause danger), abnormal ECG, any unstable illness, uncorrected thyroid disorder, pregnancy, initiation of female hormonal treatments less than 3 months prior to screening
• Females of childbearing age required to use contraception
• Psychotherapy and other nonpharmacological antidepressants not permitted

Intervention
• After at least a 2-week psychotropic-medication-free period (except zolpidem), total sample received single dose IV ketamine 0.5 mg/kg over 40 minutes as inpatients
• If distressing psychotic symptoms during infusion #1, dose for infusion #2-#6 decreased
  o Based on increase in BPRS+ and verbal report
  o Dose decreased by \(.0125 \times 0.80 \times T_i\) (e.g., 40 minutes, dose decreased to 0.4 mg/kg)
• Responders on day 2 received infusions #2-#6 (day 3, 5, 8, 10, 12) as outpatients
• Responders after infusion #6 remained medication-free
Outcomes
- **Primary**: Montgomery Asberg Depression Rating Scale (MADRS) for infusion #1: t, t+2h, t+4h, t+24h; infusions #2–#6: t, t+4h; follow-up: 2x/week for ≥4 weeks or until relapse
- **Secondary**
  - Quick Inventory for Depressive Symptoms (QIDS-SR16) – same timepoints as MADRS
  - BPRS+: infusion #1: t, q5min, t+40min, t+2h, t+4h, t+24h; infusions #2–#6: t, t+4h
  - Clinician-Administered Dissociative States Scale (CADSS): infusion #1: t, t+40min, t+2h, t+4h, t+24h; infusions #2–#6: t, t+4h
  - Patient expectations: infusion #1: t, t+24h; infusions #2–#6: t, t+4h
- Systematic Assessment For Treatment Emergent Effects Self-Report Inventory (SAFTEE-SI): infusion #1: t, t+40min, t+2h, t+4h, t+24h; infusions #2–#6: t, t+4h; follow-up: 2x/week for ≥4 weeks or until relapse
- Relapse: MADRS >50% of pre-ketamine baseline and >20 for 2 consecutive visits OR Clinical Global Impression-Improvement scale (CGI-I) score=6 (much worse) at any visit; remission: MADRS ≤9

<table>
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<th>Table 3. Select baseline demographics (n=10)</th>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>Single MDE in lifetime</td>
</tr>
<tr>
<td>Comorbid anxiety disorder</td>
</tr>
<tr>
<td>Past alcohol use</td>
</tr>
<tr>
<td>Family history of alcohol use disorder</td>
</tr>
<tr>
<td>Past substance use disorder</td>
</tr>
<tr>
<td>Family history of MDD</td>
</tr>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Adequate antidepressant trials (n)</td>
</tr>
<tr>
<td>Age at first MDE (y)</td>
</tr>
<tr>
<td>Duration of current MDE (y)</td>
</tr>
<tr>
<td>Baseline depression (IDS-C30 score)</td>
</tr>
<tr>
<td>Patient expectancy rating (1 = lowest, 5 = highest)</td>
</tr>
<tr>
<td>Education (y)</td>
</tr>
</tbody>
</table>

Primary Outcome

**Figure 3. Mean MADRS and QIDS-SR16 scores at t and t+4h for six IV ketamine infusions**

- Mean MADRS score at t₀ (n=10): 32.7 ± 6.4
- Responders (n=9): significant main effect of time (P<0.0001) at infusion #1
Secondary outcome

- MADRS - infusion #6, t+4h: 9/9 responders, 8/9 remitters
- Naturalistic follow-up
  - Relapse rate: 8/9
  - Time to relapse after infusion #1: 30 ± 13 days; after infusion #6: 19 ± 13 days
  - Relapses: <1 week post-treatment (n=1), <2 weeks (n=3), <3 weeks (n=2)
  - Depression-free: >4 weeks (n=1), ~7 weeks (n=1), >3 months (n=1)
  - Mean MADRS at exit (n=7, score unavailable for one patient): 29.7 ± 6.4
- QIDS-SR16 scores similar trends as MADRS
- Patient expectancies: no significant correlation with MADRS reductions (r=0.37, P=0.4); did not significantly differ before infusions #1 and #6 (p=0.6)
- BPRS+: no significant score increases
  - No reports of distressing psychotic symptoms
  - Infusion #1 - no significant correlation with MADRS scores at t+24h and BPRS+ scores during infusion (r=-0.11, P=0.75)
  - Peak scores across all infusions not significantly different
  - Minimum at each t+4h rating
- CADSS: significant score increase from t to t+40 min: 1.0 ± 2.1 to 14.9 ± 23.1, (P=.03)
  - High/very high scores ≥11 (n=3) returned to normal at t+2h (0.4 ± 0.8)
  - Infusion #1 - no significant correlation with MADRS scores at t+24h and CADSS scores at t+40min (r=-0.24, P=0.5)
  - CADSS scores at t+40min not significantly different
  - Low (<3) at each t+4h rating

SAFTEE-SI

- Severe increases from t to t+t4h
  - Week 1 (infusions #1-#3): abnormal sensations, blurred vision, diminished mental capacity, headache, numbness or tingling
  - Week 2 (infusions #4-#6): abnormal sensations, blurred vision, diminished mental capacity, headache, numbness or tingling
- From week 1 to week 2: greater prevalence of abnormal sensations and weakness/fatigue
- Naturalistic follow-up (7/9 repeated-dose patients): moderate increase in sleep disturbance, increase in blurred vision; no increase in poor memory, trouble concentrating, word-finding difficulties

Vital Signs

- Brief hypertensive episodes and transient tachycardia (n=2) during infusion #1– resolved <5min post-infusion and occurred during infusions #2-#6
- Transient tachycardia, HR max 124 bpm (n=1) during infusion #1 - occurred during infusions #2-#6; premature ventricular contractions infusions #4-#5; resolved by t+2h
- Bradycardia (n=1) during infusion #1, HR 50-55 bpm – resolved by t+1h; occurred during infusions #2-#6, resolved by t+2h
- Hypotension (n=1) t+13h post-infusion #1, BP 80/55 mmHg – low until discharge at t+24h (85/59 mm Hg); asymptomatic; occurred for two more infusions with resolution shortly post-infusion (patient had low BP 107/48 at baseline)
- Oxygen saturation 99% to 94% (n=1) during infusion #1 – 95% at discharge; occurred after infusion #4 (min 94%); also had bradypnea (RRmin = 7) with no effects post-repeated infusions
- No parameters resulted in infusion discontinuation

### Authors’ Conclusion
Repeated IV ketamine infusions were tolerable and did not result in distressing psychotic symptoms. Patients who responded to an initial IV ketamine infusion maintained response for subsequent infusions and for less than 1 week after. The response sustainability of repeated IV ketamine infusions vs. single infusion may be greater.

### Critique
**Strengths**: outpatient population, multiple rating scales (clinician-administered, self-rated), naturalistic follow-up, studied hemodynamic parameters, repeated doses, studied patient expectations, psychotropic-medication free during infusion period (limits confounding variables)

**Limitations**: open-label, small sample size, included responders to a single IV ketamine dose (type I error possible), generalizability, did not measure depression scores at t+40min, patients were medication-free in naturalistic follow-up period, psychotropic medication-free (not generalizable), duration of current MDE lengthy and questionable

### Study #3

<table>
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<tbody>
<tr>
<td>Question</td>
<td>What is the pattern and durability of antidepressant effects of repeated ketamine infusions?</td>
</tr>
<tr>
<td>Description</td>
<td>Open label; includes findings from the original ten subjects of a repeated dose study by aan het Rot et al.</td>
</tr>
</tbody>
</table>
| Patients | **Inclusion**: chronic or recurrent MDD (primary presenting problem), failure to respond to ≥2 U.S. Food and Drug Administration (FDA)-approved antidepressants in current MDE per ATHF, score of ≥32 on IDS-C30 at screening and baseline, negative urine toxicology screen, negative pregnancy test  
**Exclusion**: uncontrolled hypertension, unstable medical condition, any Axis I disorder other than MDD deemed a primary problem, substance abuse or dependence in 3 months before screening, lifetime history: psychosis, any psychotic disorder, bipolar disorder, developmental disorder, recreational use or abuse of ketamine or phencyclidine |
| Intervention | Phase 1: After a 2-week antidepressant-free period, six IV ketamine 0.5mg/kg infusions administered on Monday-Wednesday-Friday over 12-day period; only infusion #1 required inpatient stay, subsequent infusions were outpatient  
Participants from previous study did not receive subsequent infusions if they did not respond at t+24h after infusion #1 (n=1 out of 10)  
However, protocol changed so that all patients could remained in study (responders, nonresponders) (n=14)  
Phase 2: ketamine responders after last dose of phase 1 followed until relapse or for maximum follow-up time up to 83 days after the last infusion |
• Responder status determined based on score after infusion #6 or last observation (noncompleters)
• Followed 2x/week x 4 weeks then every other week x 8 weeks or until relapse

Participants were antidepressant-free throughout the infusion period but were permitted to use antidepressants during the naturalistic follow-up period.

Outcomes

• **Primary**: change in MADRS over 12-day infusion period; infusion #1 measurements obtained at t-60min, t+2h, t+4h, t+24h; infusions #2-#6 at t-60min, t+4h
• **Secondary**: CADSS, BPRS+, YMRS, Visual Analog Scale (feelings of being high) infusions #1-#6: t-60min, t+40min, t+4h
• SAFTEE-SI infusions #1-#6: t-60min, t+40min, t+4h
• Clinically significant vital sign changes: BP>180/100 or >20% increase above pre-infusion reading, tachycardia >110 bpm; infusion discontinued if changes nonresponsive to medication intervention
• Response: ≥50% improvement in MADRS; relapse: <50% improvement in MADRS score at visit compared with baseline for 2 consecutive visits

Results

Enrollment: at least 1 infusion (n=24), at least 2 infusions (n=22), all infusions (n=21); drop out due to nonresponse (based on first study protocol), blood pressure elevation, consent withdrawal (lack of perceived response, desire for standard treatment)

Table 3. Baseline demographics (n=24)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responders (n=17)</th>
<th>Nonresponders (n=7)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Male gender</td>
<td>10 (59)</td>
<td>5 (71)</td>
<td>NS</td>
</tr>
<tr>
<td>First-degree relative with mood disorder</td>
<td>10 (59)</td>
<td>4 (57)</td>
<td>NS</td>
</tr>
<tr>
<td>Lifetime history of ECT</td>
<td>2 (12)</td>
<td>2 (29)</td>
<td>NS</td>
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<tr>
<td>Lifetime history of suicide attempt</td>
<td>1 (6)</td>
<td>2 (29)</td>
<td>NS</td>
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<tr>
<td>Past substance use disorder</td>
<td>5 (29)</td>
<td>3 (43)</td>
<td>NS</td>
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<tr>
<td>Current anxiety disorder</td>
<td>4 (24)</td>
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<td>NS</td>
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<tr>
<td>Current pain disorder</td>
<td>2 (12)</td>
<td>1 (14)</td>
<td>NS</td>
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<td><strong>Age at enrollment (y)</strong></td>
<td>48.9 ± 11.8</td>
<td>46.1 ± 16.5</td>
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<td>Education (y)</td>
<td>15.2 ± 2.7</td>
<td>17.1 ± 1.0</td>
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<td>Age at MDD onset (y)</td>
<td>26.4 ± 14.2</td>
<td>14.0 ± 6.8</td>
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<tr>
<td>Duration of current MDE (y)</td>
<td>17.0 ± 16</td>
<td>20.6 ± 19.4</td>
<td>NS</td>
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<tr>
<td>Lifetime episodes (n)</td>
<td>1.7 ± 0.9</td>
<td>2.0 ± 1.5</td>
<td>NS</td>
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<tr>
<td>Failed antidepressants (current MDE) (n)</td>
<td>6.1 ± 3.6</td>
<td>6.0 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Failed antidepressants augmentations (current MDE) (n)</td>
<td>2.4 ± 2.2</td>
<td>2.0 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline MADRS score</td>
<td>31.6 ± 6.3</td>
<td>32.1 ± 6.2</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline IDS-C30 score</td>
<td>45.1 ± 10.5</td>
<td>41.6 ± 8.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Statistical significance: P<0.05
NS: not significant
Baseline MADRS Score 31.8

Current Pain Disorder, Current Anxiety Disorder, compared with baseline, depression severity was measured in the morning before each infusion and then at 4 hours. *MADRS score significantly decreased at given time point

Figure 1. Change in depression severity after repeated ketamine infusions in treatment-resistant major depression. Figure depicts change in depression scores over a 12-day period.

**Primary Outcome**

**Figure 5. Change in MADRS scores over 12-day period**

*MADRS score significantly decreased compared to baseline, P<0.05; #MADRS score significantly different between subgroups; *three subjects in the nonresponder subgroup did not receive all six ketamine infusions

- Baseline to t+2h change in MADRS for total sample: 18.9 ± 6.6 (decrease from 31.8 to 12.9, P<0.001)
  - Improvement in depressive symptoms for total sample persisted with mean MADRS score decrease per day: 0.128 ± 0.17 (P=0.45)
  - Phase I responders mean MADRS score decrease per day after 2-hour improvement: 0.35 ± 0.10 (P=0.004)
  - Phase I nonresponders mean MADRS score increase per day after 2-hour improvement: 0.78 ± 0.40 (P=0.096)
- MADRS scores at t+4h: responders (10.35 ± 5.74) vs. nonresponders (19.0 ± 6.46), P=0.013
- MADRS scores at t+24h: responders (8.35 ± 4.2) vs. nonresponders (18.8 ± 5.5), P=0.002

**Secondary Outcomes**

- Response rate (end of phase I): 70.8% (17/24)
- Response rate (infusion #1, t+4h) responders vs. nonresponders: 94% vs. 29%
- 2-hour nonresponder relative risk of overall study nonresponse: 4.0 (95% CI: 1.23-12.99)
- Phase I MADRS individual items
  - Infusion #1, t-60min to t+2h: significant reduction in each item (total sample) (P<0.01; except appetite and sleep, not examined at t+2h)
  - Nonresponders: significant reductions for only sadness, inner tension, pessimistic thoughts, suicidal thoughts (P<0.05)
  - Largest difference for nonresponders vs. responders at t+2h: change in lassitude (d=1.34); decrease in apparent sadness (d=0.88); decrease in concentration difficulty (d=0.96)
- Phase 2 (up to 83 days post-infusion): time to relapse after response to ketamine
  - Median time to relapse: 18 days (24th and 75th percentiles: 11 and 27 days)
  - No relapse: 4/17
  - Relapse experience of subjects (3/17) enrolled in venlafaxine extended-release (ER) RCT after phase I: venlafaxine ER (n=2): relapsed at day 20 (n=1), responder at day 83 (n=1); placebo (n=1): responder at day 83
- BPRS+ mean scores: increased from 4.0 ± 0.1 (t-60min) to 4.5 ± 0.9 (infusion peak) (P=0.013);
decreased to 4.0 (t+4h)

- CADSS mean scores: increased from 0.3 ± 0.5 (t-60min) to 7.8 ± 12.0 (infusion peak) (P=0.001); decreased to baseline (t+4h)
- YMRS (P=0.002) and visual analog scale (P<0.001) exhibited similar patterns as BPRS+/CADSS
- No trend toward increasing dissociative/psychomimetic effects over trials
- Responders vs. nonresponders: no difference in above scales
- No correlation between changes in MADRS score and above scales

Side Effects
- Most common (t+4h, each infusion): feeling strange/unreal (58.3%), abnormal sensations (54.2%), blurred vision (50.0%), feeling drowsy/sleepy (45.8%); not reported at t+60min for each infusion (transient)
- Patient-reported functional impairment due to side effects: 16.7% of subjects

Hemodynamic Changes
- No clinically significant vital sign change: 16/24 (67%)
- Blood pressure and/or heart rate elevation ≥1 time during infusions: 8/24 (33%)
- Blood pressure elevation (BP max 180/115) nonresponsive to antihypertensive agent (led to study exit): stabilized after ketamine infusion discontinuation
- No serious adverse events

Authors’ Conclusion
Ketamine exhibits an antidepressant effect early and influences individual depressive symptoms. Rapid responders to first infusion likely to respond to repeated doses.

Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>long naturalistic follow-up period, outpatient population, studied individual MADRS items, studied hemodynamic changes, all patients received infusions, allowed antidepressant medication during naturalistic follow-up period</td>
<td>open label, small sample size, generalizability, included patients from a previous study (possible type I error), did not measure depression at t+40min, duration of lengthy current MDE questionable</td>
</tr>
</tbody>
</table>

Study #424

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td>Will a single dose of ketamine result in a rapid, clinically significant improvement in suicidal ideation 230 minutes post-infusion?</td>
</tr>
<tr>
<td>Description</td>
<td>Open label; patients were subsequently randomized to riluzole or placebo at t+6h; study only reports open label ketamine phase (t+230min)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>Categorized by severity of suicidal ideation using the Scale for Suicidal Ideation (SSI): SSI&gt;3 (significant suicidal ideation); SSI&lt;4 (without significant suicidal ideation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Inclusion</strong>25: adults 18-65 years*, recurrent MDD without psychotic features*, good health*, MADRS ≥22 at screening and baseline (no greater than 25% decrease in MADRS total score from screening to baseline), ≥2 failed adequate antidepressant trials per ATHF, current MDE ≥4 weeks; *Inclusion criteria listed in this study</td>
</tr>
<tr>
<td></td>
<td><strong>Exclusion</strong>25: substance abuse or dependence in 3 months before screening*, history of antidepressant or substance-induced (hypo)mania, serious unstable medical illness, previous ketamine/riluzole/PCP use, treatment with psychotropic medications or ECT 2 weeks pre-ketamine infusion, pregnant/nursing females; *Exclusion criteria listed in this study</td>
</tr>
<tr>
<td></td>
<td>Permitted comorbid axis I anxiety disorder diagnoses if not primary focus of treatment in</td>
</tr>
</tbody>
</table>
Outcomes

- **Primary**: SSI measured at t-60min, t+40min, t+80min, t+120min, t+230min
- **Secondary**: MADRS, HDRS-17, BDI, CADSS, BPRS (obtained at same time as primary outcome)

### Results

**Table 4. Baseline demographics (n=33)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SSI&gt;3 (n=10)</th>
<th>SSI&lt;4 (n=23)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>49.3 ± 13.4</td>
<td>45.0 ± 13.9</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Age of onset (y)</strong></td>
<td>21.6 ± 10.4</td>
<td>20.7 ± 12.3</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Duration of Illness (y)</strong></td>
<td>28.8 ± 11.7</td>
<td>24.3 ± 13.0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Duration of current MDE (mo)</strong></td>
<td>92.0 ± 123.4</td>
<td>100.7 ± 148.3</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Previous MDE (n)</strong></td>
<td>44.1 ± 51.3</td>
<td>24.4 ± 40.7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Suicide attempt, self (n)</strong></td>
<td>7 ± 70</td>
<td>3 ± 13</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Suicide attempt, family history (n)</strong></td>
<td>4 ± 40</td>
<td>8 ± 35</td>
<td>NS</td>
</tr>
<tr>
<td><strong>SSI</strong></td>
<td>8.7 ± 7.0</td>
<td>0.6 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>HDRS suicide item</strong></td>
<td>2.3 ± 0.8</td>
<td>0.5 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>MADRS suicide item</strong></td>
<td>3.4 ± 1.0</td>
<td>1.7 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>HDRS</strong></td>
<td>24.5 ± 5.0</td>
<td>18.7 ± 2.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>MADRS</strong></td>
<td>36.8 ± 4.5</td>
<td>31.6 ± 3.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Anxiety (HDRS subscale)</strong></td>
<td>7.2 ± 2.3</td>
<td>5.9 ± 1.2</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>BPRS</strong></td>
<td>36.7 ± 5.8</td>
<td>35.4 ± 5.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CADSS</strong></td>
<td>7.9 ± 12.7</td>
<td>3.5 ± 5.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>SSI&gt;3 (n=10)</th>
<th>SSI&lt;4 (n=23)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male gender</strong></td>
<td>6 (60)</td>
<td>14 (61)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>University education (college graduate)</strong></td>
<td>4 (40)</td>
<td>14 (61)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mood disorder family history</strong></td>
<td>8 (80)</td>
<td>20 (87)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Hospitalized (lifetime)</strong></td>
<td>7 (70)</td>
<td>10 (43)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Suicidal ideation, lifetime</strong></td>
<td>9 (90)</td>
<td>11 (48)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Suicidal ideation, admission</strong></td>
<td>8 (80)</td>
<td>4 (17)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Statistical significance**: P<0.05

NS: not significant

Primary Outcome

**Figure 6. SSI scores**

![SSI scores graph](image-url)
- Significant improvement in SSI scale at t+40 minutes through t+230 minutes after ketamine infusion for total sample (P<.001)

**Secondary Outcomes**
- Time to SSI<4 for high SSI (baseline SSI>3) - t+40min: 9/10 (90%), t+80min: 1/10 (10%), mean time (min) to SSI<4: 44 ± 4
- Time to SSI=0 for high SSI (baseline SSI>3) - t+40min: 5/10 (50%), t+80min: 1/10 (10%), mean time (min) to SSI=0: 120 ± 29
- SSI, HDRS suicide item, MADRS suicide, BDI suicide item for total sample: scores significantly lower at t+40min through t+230min for each scale (P<0.001); effect size t+40min: d=1.05, 95% CI: 0.65-1.45; effect size t+230min: d=0.45, 95% CI: 0.12-0.77
- HDRS, MADRS, BDI (depression, anxiety symptoms, hopelessness) significantly lower at t+40min through t+230min for total sample: P<0.001 for HDRS, HDRS anxiety subscale, MADRS, BDI, BDI hopelessness subscale
- Subgroup analysis: baseline SSI score >3 - effect size t+40min: d=2.36, 95% CI: 1.56-3.16; t+230min: d=1.27, 95% CI: 0.62-1.92

**Adverse Effects**
- Mild perceptual disturbances
- No serious adverse events

### Authors’ Conclusion
Ketamine resulted in rapid and statistically significant improvement within 230 minutes in patients with severe suicidal ideation (SSI>3).

### Critique
**Strengths:** multiple rating scales, included severely suicidal patients, suicide items correlated with depression/anxiety scales

**Limitations:** small sample size, open-label, incorrect demographic calculations, did not state all inclusion/exclusion criteria, no follow-up to assess relapse, generalizability, did not state number of past failed antidepressant trials

### Study #5

**Title**

**Question**
Will a single dose of IV ketamine result in a decrease in depressive symptoms in ECT-resistant patients with TRD?

**Description**
Open label
Patients were subsequently randomized to riluzole or placebo at t+6h; study only reports open label ketamine phase (t+230min)

**Patients**
- Two groups: ECT-resistant, n=17 (nonresponse to 6 bilateral or 7 unilateral sessions per ATHF); ECT-naïve, n=23
- **Inclusion:** adults 18-65 years, MDD diagnosis, good health, currently in MDE without psychotic features, MADRS ≥22, current MDE lasting ≥4 weeks, current or past history of failure to ≥2 adequate antidepressant trials per ATHF
- **Exclusion:** substance abuse or dependence in 3 months before screening, unstable medical illness, uncorrected thyroid disorder, inadequate trial of ECT (i.e., <6 bilateral or <7 unilateral sessions)

**Intervention**
After a 2-week psychotropic medication-free period, all subjects were administered a single infusion of IV ketamine 0.5 mg/kg over 40 minutes

**Outcomes**
- **Primary:** MADRS measured at t-60min, t+40min, t+80min, t+120min, t+230min
- **Secondary:** CADSS measured at same time as MADRS
responded to an adequate trial of ECT. The results suggested that patients with treatment-resistant MDD who had previously not infusion of an NMDA antagonist would have antidepressant effects in dissociation (also administered the CADSS (patients exhibiting a substantial improvement in depressive symptoms at 230 minutes with a moderate effect size (p<140, p=0.33). The ECT-resistant group between baseline and the non-ECT exposed group (F=7.46, df=1, 46, p=0.009). The in-

When baseline was included as a time point in the mixed model, the d=0.60 (95% C.I.: 0.10

<p>| Table 5. Baseline demographics (n=40) |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>ECT-resistant (n=17)</th>
<th>ECT-naïve (n=23)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>10 (59)</td>
<td>14 (61)</td>
<td>NS</td>
</tr>
<tr>
<td>Education (college graduate)</td>
<td>13 (77)</td>
<td>10 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Substance abuse (self)</td>
<td>7 (41)</td>
<td>6 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol abuse (self)</td>
<td>7 (41)</td>
<td>5 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol abuse (1st degree relative)</td>
<td>5 (31)</td>
<td>7 (37)</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol abuse (2nd degree relative)</td>
<td>2 (13)</td>
<td>4 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>Family history (depression)</td>
<td>15 (88)</td>
<td>19 (91)</td>
<td>NS</td>
</tr>
<tr>
<td>Family history (suicide)</td>
<td>6 (38)</td>
<td>8 (35)</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>14 (82)</td>
<td>9 (39)</td>
<td>0.01</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>7 (41)</td>
<td>8 (35)</td>
<td>NS</td>
</tr>
<tr>
<td>Suicide ideation</td>
<td>13 (77)</td>
<td>12 (52)</td>
<td>NS</td>
</tr>
<tr>
<td>Suicide ideation at admission</td>
<td>5 (29)</td>
<td>9 (39)</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>ECT-resistant (n=17)</th>
<th>ECT-naïve (n=23)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>46.5 ± 10.8</td>
<td>46.6 ± 14.8</td>
<td>NS</td>
</tr>
<tr>
<td>MDD age of onset (y)</td>
<td>21.5 ± 12.3</td>
<td>21.5 ± 11.6</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of current MDE (mo)</td>
<td>99.1 ± 108.8</td>
<td>103.0 ± 163.4</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>25.4 ± 10.2</td>
<td>25.3 ± 15.3</td>
<td>NS</td>
</tr>
<tr>
<td>Previous episodes (n)</td>
<td>32.3 ± 46.5</td>
<td>17.3 ± 35.3</td>
<td>NS</td>
</tr>
<tr>
<td>MADRS</td>
<td>34.1 ± 5.6</td>
<td>32.0 ± 4.3</td>
<td>NS</td>
</tr>
<tr>
<td>BPRS</td>
<td>35.8 ± 6.1</td>
<td>36.0 ± 5.6</td>
<td>NS</td>
</tr>
<tr>
<td>CADSS</td>
<td>4.7 ± 10.1</td>
<td>4.0 ± 5.6</td>
<td>NS</td>
</tr>
<tr>
<td>Suicide ideation scale</td>
<td>4.8 ± 6.7</td>
<td>2.1 ± 4.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Statistical significance: P<0.05

NS: not significant

Primary Outcome

Figure 7. MADRS scores

- With adjustment for baseline MADRS differences, ECT-resistant group had significantly higher scores than ECT-naïve group (P=0.03); no group x time interaction (P=0.44)
- With MADRS scores considered as a time point, the ECT-resistant group had significantly higher scores than the ECT-naïve group (P=0.009); no group x time interaction (P=0.33)
ECT-resistant group: significant improvement (P<0.001); moderate effect size: d=0.50 (95% CI: 0.21-0.80)
ECT-naive group: significant improvement (P<0.001); large effect size: d=1.00 (95% CI: 0.71-1.29)

Secondary Outcomes
- Effect size ECT-naive vs. ECT-resistant at t+230min: d=0.60 (95% CI: 0.10-1.10)
- Group comparison in changes from baseline: moderate effect size: d=0.62 (95% CI:0.21-1.004)
- Proportion of patients with substantial improvement in depressive symptoms (50%): no significant difference between both groups (P=0.33)
- CADSS scores increased significantly t+40min and returned to normal at t+80 minutes; no significant difference between groups (P=0.19)

Authors’ Conclusion
Ketamine is an effective treatment for ECT-resistant patients.

Critique
Strengths: MADRS obtained at same time point as CADSS, adjusted for baseline differences in MADRS scores
Limitations: small sample size, open label, inaccurate definition of adequate ECT trial, labeled patients as ECT-naive and ECT-resistant retrospectively, did not state number of past failed antidepressant trials, generalizability, no follow-up to assess relapse, did not study hemodynamic effects

CONCLUSIONS

XIV. Current place in therapy: routine use as monotherapy in TRD patients is not recommended due to limited response sustainability, despite rapid and robust effects.

XV. Remaining questions
a. Methods to maintain response
b. “Bridge therapy”
c. Long-term effects and safety
d. Use in a “typical” TRD patient

Table 6. Ongoing trials

<table>
<thead>
<tr>
<th>Title</th>
<th>Optimization of IV Ketamine for TRD: A Randomized, Placebo-Controlled, Triple-masked, Clinical Trial</th>
<th>Intranasal Ketamine in Treatment Resistant Depression</th>
<th>N-methyl-D-aspartate Antagonist (Ketamine) Infusion for Treatment Resistant Major Depressive Disorder with Suicidal Ideation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highlights</td>
<td>Longer ketamine infusion (100-hour vs. 40-minutes) Uses clonidine to minimize psychotic/cognitive effects of ketamine</td>
<td>Ketamine vs. midazolam</td>
<td>Augmentation of antidepressants with ketamine for chronic suicidal ideation Ketamine dose titrated in nonresponders</td>
</tr>
</tbody>
</table>

Table 6. Ongoing trials

---

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### APPENDIX

<table>
<thead>
<tr>
<th>Rating Scales</th>
<th>Use</th>
<th>Rater</th>
<th>Items</th>
<th>Severity Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>Evaluation of depression symptoms in patients with depression diagnosis</td>
<td>Patient</td>
<td>21</td>
<td>Minimal: 0-9 Mild: 10-16 Moderate: 17-29 Severe: 30-63</td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale (BPRS)</td>
<td>Change in severity of psychotic symptoms (hallucinations, delusions, disorganization, hostility/anxiety/depression)</td>
<td>Clinician</td>
<td>18</td>
<td>Higher numbers associated with severe symptoms (total: 108 or 126) Total score is sum of value of each question; each question ranges from 0-6 or 1-7</td>
</tr>
<tr>
<td>Clinician Administered Dissociative Symptoms Scale (CADSS)</td>
<td>Evaluation of present dissociative symptoms (i.e., amnesia, depersonalization, derealization); useful for repeated measures</td>
<td>Clinician – 8 items Patient – 19 items</td>
<td>27</td>
<td>Higher numbers associated with severe symptoms (total: 108)</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale (HAMD or HDRS)</td>
<td>Evaluates depression symptoms in patients with primary depression</td>
<td>Clinician</td>
<td>17 or 21</td>
<td>Very severe: &gt;23 Severe: 19-22 Moderate: 14-18 Mild: 8-13 Remission: ≤7</td>
</tr>
<tr>
<td>Inventory of Depressive Symptomatology – Clinician Administered (IDS-C)</td>
<td>Severity of signs and symptoms of depression; includes all major depressive disorder criteria from the American Psychiatry Association Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV)</td>
<td>Clinician</td>
<td>30</td>
<td>Very severe: 47-84 Severe: 37-46 Moderate: 24-36 Mild: 12-23 Remission: ≤11</td>
</tr>
<tr>
<td>Quick Inventory for Depressive Symptoms (QIDS-SR16)</td>
<td>Severity of signs and symptoms of depression; includes all major depressive disorder criteria from (DSM-IV)</td>
<td>Patient</td>
<td>16</td>
<td>Very severe: 21-27 Severe: 16-20 Moderate: 11-15 Mild: 6-10 Remission: ≤5</td>
</tr>
<tr>
<td>Scale for Suicide ideation (SSI)</td>
<td>Evaluation of severity of present suicidal ideation</td>
<td>Clinician</td>
<td>19</td>
<td>Significant: &gt;3 Minimal: ≤4</td>
</tr>
<tr>
<td>Young Mania Rating Scale (YMRS)</td>
<td>Evaluation of manic symptoms at baseline and over time in patients</td>
<td>Clinician</td>
<td>11</td>
<td>Severe: 38 Moderate: 26 Mild: 20 Minimal: 13</td>
</tr>
</tbody>
</table>
REFERENCES