Learning Objectives

By the end of this presentation, the learner should be able to:

1. Describe the epidemiology of Major Depressive Disorder (MDD)
2. Discuss the currently available pharmacotherapies and their limitations
3. Explain the proposed mechanism of action for ketamine’s effects for depression
4. Analyze the studies of ketamine for MDD and suicidality
5. Discuss ketamine’s potential role in treatment of depression and suicidality
I. Epidemiology
   A. One of the most common mental disorders in the United States (U.S)  
   B. U.S. lifetime prevalence: 17%\(^1\)
   C. U.S. 12-month prevalence (2014)\(^2\)
      1. \(\sim\)15.7 million adults aged \(\geq 18\) had at least one major depressive episode (MDE), representing 6.7% of all U.S. adults  
      2. \(\sim\)2.8 million adolescents aged 12 to 17 had at least one major depressive episode, representing 11.4% of the U.S. population aged 12 to 17
   D. Women are 70% more likely than men to experience depression during their lifetime\(^3\)
      1. May be due to genetics, biology, reproduction, hormonal changes and interpersonal relationships  
      2. Men may feel more shame about their depression leading to under-diagnosis

II. Personal and Societal Costs
   A. Productivity loss\(^4\)
      1. Leading cause of medical disability for people aged 14 to 44  
      2. Individuals lose 5.6 hours of productive work weekly during depressed episodes.
   B. Sense of isolation or feeling like a burden on others
   C. Decreased life satisfaction (work, relationships, leisure time)\(^5\)
   D. Second leading cause of disability worldwide\(^6\)
   E. Suicide risk\(^7\)
      1. 10\(^{th}\) leading cause of death in the U.S.  
      2. 3\(^{rd}\) leading cause of death for young people aged 15-24  
      3. \(>\)41,000 suicides in the U.S. in 2013  
      4. Estimated 9.3 million adults (3.9% of the adult U.S. population) reported having suicidal thoughts in the past year  
      5. Males take their own lives at nearly four times the rate of females and account for \(\sim\)78% of suicides
   F. Annual economic consequences of depression estimated at \$83 billion in the U.S.\(^8\)
   G. According to the World Health Organization, major depression has the heaviest burden of disability among mental health disorders.\(^9\)

III. Clinical Features and Diagnosis
   A. Symptoms of Depression
      | Depressed Mood | Anhedonia (loss of interest or pleasure) | Change in appetite or weight |
      | Sleep disturbance (insomnia or hypersomnia) | Fatigue or less of energy | Diminished concentration |
      | Feelings of guilt or worthlessness | Psychomotor agitation or slowing | Suicidal ideation (SI) and behavior |
   B. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) Diagnosis of MDD\(^10\)
      1. Major Depressive Episode Criteria
         a. \(\geq 5\) of the nine symptoms above present during a 2-week period  
         b. At least one symptom has to be depressed mood or anhedonia  
         c. Must clinically significant distress or impairment important areas of functioning  
         d. Not attributable to the physiological effects of a substance or to other medical condition
      2. Not better explained by another psychiatric diagnosis
      3. There has never been a manic or hypomanic episode

IV. Risk Factors
   A. Family history
   B. Traumatic or stressful events
   C. Personality traits, e.g. low self-esteem, self-critical
   D. History of other mental health disorders
   E. Drug and alcohol abuse
   F. Medications, e.g. corticosteroids or interferon
   G. Being lesbian, gay, bisexual, or transgender in an unsupportive situation
V. Pathophysiology
A. The cause of depression is multifactorial including genetic, psychosocial, and biological components
B. Altered brain structure and function - unclear if these cause depression or are caused by depression
C. The monoamine hypothesis of depression: depression is due to deficiency of monoamine neurotransmitter activity: serotonin (5-HT), dopamine (DA), and norepinephrine (NE)
   1. 5-HT regulates mood, appetite, anxiety, obsessions, and compulsions
   2. DA regulates attention, motivation, pleasure, and reward
   3. NE regulates energy, anxiety, attention, and interest
D. Many antidepressant drugs increase synaptic levels of serotonin, but they may also enhance the levels norepinephrine and dopamine
E. All current pharmacotherapy revolves around the alteration of monoamine function

![Figure 1: Neurotransmitters and Theorized Depressive Symptom Clusters](image)

F. The monoamine hypothesis is an incomplete explanation of depression
   1. Despite antidepressants increasing monoamine levels immediately, full benefit is often delayed by 2-6 weeks, especially for mood and anhedonia
      a. May be due to adaptive changes in gene expression
      b. Increased monoamine binding may lead to decreased receptor synthesis and sensitivity
   2. Resistance to treatment despite reliable monoamine activity increases
   3. Structural changes in the brain
   4. Stress or depression may decrease neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which promotes neuroplasticity – adaptation in learning, memory, and mood
      a. Post-mortem studies demonstrate BDNF deficits in those with mood disorders
      b. Stress and depression decrease BDNF levels in the hippocampus
      c. Post-mortem studies have shown antidepressants may increase BDNF
      d. Antidepressants may promote neuroplasticity through increasing BDNF
      e. In animal models, BDNF blockade has also blocked antidepressant effects

Assessment and Treatment
I. Many rating scales are used in clinical trials to assess symptom severity and monitor response
   A. For most rating scales, treatment response is considered a reduction of ≥50% from baseline
   B. Remission is usually defined as below a threshold value indicating minimal symptoms (e.g. a Hamilton Depression Rating-17 score of ≤7)
C. Different versions of scales exist and can vary in the number of items
D. Scales can vary in the time period that they examine (e.g. 1 week vs. 2 weeks) and whether they are clinician-reported or self-reported
E. The Hamilton Depression Rating Scale (HAM-D) and Montgomery-Åsberg Depression Rating Scale (MADRS, Appendix A) are the most commonly used scales as primary outcomes in depression trials

### Table 1: Depression Rating Scale Scoring Ranges

<table>
<thead>
<tr>
<th>Scale</th>
<th>None/Minimal/Remission</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe–Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton Depression Rating Scale, 17-item (HAM-D$_{17}$)</td>
<td>0–7</td>
<td>8–13</td>
<td>14–19</td>
<td>20–25 (severe) 26-52 (very severe)</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale, 21-item (HAM-D$_{21}$)</td>
<td>0–8</td>
<td>9–15</td>
<td>16–22</td>
<td>23–28 (severe) 29-64 (very severe)</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale, 24-item (HAM-D$_{24}$)</td>
<td>0–9</td>
<td>10–18</td>
<td>19–26</td>
<td>27–34 (severe) 35-75 (very severe)</td>
</tr>
<tr>
<td>Montgomery-Åsberg Depression Rating Scale (MADRS)</td>
<td>0–6</td>
<td>7–19</td>
<td>20–34</td>
<td>35–60</td>
</tr>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>0–9</td>
<td>10–18</td>
<td>19–29</td>
<td>30–63</td>
</tr>
<tr>
<td>Inventory of Depressive Symptomatology (IDS$_{30}$)</td>
<td>0–11</td>
<td>12–23</td>
<td>24–36</td>
<td>37–46 (severe) 47-84 (very severe)</td>
</tr>
<tr>
<td>Quick Inventory of Depressive Symptomatology (QIDS$_{16}$)</td>
<td>0–5</td>
<td>6–10</td>
<td>11–15</td>
<td>16–20 (severe) 21-27 (very severe)</td>
</tr>
<tr>
<td>Patient Health Questionnaire 9 (PHQ-9)</td>
<td>1–4</td>
<td>5–9</td>
<td>10–14</td>
<td>15–19 (moderately severe) 20-27 (severe)</td>
</tr>
</tbody>
</table>

II. Available antidepressant agents and their associated neurotransmitters

A. Selective serotonin reuptake inhibitors (SSRIs)
   1. Includes citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine sertraline
   2. Inhibits 5-HT reuptake
   3. First-line agents

B. Serotonin-norepinephrine reuptake inhibitors (SNRIs)
   1. Includes venlafaxine, desvenlafaxine, duloxetine, levomilnacipran
   2. Inhibits 5-HT and NE reuptake
   3. First-line agents

C. Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)
   1. Bupropion is the only current NDRI
   2. Inhibits reuptake of NE and DA
   3. First-line agents

D. Serotonin and α2-Adrenergic Receptor Antagonists
   1. Mirtazapine is the only antidepressant with this mechanism
   2. Enhances central noradrenergic and serotonergic activity through the antagonism of central presynaptic α2-adrenergic autoreceptors and heteroreceptors
   3. First-line agent

E. Serotonin agonist and reuptake inhibitors
   1. Includes trazodone, nefazodone
   2. Acts as both 5-HT2 antagonists and 5-HT reuptake inhibitors

F. Serotonin modulators
   1. Includes vilazodone and vortioxetine
   2. 5-HT1$_{A}$ agonists and 5-HT reuptake inhibitors

G. Tricyclic antidepressants (TCAs)
   1. Includes imipramine, desipramine, nortriptyline, amitriptyline, clomipramine, and others
2. Inhibits 5-HT and NE reuptake
H. Monoamine Oxidase Inhibitors (MAOIs)
   1. Includes phenelzine, isocarboxazid, tranylcypromine, selegiline
   2. Increase the concentrations of NE, 5-HT, and DA within the neuronal synapse through inhibition of the MAO enzyme (which breaks down these neurotransmitters)

III. Current Treatment Guidelines
A. No antidepressant demonstrated to be superior and choice is based on tolerability and patient-specific factors
B. If symptoms persist beyond an adequate trial of 4-8 weeks, consider switching or augmentation

Table 2: American Psychiatric Association (APA) 2010 Guidelines for the Treatment of MDD15

<table>
<thead>
<tr>
<th>Level of Intervention</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| First-line            | • Mild-to-moderate depression: psychotherapy ± pharmacotherapy (SSRI, SNRI, mirtazapine, bupropion)  
|                       | • Moderate-to-severe depression: pharmacotherapy ± psychotherapy  
|                       | • Severe depression: may consider electroconvulsive therapy (ECT) |
| Second-Line           | • Switch to different medication from list above as monotherapy  
|                       | • Augment with antidepressant w/ a different mechanism  
|                       | • Augment with an atypical antipsychotic  
|                       | • Augment with psychotherapy |
| Third-Line            | • Switch to different medication from list above as monotherapy  
|                       | • Augment with an antidepressant with a different mechanism  
|                       | • Consider TCAs  
|                       | • Augment with lithium or triiodothyronine |
| Treatment Resistance  | • MAOI  
|                       | • ECT |

IV. Treatment Resistant Depression (TRD)
A. No clear definition
B. Typically refers to ≥2 failed trials of antidepressant monotherapy
C. The landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial16 studied outpatients with MDD using a four-step treatment protocol, in which they were allowed to switch or augment pharmacotherapy at each step

Figure 2: Remission Rates in STAR*D

1. Remission rates comparable for the 1st and 2nd treatments
2. Remission rates comparable for 3rd and 4th treatments – drastically lower rates
D. Remission rates decline substantially for the third and fourth steps
E. Pseudoresistance: treatment failures due to an inadequate dose or duration of pharmacotherapy, or non-adherence to treatment17

V. Limitations and areas of need with current pharmacotherapy
A. Low remission rates16
B. Low response rates as individuals progress through treatment. <50% respond to the first treatment. Per the STAR*D trial16:

Figure 3: Response Rates in STAR*D

C. Delayed onset (weeks to months)
D. No benefit in acute suicidality due to time to effect
E. Increased risk of suicidal behavior in children, adolescents, and young adults
F. Despite treatment, relapse is common
G. Lack of biomarkers predictive of response
H. Lack of novel mechanisms – new medications are variations on older themes
I. Those who respond, but do not remit are a greater rate of relapse

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**Figure 4: Relapse Rates from the STAR*D trial**

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**Ketamine and Depression**

I. Ketamine\(^{18,19}\)
   A. High-affinity, non-competitive, N-methyl-D-aspartate (NMDA) receptor antagonist
   B. Approved in the U.S. as an anesthetic and is sometimes used off-label to manage pain
   C. Structurally related to phencyclidine (PCP) and similar mechanism of action, though 10-50 time less potent NMDA blockade
   D. Used as a recreational drug, especially as a hallucinogenic “club drug” known as “Special K”
      1. Causes dissociative effects similar to PCP, described as dreamlike, out-of-body experiences (“K-Hole”)
      2. Can be insufflated, injected, or smoked
      3. Intoxicating effects are produced at doses of 1 mg/kg–2 mg/kg
   E. May cause pseudo-hallucinations, impaired thought processes, changes in perception about the body, surroundings, time and sound
   F. Long-term exposure may lead to tolerance and craving, but little evidence of withdrawal except when used chronically
   G. Physiological effects during infusion: tachycardia, increased blood pressure, insensitivity to pain, amnesia
   H. May cause neurotoxic effects with repeated dosing (animal models)\(^{20}\) and cognitive deficits with heavy use\(^{21}\)

II. Glutamate\(^{18}\)
   A. The major excitatory neurotransmitter in the brain
   B. Binds to ionotropic receptors and metabotropic glutamate receptors
   C. Ionotropic receptors include NMDA, kainate, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors
   D. Glutamate and its receptor subtypes play fundamental roles in synaptic plasticity and impact basic human processes of mood, cognition and reward.

III. The mechanism of action for ketamine in depression is not fully explained\(^{22}\)
   A. High levels of glutamate found in the plasma, serum, cerebral spinal fluid (CSF) and brain tissue in deceased persons with mood disorders. Higher levels found in those with more severe MDD.
   B. Proton magnetic resonance spectroscopy has shown altered glutamate function in vivo in persons with mood disorders. However, the extent and direction is largely unknown.
   C. Modulation of the glutamatergic system may have antidepressant effects through mechanisms of increased BDNF and neuroplasticity
   D. A study of BDNF levels of patients receiving ketamine for depression showed that BDNF levels increased in responders compared to non-responders post-infusion\(^{23}\)
The MADRS scores were negatively correlated with BDNF levels. Individuals in the comparator arm, who received midazolam did not see an increase in BDNF levels. This suggests that BDNF may be a potential biomarker of ketamine response in depression.

IV. Purported advantages of ketamine vs. current antidepressants
A. Rapid antidepressant effect – within hours
B. Novel mechanism of action
C. Possible anti-suicide benefit due to rapid antidepressant effect

V. Clinical Questions
A. How effective is ketamine as an antidepressant?
B. Does ketamine’s rapid effect have any benefit for acute suicidality?
C. If ketamine is to be used, where is its place in therapy?
D. Is ketamine’s efficacy only due to its dissociative and hallucinogenic effects? How can we be sure that the effect is not just from getting the patients high?

Literature Review
I. Multiple studies have examined the use of single-infusion ketamine for treatment of MDD. All studies except for Murrough, et al. used IV saline as a placebo.

Table 3: Studies of single-dose ketamine in patients with MDD

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Route</th>
<th>Design</th>
<th>No. of pts.</th>
<th>Treatment</th>
<th>Response</th>
<th>Duration of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman et al. (2000)</td>
<td>IV infusion</td>
<td>Crossover</td>
<td>Ketamine n=7, Placebo n=7</td>
<td>50%</td>
<td>72 h</td>
<td></td>
</tr>
<tr>
<td>Zarate et al. (2006)</td>
<td>IV infusion</td>
<td>Crossover</td>
<td>Ketamine n=17, Placebo n=17</td>
<td>71%</td>
<td>72 h</td>
<td></td>
</tr>
<tr>
<td>Lapidus et al. (2014)</td>
<td>Intranasal</td>
<td>Crossover</td>
<td>Ketamine n=20, Placebo n=20</td>
<td>44%</td>
<td>48 h</td>
<td></td>
</tr>
<tr>
<td>Mathew et al. (2010)</td>
<td>IV infusion</td>
<td>Open Label</td>
<td>Ketamine n=26, Placebo n=0</td>
<td>66%</td>
<td>72 h</td>
<td></td>
</tr>
<tr>
<td>Ibrahim et al. (2012)</td>
<td>IV infusion</td>
<td>Open Label</td>
<td>Ketamine n=17, Placebo n=0</td>
<td>62%</td>
<td>13 days</td>
<td></td>
</tr>
<tr>
<td>Murrough et al. (2013)</td>
<td>IV infusion</td>
<td>Double Blind</td>
<td>Ketamine n=47, Midazolam n=25</td>
<td>64%</td>
<td>72 h</td>
<td></td>
</tr>
</tbody>
</table>

Response is defined as ≥ 50% reduction in depressive symptoms (e.g., HAM-D or MADRS score) 24 h following IV ketamine.


Objective Evaluate the rapid antidepressant efficacy of ketamine in a large group of patients with treatment-resistant major depression.

Design Two-site, parallel-arm, double-blind, randomized controlled trial.

Population

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-80 years of age</td>
<td>Psychotic illness</td>
</tr>
<tr>
<td>Primary diagnosis of MDD (DSM IV)</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>Inadequate trial of at least 3 antidepressants (TRD)</td>
<td>Alcohol or Substance abuse in previous 2 years</td>
</tr>
<tr>
<td>Currently in a depressive episode</td>
<td>Unstable medical illness</td>
</tr>
<tr>
<td>Must have recurrent MDD or chronic depressive episode ≥2 years, at least moderate in severity (IDS₃₀ ≥32)</td>
<td>Serious suicidal or homicidal risk</td>
</tr>
<tr>
<td></td>
<td>Score of ≤27 on the Mini-Mental Status Exam</td>
</tr>
<tr>
<td></td>
<td>Taking contraindicated medications</td>
</tr>
</tbody>
</table>

Intervention Patients (n=73) randomized in a 2:1 ratio, comparing a single infusion of 0.5 mg/kg ketamine to an active control, 0.045 mg/kg midazolam infusion (both given over 40 minutes). Patients were required to
be psychotropic drug-free prior to the infusion (at least 1 week, 4 weeks for fluoxetine).

Endpoints

**Primary Outcome**
- Reduction in depression severity as assessed on the MADRS

**Secondary Outcomes**
- MADRS response rate (reduction from baseline score ≥50%)
- Change in score on self-reported symptoms (QIDS-SR)
- Scores on the Clinical Global Impression (CGI) severity and improvement measures
- Durability of benefit for up to 7 days following infusion, assessed at follow-up visits on days 1,2,3, and 7 post-infusion

Statistics

- 72 patients randomly assigned in a 2:1 ratio (ketamine vs. midazolam) provided 80% and 96% power to detect a change in MADRS scores and response rates respectively at 24 hours post-infusion
- Modified intent-to-treat analysis included all randomly assigned patients with baseline measurement and at least one post-baseline measurement
- General linear modeling to examine MADRS scores at 24 hours as a function of treatment after controlling for baseline MADRS score and site.
- Exact logistic regression for treatment response

Results

**Demographics**
Pt. baseline demographics in each intervention were similar.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ketamine (n=47)</th>
<th>Midazolam (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.9 yrs</td>
<td>42.7 yrs</td>
</tr>
<tr>
<td>Chronic index episode (≥2 yrs.)</td>
<td>33 (70%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Prior suicide attempt</td>
<td>14 (30%)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Prior psych hospitalization</td>
<td>23 (49%)</td>
<td>13 (52%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ketamine (n=47)</th>
<th>Midazolam (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS</td>
<td>32.6±6.1</td>
<td>31.1 ±5.6</td>
</tr>
<tr>
<td>MADRS Interpretation</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>QIDS-SR-16</td>
<td>16.6±4.1</td>
<td>16.3±4.5</td>
</tr>
<tr>
<td>QIDS-SR-16 Interpretation</td>
<td>severe</td>
<td>severe</td>
</tr>
</tbody>
</table>

**Primary Outcome: MADRS Score Change**

The difference between the average MADRS between the ketamine group and the midazolam group was 7.95 points at day 1. The difference in effect was statistically significant and the difference persisted at 3
days, but not 7 days. This corresponded to an effect size of 0.81 (large).

Secondary Outcomes
Response, defined as ≥50% decrease in MADRS scores, was a secondary outcome. 64% met response in the ketamine group, compared with 28% in the midazolam group (p≤0.001).

QIDS was lower in the ketamine group than the midazolam group by 3.4 points (p≤0.02). Post-treatment QIDS scores were 8.38 and 11.78 in the ketamine and midazolam groups, respectively.

The ketamine group demonstrated greater improvement on the CGI-I measure (OR 2.31; [95% CI, 1.25–4.14; p≤0.004]). The ketamine group was more likely to be rated as minimally ill or not ill at all on the CGI-S measure (OR 4.08; [95% CI, 1.76–13.51; p≤0.001]).

Table 5: Murrough, et al. (2013) Safety

<table>
<thead>
<tr>
<th>Safety – Ketamine Group (n=47)</th>
<th>Infusion Day</th>
<th>Days 1-7 After Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (45%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>20 (43%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>16 (34%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (32%)</td>
<td>15 (32%)</td>
</tr>
<tr>
<td>Dissociative Symptoms</td>
<td>8 (17%)</td>
<td>All resolved 2 hours post-infusion</td>
</tr>
</tbody>
</table>

Ketamine treatment did not increase the risk of emergent psychotic or manic symptoms

Author’s Conclusions
“A single low dose of ketamine, as compared with a psychoactive placebo control medication, was associated with a rapid-onset antidepressant effect. We found marked improvements in clinician-administered and patient self-report ratings of depression severity 24 hours after the ketamine infusion.”

Critique

**Strengths**
- Use of a psychoactive comparator
- Largest study thus far
- Double-blinded

**Limitations**
- Midazolam group experienced lower rates of psychoactive effects
- Midazolam is not a perfect control condition – though a perfect control agent may not exist
- Did not provide remission rates
- Exclusion of psychosis, substance abuse, active suicidality
- Only enrolled those who could tolerate a medication washout period
Does not provide insight into ketamine as adjunctive treatment to traditional antidepressants

Ketamine demonstrated a rapid antidepressant effect in patients with chronic and moderate-to-severe forms of depression. The use of psychoactive comparators overcomes the difficulty with blinding in the previous trials. These antidepressant effects lost statistical significance by 7 days. A larger number of people responded than had dissociative effects, suggesting that the antidepressant effect is independent of the dissociative effects.


Objective
Systematic review and meta-analysis of ketamine and other N-methyl-d-aspartate (NMDA) receptor antagonists in the treatment of major depression. (Note: for the purpose of this presentation, only ketamine results will be reported)

Design
Systematic review and meta-analysis

Method
Systematic search through MEDLINE, PsycINFO, the Cochrane Central Register of Controlled Trials, the Cumulative Index to Nursing and Allied Health Literature, and Google Scholar through May 2015 for peer-reviewed articles published in English and addressing treatment of major depression (including major depressive episodes of bipolar disorder) using ketamine.

Outcomes

Primary Outcomes
Rates of treatment response and remission of symptoms

Secondary Outcomes
Change in depression symptom severity and the frequency and severity of dissociative and psychotomimetic effects

Statistics
Odds ratios used for treatment response and remission. Standardized mean differences were used for mean difference in depressive symptom ratings.

Results
Twelve RCT studies of ketamine identified (Appendix B), enrolling 172 patients w/ MDD or bipolar. Authors included three trials of ketamine IV monotherapy, a trial of intranasal monotherapy, three studies of ketamine augmentation of a psychotropic regimen, and five studies of ketamine augmentation of ECT.

Efficacy (excluding conjunction w/ ECT)

Response Rate (%) Over Time

Figure 7: Response Rate (%) Over Time

A single IV infusion of ketamine produced rapid antidepressant effect that peaked within one day
(OR=8.42 [95% CI=3.47–20.39], p<0.001) and persisted for 1-2 weeks after infusion. This was significant for both MDD and bipolar diagnoses.

Figure 8: Remission Rates Over Time
The composite odds ratio for remission at 24 hours post-infusion was 14.5 (95% CI 2.7-78.5, p<0.002). However, this was not as durable as the response rate, losing its statistical significance between days 3 and 7.

Safety (excluding conjunction w/ ECT)
Ketamine therapy was associated with psychotomimetic and dissociative side effects. Two of the seven trials reported mean systolic blood pressure increases of 7.6 mmHg and 19 mmHg after the 40-minute infusion. Two patients had blood pressure changes that warranted discontinuation of ketamine.

Efficacy (as ECT augmentation)
Ketamine in these studies was used as part of the anesthesia prior to ECT administration. Ketamine was associated with a significantly greater reduction in depressive symptoms after the initial ECT session, but not at the end of the full ECT course. Ketamine did not improve therapeutic response rates at the end of the ECT course (OR=0.78 [95% CI=0.36–1.68], p=0.52). Remission rates were not provided by the studies.

Safety (as ECT augmentation)
One study reported increased post-ECT disorientation and restlessness when ketamine was used as part of the anesthesia regimen. One study reported higher rates of blood pressure elevation with ketamine compared to propofol (67% vs. 25%, p=0.023), but this effect was mitigated when the two medications were co-administered.

Author’s Conclusions
“Current data provide compelling evidence that the antidepressant effects of ketamine infusion are both rapid and robust, albeit transient.”

Critique
Strengths
- Only included randomized controlled trials
- Composite and stratified results for both diagnoses of MDD and Bipolar

Limitations
- Included trials that used saline as the placebo control – difficulty in blinding.
- Not all of the non-ECT studies specifically examined treatment-resistant individuals.

Take Away Points
Ketamine infusion appears to be effective for depressive symptoms, but its effects are limited by its transient duration. There is no evidence at this time to use it as augmentation to ECT, nor is it a direct
substitute for ECT given the transient nature of its benefit. There is a greater risk of psychotomimetic and dissociative side effects, though these generally resolve within hours of infusion.

II. Other studies have examined the use of repeated ketamine infusions for the treatment of MDD. Thus far, all studies have been open label.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Administration</th>
<th>Design</th>
<th>Number of patients</th>
<th>Treatment Response</th>
<th>Durability</th>
</tr>
</thead>
<tbody>
<tr>
<td>aan het Rot et al.</td>
<td>6 infusions over 12 days</td>
<td>Open label</td>
<td>10</td>
<td>65% response,</td>
<td>19 days after last infusion</td>
</tr>
<tr>
<td>(2010)</td>
<td></td>
<td></td>
<td></td>
<td>85% reduction in MADRS</td>
<td></td>
</tr>
<tr>
<td>Murrough et al.</td>
<td>up to 6 infusions over 12 days</td>
<td>Open label</td>
<td>24</td>
<td>70.8%, 19 pt.</td>
<td>18 days after last infusion</td>
</tr>
<tr>
<td>(2013)</td>
<td></td>
<td></td>
<td></td>
<td>reduction in MADRS</td>
<td></td>
</tr>
<tr>
<td>Diamond et al.</td>
<td>6 infusions over 3 weeks</td>
<td>Open label</td>
<td>28</td>
<td>29%</td>
<td>Median 70 days, range 25-168 days</td>
</tr>
<tr>
<td>(2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasmussen et al.</td>
<td>Twice weekly, until remission or</td>
<td>Open label</td>
<td>10</td>
<td>80% response,</td>
<td>Not reported</td>
</tr>
<tr>
<td>(2013)</td>
<td>4 total infusions (100-minute</td>
<td></td>
<td></td>
<td>50% remission</td>
<td></td>
</tr>
<tr>
<td></td>
<td>infusions)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

III. Ketamine for Suicidal Ideation: An open-label study (n=33) reported rapid resolution of SI after a single infusion of ketamine. Since then, two randomized controlled trials have been conducted.

**Price RB, Iosifescu DV, Murrough JW et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety. 2014 Apr;31(4):335-43.**

**Objective**
Assess the differential effects of ketamine versus midazolam on explicit and implicit measures of suicidality. This trial examined the same patient population as Murrough, et al., 2013.

**Design**
Two-site, double-blind, randomized controlled trial

**Population**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 21-80 years of age</td>
<td>• Psychotic illness</td>
</tr>
<tr>
<td>• Primary diagnosis of MDD (DSM IV)</td>
<td>• Bipolar disorder</td>
</tr>
<tr>
<td>• Inadequate trial of at least 3 antidepressants (TRD)</td>
<td>• Alcohol or Substance abuse in previous 2 years</td>
</tr>
<tr>
<td>• Currently in a depressive episode</td>
<td>• Unstable medical illness</td>
</tr>
<tr>
<td>• Must have recurrent MDD or chronic depressive episode &gt;2 years, at least moderate in severity (IDS₃₀ ≥32)</td>
<td>• Serious and imminent suicidal or homicidal risk</td>
</tr>
<tr>
<td>• Taking contraindicated medications</td>
<td>• Score of ≤27 on the Mini-Mental Status Exam</td>
</tr>
</tbody>
</table>

**Intervention**
Patients (n=73) randomized in a 2:1 ratio, comparing a single infusion of 0.5 mg/kg ketamine to an active control, 0.045 mg/kg midazolam infusion (both given over 40 minutes). Patients were required to be psychotropic drug-free prior to the infusion (at least 1 week, 4 weeks for fluoxetine). Fifteen patients from the 2013 Murrough trial did not complete the before or after assessments due to equipment/time constraints and three additional patients refused.

**Outcomes**

**Primary Outcomes**
An $S_{I\text{composite}}$ score was generated by summing z-scores from 3 components: the Beck Scale for Suicidal ideation (BSI), the MADRS suicide item (MADRS-SI), and the QIDS-SR suicidality item. The BSI is a 21-item self-report. Scores for the BSI range from 0-42, with a higher score indicating greater suicidal ideation. Patients were assessed using the MADRS, which has a suicidality item (MADRS-SI) rated on a 0-6 scale and the QIDS-SR which includes a suicidality item on a 0-3 scale. Change scores were calculated as 24-hour value – baseline value.
Implicit outcomes included results from the Implicit Association Test (IAT), assessing the strength of association between the related words “death” and “me” and the association between “escape” and “me.” The IAT is a performance-based index of implicit suicidal cognition previously demonstrated to be correlated with suicidal behavior.

Statistics

24-hour post-infusion scores were compared across groups using ANCOVA with baseline values as a covariate. Bootstrapping was used due to a positively skewed distribution.

χ² tests were used to compare groups on categorical measures.

Results

Fifty-four participants completed measures of suicidal cognition (ketamine: n = 36; midazolam: n = 21) at both baseline (1–4 days prior to infusion) and 24 hr post infusion.

Demographics were similar to the previously reported Murrough (2013) trial.³⁰

30% of individuals reported previous suicide attempt. 28% of the ketamine group had a history of suicide attempts and 38% of the midazolam group (n=8) had a history of suicide attempts.

Baseline Beck Scale for Suicidal Ideation scores were 6.1 and 6.2 for ketamine and midazolam groups respectively, suggesting similar baseline suicidal ideation.

Efficacy

At 24 hours, SIcomposite the reductions were greater in the ketamine group compared to the midazolam group, adjusting for baseline values (p=.01, effect size = 0.82).

![SI Composite Scores (z-score)](image-url)

Figure 9: SI Composite z-score change
Figure 10: % of patients with 0 on all 3 explicit SI Measures

No significant differential effects of ketamine versus midazolam on “Escape = Me” or “Death = Me” implicit associations (P-values > 0.5).

Author’s Conclusions
“Intravenous ketamine produces rapid reductions in suicidal cognition over and above active placebo. Further study is warranted to test ketamine's anti-suicidal effects in higher-risk samples.”

Critique

**Strengths**
- Studied treatment-resistant depression individuals
- Active comparator control
- Double-blinding

**Limitations**
- Ketamine group had larger proportion of individuals who scored 0 on all three explicit measures at baseline
- Did not include those who are at highest risk for suicide – only 30% reported previous suicide attempts
- Not adequately powered for these implicit measures (n=108 needed)
- Excluded substance abuse patients and those with psychosis
- Midazolam’s anxiolytic effect may affect suicidal ideation

Take Away Points
Ketamine, through its rapid antidepressant effect, may help to decrease suicidal ideation. However, the patients studied were not those who were at highest risk for suicide. Given the lack of treatment options that work in a timely fashion in the setting of acute suicidality, ketamine may be considered as a treatment option.
Objective
Assess the rapid effects of ketamine on SI in patients who presented for inpatient or outpatient treatment with clinically significant SI in the context of a range of psychiatric disorders.

Design
Single-site double-blind randomized controlled trial using midazolam as an active comparator.

Population

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
</table>
| - Initially only inpatients – amended later to include outpatients in order to enhance study feasibility and generalizability  
- Ages 18-80  
- Significant suicidal ideation (SI), defined by ≥4 on the MADRS suicide item (0-6) | - Outpatients excluded if they experienced current intent to make a suicide attempt  
- History of primary psychotic disorder  
- Current psychotic or manic symptoms  
- Substance use disorder within 1 month or positive urine toxicology  
- Lifetime abuse of ketamine or PCP  
- Unstable medical illness  
- Pregnant |

Intervention
Patients were allowed to remain on stable doses of psychotropic medications, including antidepressants. Baseline SI was assessed the morning directly prior to treatment.

27 patients were screened and 24 met enrollment criteria. This was comprised of 10 inpatients and 14 outpatients. Eligible participants received 0.5 mg/kg racemic ketamine hydrochloride (n=12) or 0.045 mg/kg i.v. midazolam (n=12) over 40 min by infusion pump under double-blind conditions.

Outcomes

**Primary Outcome**
SI severity at 24 h post-treatment measured by the 21-item self-report Beck Scale for Suicidal Ideation (BSI; score range 0–42).

**Secondary Outcomes**
MADRS Suicide Item (MADRS-SI); ranges from 0 to 6
Depression severity measured using the MADRS total score and QIDS-SR

Statistics
SI severity at 24, 48, 72 h and 7 days post-treatment were compared between the treatment groups using separate ANCOVA models, controlling for baseline SI level.

Separate models were used to examine the effect of treatment on SI as measured using the BSI and the MADRS-SI and the effect of treatment on general depression severity as measured using MADRS and QIDS-SR total score.

Sample size calculated to obtain 80% power to detect a standardized effect size of 1.2 assuming a two-tailed test and alpha set at 0.05

Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ketamine (n=12)</th>
<th>Midazolam (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45.8±15.2</td>
<td>39.1±10.6</td>
</tr>
<tr>
<td>Prev. Suicide</td>
<td>6 (50%)</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Attempt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI Score</td>
<td>17.5±7.2</td>
<td>17.9±11.9</td>
</tr>
<tr>
<td>MADRS</td>
<td>34.8±5.1</td>
<td>34.3±4.1</td>
</tr>
<tr>
<td>MADRS interpretation</td>
<td>moderate</td>
<td>moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>Ketamine (n=12)</th>
<th>Midazolam (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>6 (50%)</td>
<td>7 (58.3%)</td>
</tr>
<tr>
<td>Bipolar</td>
<td>4 (33%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>PTSD</td>
<td>1 (8.3%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Borderline</td>
<td>1 (4.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Personality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorder</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Primary Outcome – Efficacy

At 24 hours, BSI score was not significantly different between the treatment groups. A significant effect of treatment on BSI score emerged at 48 h following intervention (8.8 ± 8.3 and 15.3 ± 10.9, respectively, p = 0.047, effect size = 0.67). This difference was no longer significant at 72 h or 7 days.

Secondary Outcome – Efficacy

At 24 hours post infusion, the ketamine group’s MADRS-SI score was significantly lower than the midazolam group’s score (1.8 ± 1.9 and 3.3 ± 1.6, respectively, p = 0.05, effect size= 0.86). This statistical significance did not persist at 48 hours and beyond.

General depression levels did not differ between the treatment groups at any time point.

Author’s Conclusions

“The current findings provide support for the safety and tolerability of ketamine as an intervention for SI in patients at elevated risk for suicidal behavior. Larger, well-powered studies are warranted.”
### Critique

#### Strengths
- Diagnoses beyond MDD were allowed
- More acute SI w/ majority of patients with previous suicide attempt history
- Psychoactive control for blinding purposes
- Patients remained on concomitant medication during the study, receiving the study drug as an augmentation to standard of care – more externalizability.

#### Limitations
- Small sample size
- Trial design change to allow outpatients
- Low enrollment of non-mood disorders
- Possibly underpowered for depression measures
- Did not see a difference in primary outcome, but meet statistical significance at 48 hours.
- Treatment effect limited by transient duration
- Midazolam’s anxiolytic effect may influence for SI
- Concomitant medication may mask anti-SI effects of ketamine
- Authors examined suicidal ideation in scales rather than suicidal behavior
- Those at greatest risk for suicide were excluded from the study

### Take Away Points
Given limited available therapies, ketamine infusion may be considered for acute suicidal ideation. It may be effective for suicidal ideation in diagnoses other than MDD, but enrollment for those groups was small. These patients will need to be monitored closely and possibly admitted, given the transient nature of the benefit.

### Summary
- Ketamine is a novel, efficacious and rapidly acting treatment for depression
- Ketamine’s antidepressant effect appears independent of its dissociative and psychotomimetic effects
- Doses of ketamine used in anti-depressant studies are lower than those used in anesthesia or recreational use
- Ketamine may have anti-suicidal properties, an area where current pharmacotherapies fall short in efficacy and time to effect
- In limited studies, ketamine has thus far not increased manic symptoms in the treatment of bipolar depression
- It is limited by its short duration of effect, clinic administration and abuse potential
- While single infusion studies have demonstrated relative safety and tolerability, the long-term effects of repeated dosing and the durability of effect in long-term repeated dosing has yet to be established
- Ketamine should not be viewed as a substitute for ECT, nor is it beneficial as an augmentation to ECT

### Recommendations
- Given the potential for abuse, possible neurotoxicity, and transient nature of benefit, ketamine should only be reserved for treatment-resistant depression and multiple prior therapy failures, including augmentation strategies
- Multiple ketamine infusion “bridging” for 2-3 weeks while a patient stabilizes on an antidepressant regimen can be considered in severe depression
- May be considered in suicidal pts. given lack of therapy. Close follow-up or admission to the would still be required due to transient benefit.
- Caution use in those with pre-existing hypertension
- Recommend against long-term maintenance infusions until further studies are conducted

### Future Directions
- NMDA antagonists without dissociative effects e.g. riluzole
- “Bridging” trials – using ketamine in the interim while stabilizing with antidepressants
- Ketamine’s effects on length of psychiatric hospital stays
- More trials in bipolar and psychosis
- Safety and efficacy of long-term repeated infusions
- Administration methods to reduce dissociation (e.g. longer infusion times)


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Appendix A: Montgomery-Åsberg Depression Rating Scale (MADRS)

1. **APPARENT SADNESS** - Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up. (0-6)
   0: No sadness
   2: Looks spirited but does brighten up without difficulty
   4: Appears sad and unhappy most of the time
   6: Looks miserable all the time. Extremely despondent

2. **REPORTED SADNESS** - Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.
   0: Occasional sadness in keeping with the circumstances
   2: Sad or low but brightens up without difficulty
   4: Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   6: Continuous or unvarying sadness, misery or despondency.

3. **INNER TENSION** - Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.
   0: Placid. Only fleeting inner tension.
   2: Occasional feelings of edginess and ill-defined discomfort
   4: Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   6: Unrelenting dread or anguish. Overwhelming panic.

4. **REDUCED SLEEP** - Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.
   0: Sleeps as usual
   2: Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep
   4: Sleep reduced or broken by at least two hours
   6: Less than two or three hours sleep.

5. **REDUCED APPETITE** - Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.
   0: Normal or increased appetite
   2: Slightly reduced appetite
   4: No appetite. Food is tasteless.
   6: Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES** - Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.
   0: No difficulties in concentrating
2: Occasional difficulties in collecting one's thoughts
4: Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation
6: Unable to read or converse without great difficulty.

7. **LASSITUDE** - Representing a difficulty getting started or slowness initiating and performing everyday activities.
   0: Hardly any difficulties in getting started. No sluggishness.
   2: Difficulties in starting activities
   4: Difficulties in starting simple routine activities, which are carried out with effort
   6: Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL** - Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.
   0: Normal interest in the surroundings and in other people
   2: Reduced ability to enjoy usual interests
   4: Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
   6: The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends

   0: No pessimistic thoughts.
   2: Fluctuating ideas of failure, self-reproach or self-depreciation
   4: Persistent self-accusations, or definite but still rational ideas of guilt or sin. Pessimistic about the future.
   6: Delusions of ruin, remorse and unredeemable sin. Self-accusations which are absurd and unshakable.

10. **SUICIDAL THOUGHTS** - Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.
   0: Enjoys life or takes it as it comes.
   2: Weary of life. Only fleeting suicidal thoughts.
   4: Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
   6: Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

### Appendix B: Included Trials for Price et al. (2014)

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Ketamine Dose</th>
<th>Control</th>
<th>Concomitant Therapy</th>
<th>Diagnosis</th>
<th>n</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman et al.</td>
<td>Crossover</td>
<td>0.5 mg/kg</td>
<td>Placebo</td>
<td>None</td>
<td>MDD, bipolar</td>
<td>8</td>
<td>HAM-D-25</td>
</tr>
<tr>
<td>Lapidus et al.</td>
<td>Crossover</td>
<td>0.5 mg/kg</td>
<td>Placebo</td>
<td>None</td>
<td>MDD</td>
<td>18</td>
<td>MADRS</td>
</tr>
<tr>
<td>Murrough et al.</td>
<td>Parallel</td>
<td>0.5 mg/kg</td>
<td>Midazloam</td>
<td>None</td>
<td>MDD</td>
<td>72</td>
<td>MADRS</td>
</tr>
<tr>
<td>Zarate et al.</td>
<td>Crossover</td>
<td>0.5 mg/kg</td>
<td>Placebo</td>
<td>None</td>
<td>MDD</td>
<td>17</td>
<td>HAM-D-21</td>
</tr>
<tr>
<td><strong>Ketamine w/ psychotropics</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Diazgranados et al.</td>
<td>Crossover</td>
<td>0.5 mg/kg</td>
<td>Placebo</td>
<td>Lithium or valproate</td>
<td>Bipolar</td>
<td>16</td>
<td>MADRS</td>
</tr>
<tr>
<td>Sos et al.</td>
<td>Crossover</td>
<td>0.54 mg/kg</td>
<td>Placebo</td>
<td>Various</td>
<td>MDD</td>
<td>27</td>
<td>MADRS</td>
</tr>
<tr>
<td>Zarate et al.</td>
<td>Crossover</td>
<td>0.5 mg/kg</td>
<td>Placebo</td>
<td>Lithium or valproate</td>
<td>Bipolar</td>
<td>14</td>
<td>MADRS</td>
</tr>
<tr>
<td><strong>Ketamine w/ ECT</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdallah et al.</td>
<td>Parallel</td>
<td>0.5 mg/kg</td>
<td>Placebo</td>
<td>ECT+thiopental</td>
<td>MDD, bipolar</td>
<td>16</td>
<td>HAM-D-25</td>
</tr>
<tr>
<td>Jarventausta et al.</td>
<td>Parallel</td>
<td>0.4 mg/kg</td>
<td>Placebo</td>
<td>ECT+propofol</td>
<td>MDD</td>
<td>49</td>
<td>MADRS</td>
</tr>
<tr>
<td>Loo et al.</td>
<td>Parallel</td>
<td>0.5 mg/kg</td>
<td>Placebo</td>
<td>ECT+thiopentone</td>
<td>MDD, bipolar</td>
<td>46</td>
<td>MADRS</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>Parallel</td>
<td>0.8 mg/kg</td>
<td>Propofol</td>
<td>ECT</td>
<td>MDD</td>
<td>40</td>
<td>HAM-D-17</td>
</tr>
<tr>
<td>Yoosefi et al.</td>
<td>Parallel</td>
<td>1-2 mg/kg</td>
<td>Thiopental</td>
<td>ECT</td>
<td>MDD</td>
<td>29</td>
<td>MADRS</td>
</tr>
</tbody>
</table>