Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression


Objective: The authors conducted a systematic review and meta-analysis of ketamine and other N-methyl-D-aspartate (NMDA) receptor antagonists in the treatment of major depression.

Method: Searches of MEDLINE, PsycINFO, and other databases were conducted for placebo-controlled, double-blind, randomized clinical trials of NMDA antagonists in the treatment of depression. Primary outcomes were rates of treatment response and transient remission of symptoms. Secondary outcomes included change in depression symptom severity and the frequency and severity of dissociative and psychotomimetic effects. Results for each NMDA antagonist were combined in meta-analyses, reporting odds ratios for dichotomous outcomes and standardized mean differences for continuous outcomes.

Results: Ketamine (seven trials encompassing 147 ketamine-treated participants) produced a rapid, yet transient, antidepressant effect, with odds ratios for response and transient remission of symptoms at 24 hours equaling 9.87 (4.37–22.29) and 14.47 (2.67–78.49), respectively, accompanied by brief psychotomimetic and dissociative effects. Ketamine augmentation of ECT (five trials encompassing 89 ketamine-treated participants) significantly reduced depressive symptoms following an initial treatment (Hedges’ g = 0.933) but not at the conclusion of the ECT course. Other NMDA antagonists failed to consistently demonstrate efficacy; however, two partial agonists at the NMDA coagonist site, D-cycloserine and rapastinel, significantly reduced depressive symptoms without psychotomimetic or dissociative effects.

Conclusions: The antidepressant efficacy of ketamine, and perhaps D-cycloserine and rapastinel, holds promise for future glutamate-modulating strategies; however, the ineffectiveness of other NMDA antagonists suggests that any forthcoming advances will depend on improving our understanding of ketamine’s mechanism of action. The fleeting nature of ketamine’s therapeutic benefit, coupled with its potential for abuse and neurotoxicity, suggest that its use in the clinical setting warrants caution.


The emergence of intravenous ketamine therapy has been celebrated as perhaps “the most important breakthrough in antidepressant treatment in decades” (1). However, concern has been raised that off-label clinical utilization of ketamine as a pharmacotherapeutic agent is outpacing scientific scrutiny and may invite adverse sequelae that will exceed any accrued therapeutic benefit (2–4).

The flurry of interest in the antidepressant utility of ketamine and other N-methyl-D-aspartate (NMDA) receptor antagonists has been driven by a confluence of forces. First are the shortcomings of the current antidepressant armamentarium. The failings of existing antidepressants, which are largely thought to work primarily by enhancing monoamine neurotransmission, as well as the clear deficiencies of the underlying monoamine hypothesis of depression (5), are well-documented. When used to treat depression, currently available antidepressants are hindered by a prolonged delay of onset of action and disappointing remission rates (6). Both weaknesses are likely attributable, at least in part, to the fact that current antidepressants work via indirect mechanism(s) of action. There is considerable evidence that the therapeutic activity of antidepressants is not mediated by their direct synaptic effects, on for example monoamine reuptake, but by the brain’s adaptive response to sustained increases in monoaminergic neurotransmission produced by these agents, in a manner akin to the emergence of tolerance in the context of chronic use of habit-forming substances (7). Whatever the precise mechanism of action of currently available antidepressants truly is, their less than optimal efficacy has now been well established in large-scale clinical trials such as the Sequenced Treatment Alternatives to Relieve Depression Study (8–13) and the International Study to Predict Optimized Treatment in Depression (14).

The concatenation of the unsatisfactory remission rates and the delayed therapeutic response plaguing current antidepressants highlight the important unfilled need for an improved antidepressant pharmacopoeia, especially in view of the mortality (e.g., suicide and risk for heart disease and other major medical disorders) and morbidity associated with

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unremitted depression (15–18). Such unmet needs may be overcome by identifying interventions that more directly address the underlying pathophysiology of depression. In fact, this assumption has been the driving force behind much of the effort to identify novel antidepressant compounds over the past decade. Unfortunately, the search for novel compounds has been remarkably unsuccessful in recent years, resulting in a stagnant developmental pipeline for new antidepressant agents (19–22). It is understandable, given this otherwise bleak picture, that promising results from clinical and preclinical antidepressant studies of NMDA receptor antagonists would generate considerable excitement.

Nearly 20 years ago, several lines of evidence pointed to aberrant NMDA receptor-mediated glutamate neurotransmission as a viable neurobiological substrate on which to base a novel intervention for depression. Evidence includes alterations in central NMDA receptor binding profiles of rodents exposed to chronic stress, a laboratory animal model of depression, and postmortem tissue from suicide victims, in addition to changes in NMDA receptor activity produced by chronic antidepressant exposure (23). Indeed, the evidence that glutamateergic agents might hold antidepressant efficacy dates as far back as 50 years ago (24–26).

The complex physiology of the NMDA receptor (Figure 1) offers numerous pharmacodynamic targets for intervention. A tetramer, composed of two GluN1 subunits and two GluN2 subunits, encompassing an ion channel that regulates neuronal influx of calcium (Ca\(^{2+}\)) in addition to sodium (Na\(^{+}\)) influx and potassium (K\(^{+}\)) efflux, the NMDA receptor is unique in that it possesses both a ligand gate and a voltage gate, each of which must be opened to enable ion flow. Furthermore, the ligand gate is opened only when concurrently activated by two ligand molecules, a receptor agonist, glutamate, and a receptor coagonist, either glycine or d-serine, and the voltage gate is opened only when neuronal depolarization is triggered elsewhere (e.g., via glutamate binding the \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptors, acetylecholine binding at \(\alpha_7\) nicotinic receptors, etc.). Additional complexity is conferred by the presence of NMDA receptors not only within the synapse but at extrasynaptic sites as well. The origin of endogenous ligands at extrasynaptic NMDA receptors, though obscure, may be a variety of sources, including spillover of synaptic glutamate, glial release of glutamate, glycine, and d-serine, neuronal release of glycine and d-serine, and capillary extravasation of serum glycine (27), implying a complex physiological regulation. Moreover, activation of extrasynaptic NMDA receptors has been implicated in neuronal toxicity, whereas synaptic NMDA receptor activation has been credited with promoting neuronal survival (28). The respective roles of synaptic and extrasynaptic NMDA receptors in mediating synaptic plasticity and neuronal toxicity are likely more complex and remain a focus of intense scrutiny (27, 29, 30).

There is growing evidence of antidepressant effects of many of the compounds listed in the data supplement accompanying the online version of this article. For example, a series of preclinical antidepressant screening test studies have demonstrated antidepressant-like effects (e.g., decreased immobility time in the forced swim test) for numerous NMDA receptor antagonists, including ketamine (31–35), memantine (36–38), ifenprodil (39), and D-cycloserine (39, 40).

A plethora of open-label trials of ketamine reporting a 25%–78% reduction in depressive symptom severity have been published in recent years (41–72), including those demonstrating particular antidepressant efficacy among those with family histories of alcoholism (73–77), as well as positive open-label studies of amantadine (78) and memantine (79).

The objective of the present review by the APA Council of Research Task Force on Novel Biomarkers and Treatments was to conduct a systematic review and meta-analysis of the randomized clinical trials of ketamine and other NMDA receptor antagonists in the treatment of depression, critically examining findings for both the efficacy and adverse effects of these various agents.

**METHOD**

**Search**

We searched 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, memantine, and other NMDA antagonists. In addition, we searched ClinicalTrials.gov and screened references of included studies and relevant reviews. Only placebo-controlled, double-blind, randomized clinical trials reporting response to treatment utilizing a standardized rating scale for depression were eligible for inclusion.

**Data Extraction and Outcomes**

All data were extracted by the same reviewer (D.J.N.). The primary outcome measures were treatment response rate, defined as the proportion of patients experiencing a 50% reduction in the total score of the depression rating scale, and rate of transient remission of symptoms, defined as the depression rating scale score falling below a generally accepted threshold value. In addition, we evaluated change in depression symptom severity utilizing each study’s primary depression rating scale. All contributing studies utilized either the Montgomery-Åsberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale (HAM-D). The frequency and/or severity of dissociative, psychotomimetic, and hemodynamic effects were evaluated as secondary outcomes.

**Meta-Analytic Calculations**

Odds ratios were used for the dichotomous (i.e., treatment response and transient remission of symptom) measures. Adjustment for zero frequency cells was made by adding a fixed value (0.5) to any zero count cells prior to odds ratio calculation. Standardized mean differences were calculated as the mean difference in depressive symptom rating produced by the intervention and the control divided by the
pooled standard deviation, with Hedges’ g adjustment for small samples (80). When standard deviations were not directly reported in the article, they were calculated from other available data when possible (e.g., from 95% confidence intervals or t test p values). The risk of small study effects was assessed through visual inspection of contour-enhanced funnel plots (81) followed by an Egger regression test (82, 83) to formally test for small study effects.

Statistical analyses were performed using Comprehensive Meta Analysis software version 2.2 (Biostat, Frederick, Md.) and SAS software version 9.3 (SAS Institute, Cary, N.C.). All statistical tests were two-tailed with α set at 0.05.

RESULTS

The literature search yielded 581 citations. Most publications were excluded because they reported data from nonrandomized or open-label trials, addressed treatment efficacy for illnesses other than mood disorders, reported the response to treatment of an isolated depressive symptom (i.e., suicidality) rather than the overall syndrome, or were review articles or commentaries on the topic. Twenty-four studies (Table 1 [also see TS2 in the online data supplement]) fulfilled the a priori criteria for meta-analysis inclusion.

Ketamine Studies

The search identified 12 reports of randomized clinical trials examining ketamine in the treatment of depression (Table 1). The 12 studies encompass ketamine used as a monotherapy, to augment other psychotropic agents, and as an augmentation to ECT. In addition, ketamine was administered in these studies to treat depressive episodes of bipolar disorder, major depressive disorder, or both. It was administered through intravenous infusion in all but one of the studies, which utilized intranasal administration (84). Four of the studies specified that participants had failed a previous or current treatment for depression (84–87).

Efficacy. A single intravenous infusion of ketamine, excluding its use in conjunction with ECT, which is examined separately, consistently
TABLE 1. Characteristics of Included Randomized Clinical Trials of Ketamine

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Ketamine Regimen</th>
<th>Control Regimen</th>
<th>Concomitant Therapy</th>
<th>Diagnoses</th>
<th>Sample Size</th>
<th>Depression Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ketamine monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berman et al. (90)</td>
<td>Cross Over</td>
<td>0.5 mg/kg intravenous×1</td>
<td>Placebo</td>
<td>None</td>
<td>Major depressive disorder, bipolar disorder</td>
<td>8</td>
<td>25-Item Hamilton Depression Rating Scale (HAM-D)</td>
</tr>
<tr>
<td>Lapidus et al. (84)</td>
<td>Cross Over</td>
<td>0.5 mg intranasal×1</td>
<td>Placebo</td>
<td>None</td>
<td>Major depressive disorder</td>
<td>18</td>
<td>Montgomery-Åsberg Depression Rating Scale (MADRS)</td>
</tr>
<tr>
<td>Murrough et al. (87)</td>
<td>Parallel</td>
<td>0.5 mg/kg intravenous×1</td>
<td>Midazolam</td>
<td>None</td>
<td>Major depressive disorder</td>
<td>72</td>
<td>MADRS</td>
</tr>
<tr>
<td>Zarate et al. (88)</td>
<td>Cross Over</td>
<td>0.5 mg/kg intravenous×1</td>
<td>Placebo</td>
<td>None</td>
<td>Major depressive disorder</td>
<td>17</td>
<td>21-Item HAM-D</td>
</tr>
<tr>
<td><strong>Ketamine augmentation of psychotropic therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazgranados et al. (85)</td>
<td>Cross Over</td>
<td>0.5 mg/kg intravenous×1</td>
<td>Placebo</td>
<td>Lithium or valproic acid</td>
<td>Bipolar disorder</td>
<td>16</td>
<td>MADRS</td>
</tr>
<tr>
<td>Sos et al. (91)</td>
<td>Cross Over</td>
<td>0.54 mg/kg intravenous×1</td>
<td>Placebo</td>
<td>Various</td>
<td>Major depressive disorder</td>
<td>27</td>
<td>MADRS</td>
</tr>
<tr>
<td>Zarate et al. (86)</td>
<td>Cross Over</td>
<td>0.5 mg/kg intravenous×1</td>
<td>Placebo</td>
<td>Lithium or valproic acid</td>
<td>Bipolar disorder</td>
<td>14</td>
<td>MADRS</td>
</tr>
<tr>
<td><strong>Ketamine augmentation of ECT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdallah et al. (95)</td>
<td>Parallel</td>
<td>0.5 mg/kg intravenous pre-ECT</td>
<td>Placebo</td>
<td>ECT+thiopental</td>
<td>Major depressive disorder, bipolar disorder</td>
<td>16</td>
<td>25-Item HAM-D</td>
</tr>
<tr>
<td>Järventausta et al. (93)</td>
<td>Parallel</td>
<td>0.4 mg/kg intravenous pre-ECT</td>
<td>Placebo</td>
<td>ECT+propofol</td>
<td>Major depressive disorder</td>
<td>49</td>
<td>MADRS</td>
</tr>
<tr>
<td>Loo et al. (96)</td>
<td>Parallel</td>
<td>0.5 mg/kg intravenous pre-ECT</td>
<td>Placebo</td>
<td>ECT+thiopentone</td>
<td>Major depressive disorder</td>
<td>46</td>
<td>MADRS</td>
</tr>
<tr>
<td>Wang et al. (94)</td>
<td>Parallel</td>
<td>0.8 mg/kg intravenous pre-ECT</td>
<td>Propofol</td>
<td>ECT</td>
<td>Major depressive disorder</td>
<td>40</td>
<td>17-Item HAM-D</td>
</tr>
<tr>
<td>Yoosefi et al. (97)</td>
<td>Parallel</td>
<td>1–2 mg/kg intravenous pre-ECT</td>
<td>Thiopeptal</td>
<td>ECT</td>
<td>Major depressive disorder</td>
<td>29</td>
<td>HAM-D</td>
</tr>
</tbody>
</table>

* Agent employed as an active placebo.
* All participants anesthetized using a conventional agent (thiopental, propofol, or thiopentone).
* Employed S-ketamine.
* Three study arms: ketamine only, propofol only, ketamine and propofol.
* Participants received ketamine or thiopental.

produced a rapid antidepressant response peaking within one day of administration (Table 2). Twenty-four hours after administration, each of the six contributing studies demonstrated a statistically significant odds ratio for treatment response (Figure 2A). The composite odds ratio for therapeutic response at 24 hours postinfusion equaled 9.87 (95% confidence interval [CI] = 4.37–22.29, z = 5.50, p < 0.001). Day 1 response rates remained significant when the data were stratified by diagnosis, separating major depressive disorder (odds ratio = 8.42 [95% CI = 3.47–20.39], z = 4.72, p < 0.001) and bipolar disorder (odds ratio = 24.05 [95% CI = 2.96–195.56], z = 2.97, p = 0.003). Moreover, the response rate was also significant when limited to patients receiving ketamine as a monotherapy for major depressive disorder (odds ratio = 7.55 [95% CI = 2.89–19.76], z = 4.12, p < 0.001).

The odds ratio for treatment response declined steadily but remained statistically significant as long as 2 weeks following ketamine infusion (Table 2). Although only two of the six studies contributing data at day 7 demonstrated a statistically significant odds ratio for treatment response (Figure 2B), the composite odds ratio for response was nevertheless statistically significant (odds ratio = 4.61 [95% CI = 2.08–10.24], z = 3.75, p < 0.001). After excluding the intranasal ketamine study, which narrowly missed statistical significance (odds ratio = 4.71 [95% CI = 0.95–23.30], z = 1.90, p = 0.058), the five remaining intravenous infusion studies produced a statistically significant composite odds ratio for therapeutic response (odds ratio = 4.58 [95% CI = 1.82–11.49], z = 3.24, p = 0.001). Stratified by diagnosis, the odds ratio for treatment response at day 7 was statistically significant for major depressive
disorder (odds ratio = 4.72 [95% CI = 1.95–11.38], z = 3.45, p = 0.001) but not bipolar disorder (odds ratio = 4.16 [95% CI = 0.64–27.22], z = 1.49, p = 0.137).

Odds ratios for transient remission of symptoms followed a similar temporal pattern, though remission rates failed to achieve the same magnitude or to sustain statistical significance beyond day 3 (Table 2). The composite odds ratio for transient symptom remission was statistically significant on day 1 (odds ratio = 14.47 [95% CI = 2.67–78.49], z = 3.10, p = 0.002) but not day 7 (odds ratio = 3.08 [95% CI = 0.61–15.43], z = 1.37, p = 0.172). Stratifying by diagnosis, major depressive disorder transient remission data were provided by a single study (88), demonstrating identical results on day 1 and day 7 (odds ratio = 15.40 [95% CI = 0.83–284.53], z = 1.83, p = 0.066).

Studies of bipolar disorder patients, all utilizing ketamine to augment therapy with a conventional mood stabilizer, demonstrated a statistically significant rate of symptom remission on day 1 (odds ratio = 14.01 [95% CI = 1.73–111.70], z = 2.49, p = 0.013) but not day 7 (odds ratio = 1.51 [95% CI = 0.22–10.49], z = 0.42, p = 0.674).

Of note, ketamine infusion has also been reported to significantly outperform placebo in rapidly reducing suicidal ideation among patients with treatment-resistant depression (89).

**Psychotomimetic and dissociative side effects.** Several of the contributing studies administered the positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS) and/or

<table>
<thead>
<tr>
<th>Time Posttreatment Initiation</th>
<th>Treatment Response (Percentage)</th>
<th>Transient Symptom Remission (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ketamine</td>
<td>Control</td>
</tr>
<tr>
<td>40 Minutes</td>
<td>36.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>80 Minutes</td>
<td>51.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>2 Hours</td>
<td>51.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>4 Hours</td>
<td>47.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>1 Day</td>
<td>52.6%</td>
<td>7.0%</td>
</tr>
<tr>
<td>2 Days</td>
<td>50.0%</td>
<td>6.9%</td>
</tr>
<tr>
<td>3 Days</td>
<td>46.6%</td>
<td>8.9%</td>
</tr>
<tr>
<td>7 Days</td>
<td>31.4%</td>
<td>7.0%</td>
</tr>
<tr>
<td>14 Days</td>
<td>10.9%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
the Clinician-Administered Dissociative States Scale to determine whether ketamine therapy produced psychotomimetic or dissociative symptoms, respectively. The BPRS data (85–88, 90) indicate that psychotomimetic effects were, in fact, associated with ketamine therapy with mean BPRS positive subscale scores 0.74 (95% CI 0.46–1.01) points higher (Hedges' $g=0.82$, $z=5.73$, $p<0.001$). Similarly, the Clinician-Administered Dissociative States Scale data (85–87) reveal that ketamine therapy was associated with the emergence of transient dissociative symptoms, with mean scores on this scale 23.75 (95% CI 22.13–25.37) points higher (Hedges' $g=1.78$, $z=7.31$, $p<0.001$) among those receiving ketamine. Some studies (84, 88, 91), though not all (85, 86, 90), reported a statistically significant inverse association between the severity of dissociative or psychotomimetic side effects and subsequent reduction in depressive symptoms.

**Hemodynamic side effects.** Despite ketamine’s long-recognized sympathomimetic properties (92), the hemodynamic effects of ketamine were systematically reported in only two of the seven ketamine trials (84, 87), with those studies reporting mean systolic blood pressure increases of 7.6 mm Hg and 19.0 mm Hg, respectively, 40 minutes after infusion. Both studies reported that blood pressure measures had returned to baseline within 4 hours of infusion. Each of the six studies to report adverse event findings (84–88, 91) noted transient blood pressure increases following ketamine administration. Blood pressure changes warranting discontinuation of ketamine infusion (N=2) were observed in only one of the studies.

**Ketamine Augmentation of ECT**

**Efficacy.** The literature search identified five studies examining ketamine use in conjunction with ECT (Table 1). In these studies, ketamine was used either in addition to or in lieu of another agent to induce anesthesia prior to ECT administration. Meta-analysis indicated that ketamine augmentation was associated with a significantly greater reduction in depressive symptoms after an initial ECT session (see Figure S1A in the online data supplement) but not at the conclusion of the complete course of ECT (see Figure S1B in the online data supplement). Moreover, ketamine augmentation did not improve therapeutic response (odds ratio = 0.78 [95% CI = 0.36–1.68], $z=-0.64$, $p=0.52$) at the conclusion of the course of ECT. None of the contributing studies reported symptom remission rates.

**Psychotomimetic and dissociative side effects.** None of the ketamine-ECT studies utilized the BPRS or Clinician-Administered Dissociative States Scale measures to evaluate treatment-emergent psychotomimetic or dissociative symptoms. However, one study reported that post-ECT disorientation and restlessness were twice as common among those receiving ketamine (93), and another reported that ketamine
TABLE 3. Results of Meta-Analyses of Memantine Therapeutic Response Rates

<table>
<thead>
<tr>
<th>Time Posttreatment Initiation</th>
<th>Memantine</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Weeks</td>
<td>27.6%</td>
<td>9.7%</td>
<td>3.8</td>
<td>0.9–16.5</td>
<td>&lt;0.08</td>
<td>Anand et al. (100); Smith et al. (99)</td>
</tr>
<tr>
<td>4 Weeks</td>
<td>35.5%</td>
<td>25.8%</td>
<td>1.7</td>
<td>0.5–5.5</td>
<td>&lt;0.37</td>
<td>Anand et al. (100); Smith et al. (99)</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>38.7%</td>
<td>22.6%</td>
<td>2.7</td>
<td>0.9–9.1</td>
<td>&lt;0.10</td>
<td>Anand et al. (100); Smith et al. (99)</td>
</tr>
<tr>
<td>8 Weeks</td>
<td>26.7%</td>
<td>14.9%</td>
<td>1.6</td>
<td>0.6–4.6</td>
<td>&lt;0.38</td>
<td>Anand et al. (100); Smith et al. (99); Zarate et al. (98)</td>
</tr>
</tbody>
</table>

was associated with significantly higher rates of post-ECT delirium and fear upon waking due to psychotic symptoms (94).

Hemodynamic side effects. Cardiovascular effects of ECT augmentation with ketamine were not reported at all in two of the five studies (95, 96) and systematically evaluated in only two of the studies (94, 97). Wang and colleagues (94) reported higher rates of blood pressure elevation among subjects receiving ketamine anesthesia than among those receiving propofol (67% versus 25%, \( p = 0.023 \)), with five (42%) of the ketamine-treated subjects requiring intravenous administration of urapidil to treat the adverse effect; however, coadministration of propofol with ketamine eliminated ketamine’s adverse hemodynamic effects. Yoosefi and colleagues (97) also observed higher blood pressure measures in subjects assigned to ketamine therapy but reported no serious adverse cardiovascular events.

Seizure duration. Inclusion of ketamine in the ECT anesthetic regimen was associated with longer seizure duration, prolonged by 11.49 seconds (95% CI = 8.63–14.34) (Hedges’ \( g = 0.68, \ z = 4.21, p < 0.001 \)).

Memantine Studies

Like ketamine, memantine acts as an antagonist by binding to the NMDA receptor at a site within the receptor ion channel. The search identified three reports of randomized clinical trials examining memantine in the treatment of depression (see Table S2 in the online data supplement), including its use as a monotherapy for major depressive disorder (98) and as an augmentation agent either for major depressive disorder (99) or bipolar disorder (100). (Response rate data for use as augmentation for major depressive disorder were provided by Dr. E.G. Smith via personal communication, November 2014 [also see reference 99].) In all three studies, memantine was administered at or about a daily dose of 20 mg during an 8-week trial.

Efficacy. Meta-analysis of these three studies indicates that memantine did not outperform placebo in achieving a therapeutic response at any biweekly interval during the 8-week trials (Table 3 [also see Figure S2A in the online data supplement]) or in reducing depressive symptom severity (see Figure S2B in the online data supplement). Stratified by diagnosis, the odds ratio for treatment response at week 8 was statistically significant for neither major depressive disorder (odds ratio = 0.80 [95% CI = 0.19–3.35], \( z = −0.30, p = 0.77 \)) nor bipolar disorder (odds ratio = 3.67 [95% CI = 0.77–17.43], \( z = 1.63, p = 0.10 \)).

Symptom remission rates, reported in only one of the studies (100), were not lower among the memantine-treated group.

Psychotomimetic and dissociative side effects. The memantine studies did not utilize formal scales such as the BPRS or Clinician-Administered Dissociative States Scale to evaluate adverse effects. However, one of the studies specifically reported having observed no group differences in rates of dissociation or confusion (99), and another reported no differences in “central nervous system side (CNS) effects” (100).

Lanicemine (AZD6765) Studies

Lanicemine, formerly known as AZD6765, also binds to the NMDA receptor at a site within the ion channel. Like ketamine, lanicemine is administered through intravenous infusion. The literature search identified two published reports encompassing three randomized clinical trials examining the antidepressant utility of lanicemine (see Table S2 in the data supplement). These studies, all addressing the treatment of depressive episodes of major depressive disorder, include two trials of single intravenous infusion of lanicemine (101, 102) and an additional trial of serial intravenous infusions administered over 3 weeks at two different doses (102). There are no published randomized clinical trials evaluating lanicemine treatment of depressive episodes of bipolar disorder.

Efficacy. Whereas one of the two single infusion studies reported a transient statistically significant reduction in depressive symptom severity at 80 and 110 minutes following infusion (101), meta-analysis demonstrated that lanicemine failed to produce a statistically significant reduction in depressive symptoms at 1 day or 3 days following infusion (see Figures S3A and S3B in the data supplement). In the lone study to report rates of response and transient symptom remission (101), no significant differences were observed at any time point (data not shown).

In contrast to the single infusion lanicemine results, serial administration of lanicemine over 3 weeks demonstrated significant improvement in rates of treatment response (odds ratio = 2.62 [95% CI = 1.33–5.15], \( z = 2.80, p = 0.005 \)) and symptom remission (odds ratio = 2.33 [95% CI = 1.04–5.25], \( z = 2.05, p = 0.04 \)) (102).
Psychotomimetic and dissociative side effects. BPRS data, reported for both single infusion studies (101, 102), indicate that lanicemine therapy was not associated with psychotomimetic side effects because mean scores on the BPRS positive symptom subscale did not differ between the lanicemine and control groups (Hedges’ g = 0.04, z = 0.17, p = 0.87). Similarly, mean Clinician-Administered Dissociative States Scale scores did not differ between groups (Hedges’ g = 0.12, z = 0.96, p = 0.34), suggesting that lanicemine therapy was not associated with dissociative side effects.

Nitrous Oxide Study
Nitrous oxide (N20) is yet another NMDA antagonist that binds to the receptor at a site within the ion channel. In the lone randomized clinical trial published to date (see Table S2 in the data supplement), N20 was administered via inhalation for 1 hour in a 50% N20/50% oxygen mixture. The placebo control was a mixture of 50% nitrogen/50% oxygen. Treatment response was assessed 2 hours and 24 hours after the inhalation (103).

Efficacy. In this study, N20 was associated with a significantly greater reduction in HAM-D scores than placebo at both 24 hours postinhalation, N20 was also associated with higher rates of treatment response (odds ratio = 4.0 [95% CI = 0.45–3.579]) and transient remission of symptoms (odds ratio = 3.0 [95% CI = 0.31–28.8]), though neither achieved statistical significance.

Psychotomimetic and dissociative side effects. The BPRS and Clinician-Administered Dissociative States Scale were not administered in the existing N20 study. However, the authors report evaluating the participants for “the presence of euphoria and psychosis at each time point” and later remark that the intervention “appeared to be devoid of psychotomimetic side effects” (103).

Traxoprodil (CP-101,606) Study
In contrast to the agents reviewed thus far, traxoprodil does not bind to the NMDA receptor at a channel site, binding instead to an allosteric site outside the receptor ion channel on the GluN2B subunit. The lone traxoprodil randomized clinical trial to date (see Table S2 in the data supplement) administered the agent through intravenous infusion to augment the antidepressant paroxetine in a sample who had failed to respond to a 6-week open-label trial of paroxetine and had received a single blind intravenous placebo infusion. Treatment effects were reported using single-sided statistical tests to evaluate treatment effects at 2, 5, 8, 12, and 15 days postinfusion (104).

Efficacy. When results from this study were analyzed using more conservative two-sided testing, traxoprodil was associated with a significantly greater reduction in MADRS scores at only one of the five postinfusion intervals, 5 days postinfusion (8.9-point difference in means, p = 0.01). Because the study reported rates of response and transient symptom remission for those receiving traxoprodil but not those randomly assigned to placebo, odds ratios could not be calculated.

Psychotomimetic and dissociative side effects. Structured assessments, such as the BPRS and Clinician-Administered Dissociative States Scale, were not utilized. Of note, treatment-emergent dissociative symptoms were reported by six (40%) subjects receiving traxoprodil versus two (13%) of those randomly assigned to receive placebo.

MK-0657 (CERC-301) Study
MK-0657 also acts as an NMDA antagonist by binding to the receptor at an allosteric site on the GluN2B subunit. The lone published randomized clinical trial of MK-0657 for depression (see Table S2 in the data supplement) was prematurely terminated when the manufacturer discontinued the program. Thus, only five participants completed the crossover trial (105).

Efficacy. In this study, MK-0657 failed to demonstrate a significantly greater reduction of depressive symptoms as measured by the MADRS (p = 0.27).

Psychotomimetic and dissociative side effects. Although the BPRS and Clinician-Administered Dissociative States Scale were administered, results were not reported. The authors did report, however, “no significant difference . . . in the emergence of dissociative or psychotomimetic side effects” (105).

D-Cycloserine Studies
Distinct from the agents previously reviewed, D-cycloserine binds to the glycine coagonist binding site on the NMDA receptor, where it has been shown to act as a partial agonist (106–108). However, additional evidence suggests a more complex pharmacology, confirming that D-cycloserine acts as a partial agonist at glycine binding sites present on GluN2A, GluN2B, and GluN2D subunits of the NMDA receptor, but as a full agonist at glycine binding sites on GluN2C subunits (109, 110).

The literature search identified two randomized clinical trials of D-cycloserine treatment of depression (see Table S2 in the data supplement), both published by the same group (111, 112). The two studies used widely divergent oral D-cycloserine doses, 250 mg (111) versus 1,000 mg (112) per day. Because a dose disparity of this magnitude could dramatically alter the bioactivity of a partial agonist, the two studies are considered independently.

Efficacy. The earlier lower-dose D-cycloserine trial (111) offered no evidence indicative of efficacy in the treatment of depression. At the 250-mg daily dose, D-cycloserine was not associated with a greater reduction in 21-item HAM-D-measured...
depressive symptoms than placebo (4.4-point versus 3.1-point reduction, p=0.51).

Conversely, endpoint assessments at the conclusion of the 6-week higher-dose study (112) revealed a significantly greater reduction in depressive symptoms per the 21-item HAM-D (12.0-point versus 3.9-point reduction, p=0.005) in association with D-cycloserine therapy. Moreover, D-cycloserine treatment was associated with a significantly greater likelihood of therapeutic response (54% versus 15%, \( \chi^2 = 4.24, p=0.04 \)); however, the difference in rate of symptom remission (38% versus 15%) did not achieve statistical significance (\( \chi^2 = 1.76, p=0.19 \)).

Interestingly, a subset analysis limited to participants with baseline serum glycine levels exceeding 300 \( \mu \)M demonstrated an especially robust treatment effect, reducing depressive symptoms per the 21-item HAM-D (13.6-point versus 0.1-point reduction, \( p<0.001 \)). Preclinical studies indicate that D-cycloserine reliably functions as an NMDA antagonist in the context of higher glycine concentrations (106–108), suggesting the same may be true in this clinical trial.

**Psychotomimetic and dissociative side effects.** The Positive and Negative Syndrome Scale (PANSS) was used in the lower-dose D-cycloserine study as a proxy to measure psychotomimetic side effects. There were no group differences on the PANSS positive subscale, PANSS negative subscale, or PANSS general scale result.

In the higher-dose D-cycloserine study, the paranoia and depersonalization/derealization items on the HAM-D were used as indices of psychotomimetic and dissociative side effects, respectively. D-cycloserine was not associated with elevation of the HAM-D paranoia item (0.2 [SD = 0.4] versus 0.1 [SD = 0.2], \( p = 0.31 \)) or depersonalization/derealization item (0.0 [SD = 0.0] versus 0.0 [SD = 0.0], \( p = 0.72 \)).

**Rapastinel (GLYX-13) Study**

Like D-cycloserine, rapastinel is a partial agonist at NMDA receptor glycine binding sites (113–115). Whether rapastinel, like D-cycloserine, possesses pharmacodynamic specificity that varies by the NMDA receptor subunit on which the glycine binding site resides is unknown. The literature search identified one randomized clinical trial of rapastinel (116, 117) (see Table S2 in the data supplement), evaluating the antidepressant efficacy of a single intravenous infusion at four doses (1, 5, 10, and 30 mg/kg) with treatment effects assessed at 2, 4, 8, and 12 hours and 1, 3, 7, and 14 days postinfusion.

**Efficacy.** No statistically significant differences were observed in rates of treatment response or symptom remission associated with placebo (64% and 42%, respectively) versus rapastinel at any dose (up to 70% and 53%, respectively). However, statistically significant differences in the reduction of the 17-item HAM-D scores were observed for the 5-mg/kg dose at all intervals except day 14 (peak 17-item HAM-D reduction 3.1 points greater than placebo) and the 10-mg/kg dose at day 1 and day 3 (peak 17-item HAM-D reduction 4.3 points greater than placebo). Neither the low (1 mg/kg) nor high (30 mg/kg) rapastinel doses were associated with significant greater 17-item HAM-D score reduction than placebo, leading the authors to posit an inverted U-shape dose response curve.

**Psychotomimetic and dissociative side effects.** The BPRS positive symptom subscale was administered in this trial with no differences observed between the placebo group and any of the four rapastinel treatment groups. The Clinician-Administered Dissociative States Scale was not administered in this study.

**DISCUSSION**

To date, published results of randomized clinical trials examining the antidepressant utility of NMDA antagonists include four ion channel blockers (ketamine, memantine, lanicemine, N\(_2\)O), two antagonists that bind to allosteric sites (traxoprodil, MK-0657), and two partial agonists (D-cycloserine, rapastinel) that bind to the receptor’s glycine coagonist site. Ketamine is not only the most extensively studied NMDA antagonist, with 12 published randomized clinical trials (Table 1), followed by lanicemine (four randomized clinical trials), memantine (three randomized clinical trials), and D-cycloserine (two randomized clinical trials) as the only agents with more than one published clinical trial (see Table S2 in the online data supplement), but is the only NMDA antagonist to date consistently demonstrating antidepressant efficacy across multiple trials.

Current data provide compelling evidence that the antidepressant effects of ketamine infusion are both rapid and robust, albeit transient. For example, the odds ratio for transient symptom remission peaks on postinfusion day 1 at 14.5; however, by day 7, the odds ratio for symptom remission is no longer statistically significant and the odds ratio for treatment response, though statistically significant, has declined to 4.6 from a peak of 24.7. Surprisingly, other NMDA antagonists, including the other ion channel blockers (lanicemine, memantine, and N\(_2\)O), which bind to the receptor at the same site as ketamine, did not exhibit the same consistent evidence for antidepressant efficacy. It may be noteworthy that ketamine is also distinguished from the other NMDA antagonists by the frequency of psychotomimetic and dissociative side effects. Moreover, although ketamine-associated side effects were transient, reported only on the day of infusion, their occurrence was predictive of improvement of depressive symptoms in some of the ketamine trials (84, 88, 91).

It may be argued that ketamine’s prominent side effects compromise efforts to blind study participants and investigators to treatment assignment, thereby leading to biased results. While plausible, it is difficult to sustain this argument given the uniform evidence of rapid antidepressant efficacy for ketamine across nearly all studies (see Figure 2A [also see Figure S1A in the data supplement]), including those in which therapeutic response was not predicted by the occurrence
of psychotomimetic and dissociative side effects (85, 86, 90). A randomized controlled trial comparing ketamine with other psychotomimetic agents previously described to possess anxiolytic and antidepressant properties with a dramatically different mechanism of action, such as psilocybin (118), may be worthwhile to address this potential bias. Alternatively, some have speculated that the psychotomimetic and dissociative side effects of ketamine may be necessary for its antidepressant efficacy (91, 119), suggesting that ketamine may produce its antidepressant, psychotomimetic, and dissociative effects via the same mechanism. However, findings of antidepressant efficacy for other NMDA receptor antagonists in the absence of prominent psychotomimetic or dissociative side effects (102, 112, 116, 117) argue against this contention.

Notably absent in the literature are studies demonstrating that ketamine’s antidepressant effects can be sustained with serial infusions or transition to an alternative maintenance pharmacotherapy. Three small open-label studies of a series of four to six ketamine infusions administered over a 2-week interval reported relapse rates of 55%–89% in the month following treatment (41, 63, 68). Similarly, maintenance therapy with riluzole, a glutamatergic modulator, failed to outperform placebo in sustaining the therapeutic response to a single ketamine infusion in two randomized clinical trials, with relapse rates of 67%–80% among those randomly assigned to riluzole (51, 120). Of note, the literature includes a single case report of a woman who received 41 ketamine infusions yet remained significantly depressed and was ultimately referred for deep brain stimulation (121).

The following concatenation of findings emerges from the meta-analysis of existing NMDA antagonist studies: 1) intravenous infusion of subanesthetic doses of ketamine reliably produces a rapid antidepressant effect; 2) ketamine infusion also commonly produces prominent dissociative and psychotomimetic side effects; 3) ketamine’s therapeutically benefit quickly dissipates; and 4) other NMDA antagonists have failed to match ketamine’s consistent evidence of antidepressant efficacy across multiple randomized clinical trials. These findings, in turn, invite a series of seminal questions: 1) What conclusions regarding ketamine’s antidepressant mechanism of action can be gleaned from the existing clinical trial data? 2) To what extent is ketamine’s emerging use as an antidepressant in the clinical setting supported by the current data? 3) What lies ahead for future research regarding the role of NMDA antagonists in the treatment of depression?

Ketamine’s Mechanism of Action

Exploring the discrepant findings between ketamine and other NMDA antagonists, particularly the other NMDA ion channel blockers whose pharmacodynamic activities most closely resemble ketamine, may help elucidate ketamine’s antidepressant mechanism of action. That other NMDA channel blockers have yet to replicate ketamine’s rapid antidepressant effects has led to speculation that ketamine’s antidepressant properties may not be mediated via the NMDA receptor at all (122). Indeed, ketamine possesses a rich pharmacology, including activity at sigma receptors (123, 124). Moreover, actions within dopaminergic (125–127) or serotonergic (128–132) systems have also been postulated as alternate mechanisms for ketamine’s antidepressant effects. Conversely, ketamine’s unique antidepressant properties may be attributable to distinctions in its pharmacodynamic activity within the NMDA receptor (34, 122).

Comparing ketamine and memantine may be particularly illustrative. Despite the fact that both agents bind to the NMDA receptor at the channel binding site, memantine’s absence of antidepressant efficacy is in stark contrast to the positive ketamine results. Numerous studies, both clinical and preclinical, comparing the pharmacodynamic profiles of ketamine and memantine may explain the apparent inconsistency (see Table S3 in the data supplement). For example, whereas both agents reduce postsynaptic currents in vitro neuronal cultures, only ketamine does so when magnesium is added to the culture to mimic physiologic conditions (34). This pivotal distinction suggests that ketamine, but not memantine, readily exceeds the physiologic capacity of the NMDA receptor’s magnesium-dependent voltage gating (Figures 1B and 1C) to impede ion flow through the receptor channel. Ketamine’s superior capacity for blocking ion flow is unlikely to be a consequence of differential affinity for the NMDA channel binding site (133) but instead ketamine’s greater propensity, relative to memantine, for becoming trapped, once bound, within the channel (134).

Additional differences have been observed in the capacities for ketamine and memantine to activate intracellular signaling pathways linked to synaptic plasticity. Indeed, some have postulated that ketamine-induced synaptogenesis is crucial to its antidepressant effects (122, 135–137). Ketamine has been more reliably associated with a cascade of increased phosphorylation of eukaryotic elongation factor 2 (eEF2), increased synthesis of brain-derived neurotrophic factor (BDNF), and heightened activation of mammalian target of rapamycin (mTOR) than memantine (see Table S3 in the data supplement). BDNF’s role in ketamine’s mechanism of action is further suggested by the elimination of its antidepressant-like effects in a BDNF knockout model (32). In addition, both a clinical and preclinical study (138, 139) have reported altered antidepressant effects of ketamine in association with a BDNF functional polymorphism. Similarly, pretreatment with rapamycin, an mTOR inhibitor, extinguished ketamine-induced synaptogenesis and antidepressant-like effects in two rodent studies (140, 141).

Activation of these synaptic signaling proteins may not, however, be an immediate consequence of ketamine’s antagonism of the NMDA receptor. Additional evidence indicates that activation of glutamatergic AMPA receptors is necessary for ketamine’s antidepressant effects. Specifically, coadministration of an AMPA receptor antagonist has been shown to block ketamine’s antidepressant-like behavioral effects (32, 142, 143) and ketamine’s induction of synaptogenesis by synaptic signaling proteins (e.g., mTOR and BDNF) (35, 144).
The mechanism whereby ketamine infusion produces glutamatergic activation of AMPA receptors remains obscure. Some studies (145–147), though not all (148, 149), suggest that NMDA antagonists trigger presynaptic release of glutamate, which, in turn, binds to AMPA receptors. No matter what the underlying mechanism, the apparent linkage between NMDA antagonism and AMPA receptor activation may help clarify how ketamine can be neuroprotective (150, 151) in some contexts but potentially neurotoxic (151–153) in others. The necessity of AMPA activation implies that ketamine induces synaptogenesis by increasing glutamate signaling rather than by protecting neurons from glutamate excitotoxicity. Thus, excessive or ill-timed NMDA antagonism by an agent such as ketamine may leave neurons vulnerable to glutamate excitotoxicity. Ketamine’s potential to be either neuroprotective or neurotoxic must be considered when contemplating ketamine therapy in the clinical setting.

Clinical Use of Ketamine

That the encouraging results from published ketamine trials would generate excitement is certainly understandable. Yet, this enthusiasm should be tempered with the realization that ketamine’s clinical trial data, although positive, remain limited and demonstrate only a transient benefit.

Current efficacy data suggest that ketamine infusion provides a rapid therapeutic response for many patients suffering with treatment-resistant depression. It is perhaps understandable that infusion centers, employing ketamine as an alternative to ECT (154), have rapidly appeared across the nation. Upon closer inspection, however, the available data do not support ketamine infusion as an ECT alternative for acute treatment of depression. Whereas relapse rates approach 50% in the 6 months following ECT (155), relapse rates range up to nearly 90% only 4 weeks following serial ketamine infusions (41, 63, 68). As with ECT (156), achieving sustained remission of illness with ketamine may require continuation or maintenance treatment. However, there are currently no data regarding the efficacy and safety of continuation or maintenance therapy with ketamine delivered intravenously, intranasally, or via other routes.

Despite the attractiveness of such options as ketamine infusion centers or intranasal ketamine for home use, serious safety concerns remain. First, ketamine, in some contexts, could be neurotoxic. Soriano describes three risk factors for ketamine-induced neurotoxicity: 1) administration in early development during peak synaptogenesis, 2) administration at high doses, and 3) extended exposure (157).

In preclinical studies, ketamine has been associated with neuronal apoptosis in the developing CNS of both rodents (151, 158) and rhesus monkeys (159, 160). Additional evidence suggests that repeated ketamine administration to human infants may adversely affect neurodevelopment (152). However, other data support a neuroprotective role for ketamine in the developing brain by inhibiting inflammation in the context of a noxious stimulus such as pain (151). In addition, ketamine related neuronal apoptosis has been demonstrated in adult rodents (161). It is unclear if ketamine would have similar effects in adult humans.

Reliance upon low, subanesthetic doses in ketamine therapy for depression arguably safeguards against neurotoxic effects. For example, an in vitro study exposing human dopaminergic neurons to varying ketamine concentrations demonstrated apoptosis at high (500 µM) concentrations and evidence of oxidative stress at concentrations consistent with clinical use during anesthesia induction (100 µM); however, lower (20 µM) concentrations that would be typical of subanesthetic administration produced no evidence of neuronal injury (162).

As part of a general anesthetic regimen, ketamine is seldom administered repeatedly over days and weeks. Conversely, used as an intervention for depression, repeated administration of ketamine could potentially have a very different safety profile, including the risk for neurotoxicity. For example, in adult rodents, weekly serial ketamine administration has been observed to lead to the development of locomotor sensitization (163). Unfortunately, to date there is no substantive evidence to clarify whether there exists a duration of exposure safety threshold for ketamine neurotoxicity in adult humans.

An additional concern is the addictive/abuse liability of ketamine (4). Ketamine abuse is a widely recognized social problem in several countries in Europe and Asia, as well as in the United States (164). When abused, the intoxicating effects of ketamine are produced at doses (1 mg/kg–2 mg/kg) that are only marginally higher than the doses used in existing randomized clinical trials of ketamine. Widespread dissemination in the outpatient setting could readily produce physiological and psychological dependence on ketamine. Furthermore, diversion of prescribed ketamine for illicit use could rival, or even exceed, problems currently encountered with prescription opiates and sedative-hypnotics. Indeed, clinicians should be wary of the slippery slope posed by off-label use of ketamine (3). It should be noted that the history of pharmacology is replete with examples of new drug development with the promise of major therapeutic advances leading instead to disastrous public health consequences (e.g., heroin as a less addictive and more effective analgesic than morphine) (165).

Future Research Directions

Forthcoming ketamine research should continue to examine three central concerns: 1) elucidating ketamine’s mechanism of action; 2) understanding the administration profile necessary to provide a sustained therapeutic benefit; and 3) examining ketamine’s safety profile, particularly with repeated and likely low-dose administration.

Among the other NMDA antagonists studied to date, most intriguing are the recent studies of high-dose D-cycloserine (112) and rapastinel (116, 117). Because the therapeutic effect of D-cycloserine is most prominent at a higher dose in the context of high glycine concentrations, the binding site’s endogenous ligand, the partial agonist can be reliably assumed to be functioning as a relative antagonist. Yet, both preclinical (166, 167) and clinical (168–170) studies reveal an inverted
U-shape dose-response curve for D-cycloserine, which is not typical for classic partial agonists. Interestingly, the rapastinel randomized clinical trial for depression suggested a similar dose-response curve (116, 117). One plausible explanation is that these agents behave as classic partial agonists within a low (weak agonist activity) to moderate (relative antagonist activity) dose range but at especially high doses exhibit full agonist activity via GluN2C glycine binding sites activation. These agents are certainly worthy of further scrutiny.

Future studies may not be limited to NMDA receptor antagonists. Additional targets within the glutamatergic system include other ionotropic receptors (AMPA, kainate) (171, 172), metabotropic receptors (173), and glutamate transporters.

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