Review

KETAMINE FOR TREATMENT-RESISTANT UNIPOLAR AND BIPOLAR MAJOR DEPRESSION: CRITICAL REVIEW AND IMPLICATIONS FOR CLINICAL PRACTICE

William V. Bobo, M.D., M.P.H.,* Jennifer L. Vande Voort, M.D., Paul E. Croarkin, D.O., M.Sc., Jonathan G. Leung, Pharm.D., Susannah J. Tye, Ph.D., and Mark A. Frye, M.D.

There is an urgent need for more rapidly effective pharmacotherapies for major depressive disorder and bipolar disorder (BP) that are efficacious and tolerable for depressed patients who respond poorly to conventional treatments. Multiple controlled trials have now demonstrated a rapid, nonsustained antidepressive response to a single intravenous infusion of ketamine. Early controlled studies of intranasal or serial infusion therapy appear promising. The effective dose for depression is lower than the typical anesthetic doses, and side-effects are generally mild and transient. The data investigating the adjunctive use of concurrent ketamine in the course of electroconvulsive therapy (ECT) for depression do not suggest efficacy or tolerability. The therapeutic potential of ketamine has stimulated considerable excitement among clinicians, patients, and industry, and has led to the increasing use of ketamine as an off-label substitute for ECT and other antidepressive treatments. This clinical review of ketamine will assess the evidence-based use of ketamine and initial clinical implications of further development of a potentially novel treatment for rapid reduction of symptoms in depressed patients. Depression and Anxiety 33:698–710, 2016. *© 2016 Wiley Periodicals, Inc.*

Key words: *ketamine; treatment-resistant depression; major depression; bipolar depression; bipolar disorder*

INTRODUCTION

For years, there has been an urgent need for more effective antidepressants that do not require several weeks in order to take effect, and that engage pharmacological targets other than monoamine transporters or enzymes responsible for their degradation.[1,2] Multiple controlled trials have now demonstrated the short-term effectiveness of single or serial administration low-dose intravenous (IV) ketamine,[3] a potent noncompetitive glutamatergic *N*-methyl-D-aspartate (NMDA) antagonist,[4] for treating the symptoms of nonpsychotic treatment-resistant major depressive disorder (MDD) and bipolar (BP) depression. Those who benefitted from ketamine experienced rapid (within hours) onset of clinical antidepressive response. Positive benefit from ketamine persisted for 3–14 days on average after single infusions, a duration of impact well in excess of what would be predicted by its short elimination half-life of 2–3 hrs.[5,6] In general, the administration of low-dose ketamine for antidepressive effect was well tolerated, resulting in benign and transient adverse effects.

The therapeutic potential of ketamine (i.e., rapid symptom relief and response in treatment-resistant patients) has stimulated considerable interest in the psychiatric community.[7] However, ketamine does not have regulatory approval for treatment-resistant depression in the United States or elsewhere, and is still considered investigational for that indication. Nevertheless, an

Department of Psychiatry & Psychology, Mayo Clinic, Rochester, Minnesota

Contract grant sponsor: Mayo Foundation.

*Correspondence to: William V. Bobo, 200 First Street SW, Rochester, MN 55905. E-mail: bobo.william@mayo.edu
Received for publication 26 January 2016; Revised 9 March 2016; Accepted 11 March 2016

DOI 10.1002/da.22505
Published online 6 April 2016 in Wiley Online Library (wileyonlinelibrary.com).

© 2016 Wiley Periodicals, Inc.

increasing number of outpatient infusion centers and psychiatric clinics are offering IV ketamine as an unregulated, off-label substitute for electroconvulsive therapy (ECT) and other antidepressive treatments,[7–9] including repeated maintenance infusions for purposes of sustaining initial antidepressive effects.[10–14] There are also reports of the use of extemporaneously prepared intranasal formulations of ketamine for treating depression in routine outpatient settings.[15] Others have reported the use of increased doses of IV ketamine for patients who respond suboptimally to a conventional antidepressive dose of ~0.5 mg/kg.[16] The lack of regulatory approval necessitates that the cost of ketamine for depression for both acute and maintenance treatment is not reimbursed through third-party payers.

Evidence of increasing unregulated use of ketamine, particularly over the long term and as a putative substitute for ECT, has raised important questions about the effectiveness and safety of these practices.[8,15,17,18] This clinical review of ketamine will assess the evidence-based use of ketamine and initial clinical implications of further development of a potentially novel treatment for the rapid reduction of symptoms associated with MDD and BP depression.

KETAMINE AND THE UNMET NEEDS IN THE TREATMENT OF DEPRESSED PATIENTS

The prospect of rapid reduction of treatment-resistant depressive symptoms with ketamine in patients with MDD and BP depression has generated understandable interest and excitement among patients, clinicians, advocacy groups, industry, and the press.[7,19–22] Unlike conventional antidepressive treatments that require several weeks to take effect, ketamine has been shown to induce a rapid positive clinical response within hours of administration in many patients who have not benefitted from conventional pharmacotherapies and other forms of treatment. This excitement has also been extended to the putative antisuicidal effects of ketamine, which have also been shown to occur rapidly in positive ketamine responders,[23–27] although it remains to be seen if ketamine exerts a specific antisuicidal effect independent of antidepressive, anxiolytic, and other effects.[28]

Clinically, it appears that ketamine therapy may address critical unmet needs in the treatment of MDD and BP depression. Pharmacotherapy with conventional antidepressants and mood stabilizing medications is ineffective for many patients. Up to a third of MDD patients do not respond to conventional antidepressants and fewer than a third of patients experience full symptomatic remission.[29] Depression is also the predominant mood state in patients with BP over the course of illness[30,31]—yet, few pharmacological treatments have been shown to be effective for treating depressive episodes associated with BP in adults.[32] Not surprisingly, treatment resistance occurs frequently for patients with BP depression despite intensive pharmacotherapy.[33] Moreover, response to vigorous pharmacological treatment is incomplete or absent for many patients with BP depressive episodes,[34] thus contributing to high rates of recurring and persisting depressive symptoms,[35] psychiatric and general medical morbidity,[36,37] and suicide in bipolar patients.[38] Finally, with notable exceptions (i.e., clozapine and lithium), few standard therapies for MDD or BP have been associated with clear antisuicidal benefit, and none have been associated with the reduction of suicidality.[39]

The field has begun to focus its attention on studying the most effective and safe means of translating ketamine treatment protocols from clinical trials to everyday practice.[40] As is the case with any important undertaking, enthusiasm must be tempered by the available facts or, in the case of ketamine for depression, by data from carefully conducted studies of its safety and effectiveness for both short- and long-term use.

REVIEW OF THE EVIDENCE

RAPID BUT VARIABLE AND SHORT-LIVED ANTIDEPRESSIVE EFFECTS

Nine meta-analyses of acute-phase randomized short-term trials (up to 14 days, on average) of ketamine for depression have now reported statistically significant advantages of ketamine over placebo or active control conditions, across a variety of measures of antidepressive effect.[41–49] The design features of included studies across individual meta-analyses are summarized in Table 1. Collectively, the pooled data analyses show that the efficacy advantage of ketamine (vs. saline or midazolam placebo) was most consistently observed within hours of initiating ketamine therapy through postadministration day 7, with peak effects occurring at 24 hrs in most cases. As shown in Fig. 1, ketamine was associated with a large effect on reducing symptoms of depression (vs. controls) at 24 hrs postadministration, with generally smaller-to-medium effects at 7 days.

When the results from both controlled and uncontrolled studies are considered, there is a striking degree of variability in cumulative rates of positive antidepressive response to ketamine over short-term treatment, ranging from 29–90%.[40,50] Nevertheless, pooled effect sizes for positive response and remission from controlled studies of ketamine (vs. controls) were large at 24 hrs and at 7 days, as shown in Fig. 2 (odds ratios) and Fig. 3 (number needed to treat). A separate meta-analysis by Xu et al.[41] also reported large effects favoring ketamine for short-term positive response (pooled response rate 50 vs. 13%, RR 2.6, 95% CI: 1.6–4.4 at 24 hrs; pooled response rate 31 vs. 7%, RR 3.4, 95% CI: 1.6–7.1 at 7 days), and remission (pooled remission rate 28 vs. 3%, RR 5.2, 95% CI: 2.1–12.9 at 24 hrs; pooled remission rates 24 vs. 6%, RR 2.6, 95% CI: 1.2–5.7 at 7 days)

TABLE 1. Main results of meta-analyses of short-term studies of ketamine for unipolar or bipolar major depression

					Ketamine administration			
Reference	Sample (*n* studies)	Subjects (*n*)	Study designs (*n* subjects)	Control groups (*n* studies)	Dose range	Route of administration (*n* subjects)	Monotherapy versus adjunctive (*n* subjects)	Single dose versus repeated dose (*n* subjects)
Newport et al. 2015[42]	Total ($n = 7$) MDD only ($n = 4$) BP only ($n = 2$) MDD or BP ($n = 1$)	172	Cross-over ($n = 100$) Parallel group ($n = 72$)	Saline ($n = 6$) Midazolam ($n = 1$)	0.50–0.54 mg/kg IV 50 mg IN	IV ($n = 154$) IN ($n = 18$)	Monotherapy ($n = 115$) Adjunctive ($n = 57$)	Single ($n = 172$) Repeated ($n = 0$)
McGirr et al. 2015[43]	Total ($n = 7$) MDD only ($n = 4$) BP only ($n = 2$) MDD or BP ($n = 1$)	183	Cross-over ($n = 110$) Parallel group ($n = 73$)	Saline ($n = 6$) Midazolam ($n = 1$)	0.50–0.54 mg/kg IV 50 mg IN	IV ($n = 163$) IN ($n = 20$)	Monotherapy ($n = 120$) Adjunctive ($n = 63$)	Single ($n = 183$) Repeated ($n = 0$)
Xu et al. 2015[41]	Total ($n = 9$) MDD only ($n = 6$) BP only ($n = 2$) MDD or BP ($n = 1$)	201	Cross-over ($n = 129$) Parallel group ($n = 72$)	Saline ($n = 161$) Midazolam ($n = 40$)	0.10–0.54 mg/kg IV 50 mg IN 0.1–0.5 mg/kg IM or SC	IV ($n = 145$) IN ($n = 20$) IM ($n = 5$) SC ($n = 6$)	Monotherapy ($n = 119$) Adjunctive ($n = 82$)	Single ($n = 182$) Repeated ($n = 19$)
Lee et al. 2015[44]	Total ($n = 6$) MDD only ($n = 3$) BP only ($n = 2$) MDD or BP ($n = 1$)	159	Cross-over ($n = 87$) Parallel group ($n = 72$)	Saline ($n = 87$) Midazolam ($n = 25$)	0.50–0.54 mg/kg IV	IV ($n = 134$) IN ($n = 0$)	Monotherapy ($n = 74$) Adjunctive ($n = 60$)	Single ($n = 134$) Repeated ($n = 0$)
Romeo et al. 2015[45]	Total ($n = 6$) MDD only ($n = 3$) BP only ($n = 2$) MDD or BP ($n = 1$)	103	Cross-over ($n = 103$) Parallel group ($n = 0$)	Saline ($n = 6$) Midazolam ($n = 0$)	0.50–0.54 mg/kg IV 50 mg IN	IV ($n = 85$) IN ($n = 18$)	Monotherapy ($n = 43$)	Single ($n = 103$) Repeated ($n = 0$)
Coyle and Laws [46]	Total ($n = 21$) MDD only ($n = 14$) BP only ($n = 4$) MDD or BP ($n = 2$) Other ($n = 1$)[a]	437	Cross-over ($n = 96$) Parallel group ($n = 77$) Single-arm ($n = 264$)	Saline ($n = 6$) Midazolam ($n = 1$) None ($n = 13$) Other ($n = 1$)	0.20–0.54 mg/kg IV 50 mg IN	IV ($n = 419$) IN ($n = 18$)	Monotherapy ($n = 298$) Adjunctive ($n = 109$) Adjunct to ECT ($n = 30$)	Single ($n = 364$) Repeated ($n = 73$)
Parsaik et al. 2015[47]	Total ($n = 5$) MDD only ($n = 0$) BP only ($n = 4$) MDD or BP ($n = 1$)[b]	111	Cross-over ($n = 69$) Parallel group ($n = 0$) Other ($n = 56$)[c]	Saline ($n = 69$) Midazolam ($n = 0$)	0.50 mg/kg IV 10 mg SL[d]	IV ($n = 97$) IN ($n = 0$) SL ($n = 14$)	Monotherapy ($n = 0$) Adjunctive ($n = 111$)	Single ($n = 97$) Repeated ($n = 14$)
Fond et al. 2014[48]	Total ($n = 9$) MDD only ($n = 6$) BP only ($n = 2$) MD or BP ($n = 1$)	226	Cross-over ($n = 100$) Parallel group $n = 126$)	Saline ($n = 6$) Midazolam ($n = 1$) Other ($n = 2$)***	0.40–0.80 mg/kg IV	IV ($n = 226$) IN ($n = 0$)	Monotherapy ($n = 145$) Adjunctive ($n = 81$)	Single ($n = 208$) Repeated ($n = 18$)
Caddy et al. 2014[49]	Total ($n = 5$) MDD only ($n = 2$) BP only ($n = 2$) MDD or BP ($n = 1$)	65	Cross-over ($n = 65$) Parallel group ($n = 0$)	Saline ($n = 65$) Midazolam ($n = 0$)	0.50 mg/kg IV	IV ($n = 65$) IN ($n = 0$)	Monotherapy ($n = 35$) Adjunctive ($n = 30$)	Single ($n = 65$) Repeated ($n = 0$)

Key: BP, bipolar I or II disorder, depressed phase; IM, intramuscular; IN, intranasal; IV, intravenous; MDD, major depressive disorder (unipolar); SC, subcutaneous; SL, sublingual; SMD, standard mean difference; TRD, treatment-resistant depression.

[a]The study sample in one reviewed study consisted of depressed patients presenting acutely to an emergency room with suicidal ideation.

[b]One study enrolled patients with BP or MDD; however, only data from patients with BP were included in the meta-analysis.

[c]One report included in the analysis was an open case series ($n = 14$ patients); another report included in the analysis was an open single-arm study ($n = 42$ patients).

[d]Three studies included in the meta-analysis were randomized, cross-over trials of IV ketamine, 0.5 mg/kg. One study was an open trial of IV ketamine, 0.5 mg/kg. One study was an open-label trial of sublingual (SL) ketamine, 10 mg from a 100 mg/ml solution for 5 min and swallowed.

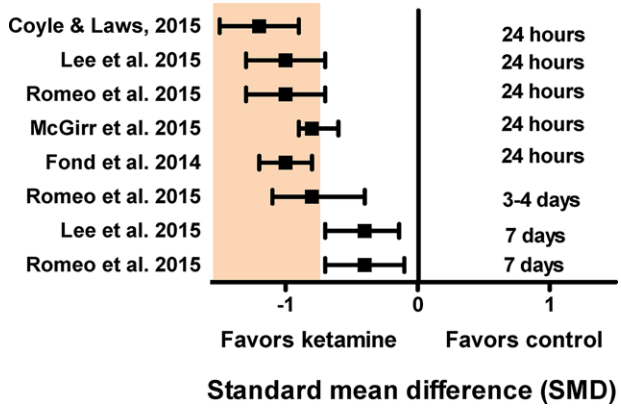

Figure 1. Short-term effect of ketamine on symptoms of depression, reported as standard mean difference (SMD) in five meta-analyses. SMDs (ketamine vs. controls) in the change from baseline in depressive symptom scores (black squares) and 95% confidence intervals (horizontal lines) are shown at 24 hrs, 3–4 days, and 7 days. More negative values indicate larger effect size advantage for ketamine than controls. The shaded area represents a range of SMD values consistent with large effect sizes (at a threshold of −0.8).[72]

after restricting the analysis of results from randomized cross-over trials to the first study phase.

By 14 days postadministration, the efficacy advantages of ketamine over controls were less consistently positive. Coyle and Laws[46] reported a significant and large effect of ketamine for reducing depressive symptoms at 12–14 days (standard mean difference [SMD] −1.7, 95% CI: −2.9 to −0.5); however, Romeo et al.[45] reported a much weaker and nonstatistically significant trend-level advantage of ketamine over controls at 14 days (SMD −0.4, 95% CI: −0.9–0.1). These results were consistent with the very low pooled rates of positive response with ketamine (vs. controls) at 14 days (11 vs. 0%) reported by Newport et al.[42] In that report, between-group differences in response rates were evident only at the level of strong statistical trend at 14 days (OR 4.4, 95% CI: 1.0–18.8, $P = .05$).[42] Moreover, the results of individual placebo-controlled trials of single doses of IV ketamine for depression documented high rates of depressive relapse at 7 days among subjects who responded well initially, and showed that nearly all patients relapsed within 2 weeks postadministration.[25,51–53]

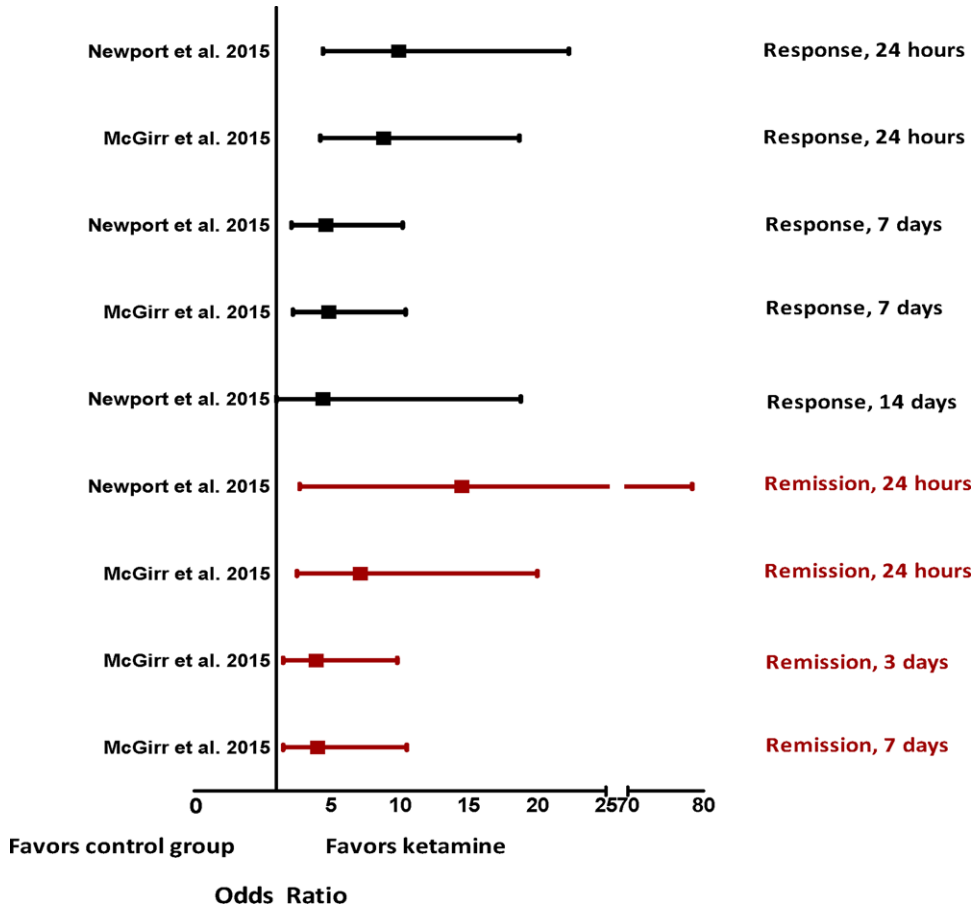

Figure 2. Odds ratios (ORs) for short-term antidepressive response or remission, reported in two meta-analyses. ORs for response (black squares) and remission (red squares) with corresponding 95% confidence intervals (horizontal lines) are shown at 24 hrs, 3 days, 7 days, and 14 days.

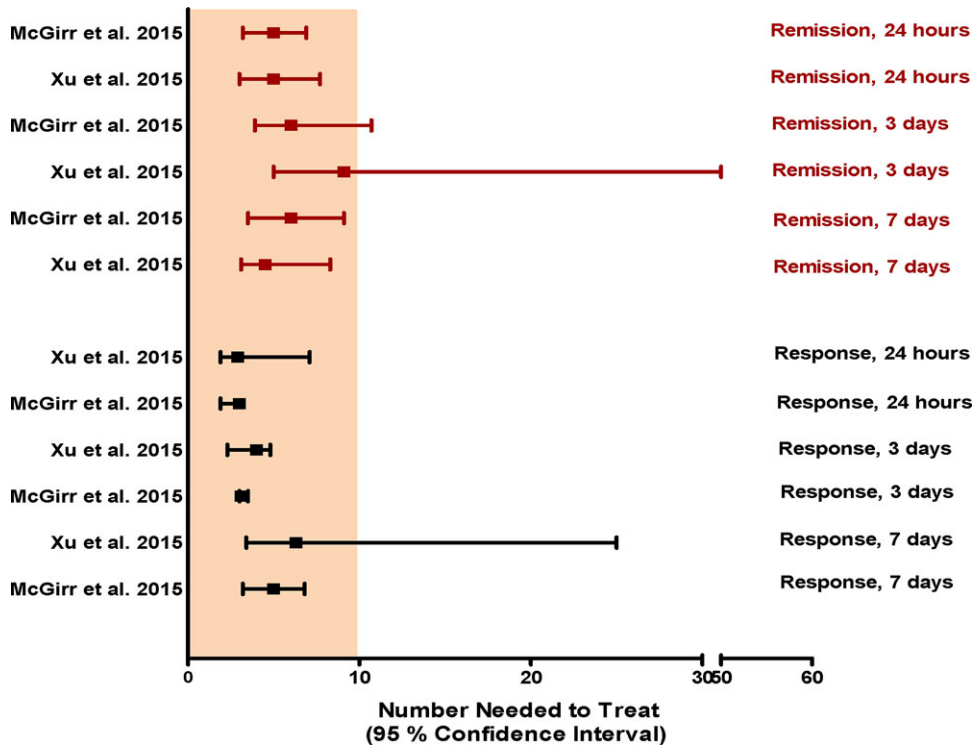

Figure 3. Number needed to treat (NNT) for short-term antidepressive response or remission, reported in two meta-analyses. NNT for response (black squares) and remission (red squares) with corresponding 95% confidence intervals (horizontal lines) are shown at 24 hrs, 3 days, and 7 days. Lesser values indicate larger effect size advantage for ketamine than controls. The shaded area represents a range of NNT values that exceeds the minimal clinically important difference threshold of 10 for antidepressant-placebo comparisons from randomized trials (at a threshold of 10).[73]

SINGLE VERSUS SERIAL ACUTE-PHASE ADMINISTRATION OF KETAMINE

One meta-analysis investigated the differential effects of single and serial IV infusions of ketamine on depressive symptoms.[46] Of the 21 included studies, 17 investigated the clinical effects of single infusions, and four assessed the effects of repeated infusions. Serial ketamine infusion (most commonly six IV infusions provided over 12–14 days) was associated with larger reductions in depressive symptoms (vs. controls) than single ketamine infusion at 4 hrs (SMD −3.3 vs. −1.1), 24 hrs (−4.2 vs. −1.1), 7 days (−2.0 vs. −0.9), and at 12–14 days (−3.0 vs. −0.9).[46] In two individual controlled trials, patients with treatment-resistant depression received approximately thrice-weekly IV ketamine infusions (up to six treatments, at 0.5 mg/kg) and reported response rates of 71–89% following the first infusion.[54,55] These response rates were generally higher than those reported in the single-infusions studies, and were sustained throughout the repeated infusion period; however, relapse rates were high, with mean or median times to relapse of 18–19 days.[54,55] Some study participants had more durable responses to ketamine, including one patient that remained depression-free for 3 months after the final infusion[54]; however, this type of response is likely an extreme outlier based on what existing evidence would suggest is the typical antidepressive response to serially infused ketamine.

The results of two small, open-label studies of twice-weekly ketamine infusions administered over 2 weeks highlight the potential of serially infused ketamine for increasing overall remission rates.[56,57] In the first study of treatment-resistant depressed patients, 5 (50%) of 10 enrolled subjects eventually met predefined criteria for depressive symptom remission.[56] Cumulative remission rates after one, two, and four infusions were 10, 40, and 50%, respectively. Three of the five patients who remitted during the course of receiving serial ketamine infusions experienced depressive relapses over the next 4 weeks despite receiving ongoing treatment with oral antidepressants and, in one case, with ECT. In the second study, 11 of 12 (92%) treatment-resistant depressed subjects were positive treatment responders, and 8 of 12 (67%) subjects remitted.[57] Of the 11 who responded well to ketamine, only five retained their positive response for at least 4 weeks. For the remaining six patients, the mean time to relapse was 16 days following their final infusion.

LACK OF ESTABLISHED DOSE RANGE OR DOSE-RESPONSE RELATIONSHIP

One meta-analysis of nine clinical trials (201 subjects) of low- (six trials, 0.5 mg/kg IV) and very low-dose

ketamine (three separate trials, 0.1–0.4 mg/kg IV, 50 mg intranasal, 0.1–0.5 mg/kg IV, intramuscular, or subcutaneous) showed a significantly larger reduction in depressive symptoms with low-dose ketamine in comparison to very low-dose ketamine at 24 hrs (SMD −1.1, 95% CI: −1.7 to −0.6) and 3 days (SMD −0.8, 95% CI: −1.4 to −0.3), and a trend-level difference favoring low-dose ketamine at 7 days (SMD −0.5, 95% CI: −1.0–0.1).[41] These results suggest that the antidepressive effects of ketamine may be dose-related. The antidepressive effects of four IV doses of ketamine (0.1, 0.2, 0.3, and 0.4 mg/kg infused over 2–5 min) were tested in a small, double-blind, placebo-controlled cross-over pilot study of four depressed subjects, using an ascending dose design.[58] Three of the four enrolled subjects achieved antidepressant response. Positive response occurred at the lowest dose for two subjects, but the greatest improvement in depressive symptoms occurred at the highest dose received. All positive treatment responders relapsed within 7 days. In a recent open study, 14 patients with treatment-resistant MDD were given three IV infusions of ketamine at an initial dose of 0.5 mg/kg, followed by three infusions at a dose of 0.75 mg/kg. All infusions were administered over 45 min.[59] Only one patient (7.1%) had a positive treatment response after the first three infusions, whereas a higher proportion of persons (5 out of 12, 41.7%) who completed all six infusions were classified as having responded positively to treatment. All but one positive treatment responder relapsed within 14 days. To our knowledge, no other dose-finding or dose-escalation studies have been published. We are also unaware of any dose-escalation studies of ketamine in patients who respond suboptimally to conventional antidepressive doses of ~0.5 mg/kg (50 mg for intranasal ketamine).

SHORT-TERM ANTIDEPRESSIVE RESPONSE IN MDD VERSUS BP DEPRESSION

Six meta-analyses presented data on the short-term antidepressive effects of ketamine (vs. controls) within separate MDD and BP subgroups.[42–46,48] As shown in Table 2, ketamine was associated with large reductions in depressive symptoms at 24 hrs in both MDD and BP patients. Interestingly, the effect sizes for reduction of depressive symptoms were numerically greater at 24 hrs for patients with MDD than those with BP in some[43,46] but not all reports.[44,45,48] McGirr et al.[43] reported a

TABLE 2. Results of meta-analyses of short-term studies of ketamine for unipolar (MDD) or bipolar major depression (BP), results by diagnosis group (MDD, BP)

	Main results, by diagnosis						
Reference	Diagnosis group	*N* subjects	Endpoint	Time point	OR (vs. controls)	95% CI	*P*-value
Newport et al. 2015[42]	MDD	142	Response	7 days	MDD 4.7	2.0–11.4	0.001 versus controls
	BP	30			BP 4.2	0.6–27.2	0.14 versus controls
			Transient remission	24 hrs	MDD 15.4	0.8–284.5	0.07 versus controls[a]
					BP 14.0	1.7–111.7	0.01 versus controls
				7 days	MDD 15.4	0.8–284.5	0.07 versus controls[a]
					BP 1.5	0.2–10.5	0.67 versus controls
			Effect measure	Time point	Estimate	95% CI	*P*-value
McGirr et al.2015[43][b]	MDD	149	SMD	24 hrs	MDD −1.1	−1.4 to −0.7	<0.001 versus controls
	BP	34			BP −0.7	−0.9 to −0.5	<0.001 versus controls
							.05 (MDD vs. BP)
Lee et al. 2015[44]	MDD	117	SMD	24 hrs	MDD −0.9	−1.4 to −0.5	<0.001 versus controls
	BP	33			BP −1.3	−1.9 to −0.8	<0.001 versus controls
				7 days	MDD −0.5	−0.8 to −0.1	0.004 versus controls
					BP −0.3	−0.8 to −0.2	0.26 versus controls
Romeo et al. 2015[45]	MDD	69	SMD	24 hrs	MDD -0.9	−1.3 to −0.5	
	BP	34			BP -1.3	−1.8 to −0.7	
				3-4 days	MDD -0.8	−1.3 to −0.3	
					BP -0.8	−1.3 to −0.3	
				7 days	MDD −0.4	−0.8 to −0.1	
					BP −1.3	−1.9 to −0.8	
Fond et al. 2014[48]	MDD	192	SMD	24 hrs	MDD −0.9	−1.2 to −0.6	<0.01 versus controls
	BP	34			BP −1.3	−1.9 to −0.8	<0.01 versus controls
Coyle and Laws, [46]	MDD		Hedge's *g*	24 hrs	MDD −1.4	−1.7 to −1.0	<0.001 versus controls
	BP				BP -0.6	−0.8 to −0.5	<0.001 versus controls

Key: BP, bipolar I or II disorder, depressed phase; MDD, major depressive disorder (unipolar); SMD, standard mean difference.

[a]Data for stratified analyses of the association between ketamine treatment and transient remission in persons with MDD were provided in only one study.[51]

[b]No evidence of heterogeneity regarding either response or remission as discrete endpoints between MDD and BP subsamples at 24 hrs, 3 days, or 7 days.

comparatively larger reduction in depressive symptoms with ketamine (vs. controls) for patients with MDD than those with BP, with between-group differences (MDD vs. BP) occurring at the level of strong statistical trend ($P = .05$) at 24 hrs. By 7 days, nearly all meta-analyses of the effects of ketamine on depressive symptoms showed generally diminished effects relative to those observed at 24 hrs in both patient subgroups (Table 2). As was the case at 24 hrs, some reports showed numerically smaller antidepressive effects with ketamine among subjects with MDD than those with BP at 7 days,[45] whereas others showed just the opposite.[44] In a meta-analysis by Lee et al.,[44] ketamine was associated with significantly greater reductions in depressive symptoms at 7 days in the MDD subgroup, but not the BP subgroup. These results were consistent with the those of a separate meta-analysis by Newport et al.,[42] which showed higher rates of positive treatment response and remission with ketamine (vs. controls) for subjects with MDD than for those with BP at 7 days (Table 2).

KETAMINE EFFECTS ON SUICIDE RISK

The results of some studies in patients with MDD and BP have suggested that a significant reduction in suicidal ideation may occur within hours of IV ketamine administration.[23–26] In a pooled analysis of seven trials that evaluated ketamine effects on suicide measures derived from the suicide component of depression rating scales, a significant reduction in suicide item scores with ketamine (vs. controls) was shown at 24 hrs and at 3 days postadministration, but not at 7 days postadministration.[41] One individual study reported suicide outcomes using the Beck Scale for Suicidal Ideation (BSI) scores, and found significantly lower mean BSI scores with IV ketamine than with IV midazolam (control group) at 48 hrs, but not at 72 hrs or at 7 days.[27] Two uncontrolled studies reported more sustained reductions of suicidal ideations over a 12–14 day period following repeated ketamine infusions that were delivered over a 2-week period.[24,56] No studies, to our knowledge, have investigated the effects of ketamine on suicide attempts or death by suicide when administered to depressed patients.

KETAMINE IS WELL TOLERATED DURING SHORT-TERM, ACUTE-PHASE TREATMENT

Across multiple short-term clinical trials, ketamine was associated with mild and transient adverse effects, the most common of which included increases in blood pressure and heart rate, dry mouth, headache, anxiety, confusion, and dissociation.[41,42,45,48,60] In general, these adverse effects resolved within 2 hrs after completing IV ketamine infusions, and rates of early study discontinuation due to adverse effects were low. In one meta-analysis of 158 ketamine-treated depressed subjects that were included in the safety dataset, drop-out rates were 13% with ketamine and 7% with control interventions.[43] Despite the near-doubling in drop-out rates between ketamine and controls, between-group differences were not statistically significant (OR 2.0, 95% CI: 0.9–4.4, $P = .11$).[43] Across studies of single doses of IV or intranasal ketamine, the severity of psychotomimetic effects, as measured by scores on the Brief Psychiatric Rating Scale (BPRS) positive symptom subscale,[61] was significantly higher with ketamine therapy than controls (Hedge's $g = 0.8$, $P < .0001$, large effect).[42] Dissociative symptom severity, as measured by the Clinician-Administered Dissociative States Scale, was also significantly higher with ketamine administered as single IV or intranasal doses than controls (Hedge's $g = 1.78$, $P < .001$, large effect).[42]

Whether slower than usual infusions of antidepressive doses of IV ketamine can reduce the incidence of cardiovascular and neuropsychiatric adverse effects has received preliminary investigation. In one small open trial (10 subjects), up to four infusions of IV ketamine (0.5 mg/kg) were administered to depressed subjects over 100 min,[56] an infusion time that is much longer than the 40–60 min reported in other studies. None of the subjects experienced significant changes in hemodynamic parameters. There were no significant changes from baseline in Young Mania Rating Scale, BPRS total, or BPRS positive symptom subscale scores. One patient experienced a transient visual hallucination. Dissociation was not assessed using a formal rating scale. Adverse effects assessed by spontaneous report included drowsiness ($n = 4$), dizziness ($n = 3$), dysmegalopsia ($n = 1$), diplopia ($n = 1$), and vertigo ($n = 1$).

KETAMINE VERSUS ECT

There is a paucity of data directly comparing the antidepressive effects of ketamine with those of ECT. We are aware of only one small, open, parallel-group study that compared the very short-term effects of IV ketamine (0.5 mg/kg) and bilateral ECT in 18 patients (nine per treatment group) who were hospitalized with an acute episode of MDD.[62] Study interventions were provided on three occasions total, delivered every 2 days. Depressive symptoms were assessed at baseline, at 24 hrs after each treatment, and at 3 and 7 days following the third (final) treatment. Significant improvement in depressive symptoms, relative to baseline, was observed in each treatment group. Between-group differences in depressive symptom improvement were significantly in favor of ketamine, but only after the first and second treatments. We are not aware of any published randomized head-to-head comparisons of ketamine versus an adequate acute course of ECT.

The efficacy of ketamine as an augmenting agent for depressed patients with MDD or BP undergoing ECT treatment was summarized in a recent meta-analysis of five studies (182 patients, 165 with MDD, 17 with BP). There were no significant differences in depressive symptom improvement (SMD 0.38, 95% CI: −0.41–1.17), or rates of positive response (risk difference [RD] −0.01, 95% CI: −0.11–0.08) or remission

(RD 0.00, 95% CI: −0.08–0.10), between patients who received adjunctive ketamine versus controls. Ketamine augmentation was associated with significantly higher rates of disorientation, confusion or prolonged delirium (OR 6.59, 95% CI: 1.28–33.82, number needed to harm = 3), but not agitation, hypertensive blood pressure changes, or affective switches.[63]

LONGER-TERM SAFETY AND EFFECTIVENESS

There are only case reports or small case series that describe the successful long-term maintenance of an initial antidepressive responses to ketamine using repeated administrations.[10–14] In general, the cases described were of profoundly treatment-resistant depressed patients who responded initially to a single acute-phase administration of IV or intramuscular ketamine. Repeated administrations of ketamine were then scheduled on an individualized basis. We are aware of no controlled or uncontrolled studies of repeated ketamine administration for long-term maintenance of initial antidepressive responses.

There is also a nearly complete lack of data regarding the long-term safety of the repeated administration of ketamine for depression. Major long-term safety concerns about ketamine stem mainly from its abuse potential. Ketamine is a dissociative anesthetic that has a well-documented abuse liability after prolonged administration.[64,65] Cases of incident ketamine abuse or dependence have not been reported from controlled studies. However, there are recent case reports of patients who received antidepressive treatment with ketamine acutely, followed by escalation of ketamine use with repeated dosing, with the eventual development of ketamine dependence.[66,67] A few risk factors for ketamine dependence in the general population have been identified, including young adulthood status and the recreational use of other types of substances.[68] No studies to our knowledge have identified risk factors specifically for the development of ketamine dependence when ketamine is used as an antidepressant, although having a current comorbid substance-use disorder may be expected to increase such risk.

Additional long-term safety concerns with ketamine for treating depression stem from preclinical studies and from adverse effects observed in long-term recreational users of ketamine. These risks include neurocognitive dysfunction, the development of urinary cystitis, and adverse changes in brain structure and function.[69–72] Very few studies have assessed the risks of these potential concerns with ketamine in depressed patients. In a secondary analysis of data from a randomized short-term antidepressive efficacy trial,[73] neurocognitive performance was measured using components of the MATRICS Consensus Cognitive Battery[74] before study drug infusion, and at 24, 48, and 72 hrs, and 7 days postadministration.[73] No differential effect of treatment on neurocognitive performance was observed. A secondary analysis of data from a separate short-term clinical trial of open-label IV ketamine showed that a single ketamine dose was associated with a small but statistically significant reduction in delayed recall at 40 min postinfusion, but ketamine effects on cognitive performance beyond this time point were not reported.[75] By contrast, six repeated open-label IV ketamine infusions administered over 2 weeks to 15 patients with treatment-resistant depression was associated with significant improvements in measures of visual and working memory[57]; however, the improvements in cognition were accounted for by improvements in depressive symptoms. We are unaware of any published reports quantifying the risk of treatment-emergent urinary cystitis or the long-term effects of ketamine treatment on brain structure or function in depressed persons receiving treatment with ketamine.

DISCUSSION

The evidence base to date would suggest measured enthusiasm regarding the therapeutic potential of ketamine for treatment-resistant MDD or BP depression. For very short-term use, the available data shows a clear and consistent antidepressive effect of ketamine treatment, relative to a variety of control conditions, beginning within hours of administration, and lasting up to 7 days after a single dose. Effect sizes during short-term follow-up (up to 7 days) were clinically significant across treatment outcomes, based on accepted definitions.[76,77] It is not yet clear if the responsiveness to ketamine therapy differs to a clinically significant degree in patients with BP from those with MDD. However, even if ketamine is eventually found to be slightly less effective for patients with treatment-resistant bipolar depression than for unipolar depression, modest differences in efficacy may not be meaningful given that there are so few established options for treating pharmaco-resistant bipolar depressed states. Nevertheless, the response rates associated with ketamine for BP depression stands in marked contrast to the clear differential response rate of conventional antidepressants in unipolar versus bipolar depression.[78]

The need for more effective therapeutics is also pressing for patients who do not respond clinically to, or cannot tolerate, standard antidepressive treatments. Regardless of underlying mood disorder, nearly all studies of ketamine for MDD or BP depression enrolled patients that were resistant to conventional antidepressant or mood stabilizing medications. A putative antisuicidal effect of ketamine has also garnered deserved attention, given the limitations of most existing therapeutics for reducing suicide risk in depressed patients. From the viewpoint of very short-term antidepressive benefits for persons suffering from severe and treatment-resistant depressive states, the enthusiasm about ketamine is understandable and may even appear to justify its routine adoption into clinical care.

Methodological factors that may limit the internal validity of clinical trial results with ketamine for

depression have been previously discussed, including the possibility of inadequate blinding due to ketamine side-effects.[9,17] But there are additional limitations with the available knowledge base that temper our enthusiasm and raise significant concerns about the early adoption of ketamine into routine clinical practice, outside of research settings.

The first major concern deals with generalizability of the study findings. Controlled trials of ketamine for depression were conducted at research centers with sufficient resources to safely test and evaluate novel therapeutics, under the auspices of rigorous, protocol-driven monitoring procedures and accountability to institutional review boards. Across individual trials, major exclusion criteria included alcohol- or other substance-use disorders, psychotic illness features, unstable medical illnesses, and serious risk for suicide. On the one hand, these are sensible exclusion criteria and are precautions that one would apply to any investigational drug for depressed patients. On the other hand, the proportion of screened subjects who were deemed ineligible to participate in randomized, placebo-controlled trials of ketamine for MDD or BP depression ranged from 21 to 67%,[25,51–53,79–81] and no short- or long-term effectiveness data on use of ketamine for depression derived from naturalistic, nonacademic treatment settings are available. We are left to wonder how well the results of published randomized trials of ketamine for depression apply to routine practice and to the specific types of patients served in those settings. There are additional concerns that focus on potential drug–drug interactions with medications not allowed in clinical trial investigation that may impact overall antidepressive response or safety. For example, recent data have suggested that concomitant benzodiazepine use may reduce ketamine treatment response.[82] Additionally, it is unclear if the concomitant use of benzodiazepines, atypical antipsychotic drugs, and mood stabilizers contributed to the conspicuously low rate of positive treatment response (7.1%) associated with the 0.5 mg/kg dose in the IV ketamine dose-escalation study reviewed earlier.[59] Such data may impact how adjunctive medications will be monitored in the context of ketamine treatment.

Similar limitations in the generalizability of study findings apply to the short-term data suggesting that ketamine may exert antisuicidal effects. Many of the early studies of IV ketamine were focused specifically on antidepressive effects (not suicidal ideation), and nearly all of these studies excluded actively suicidal patients from participating. Crucially, no studies, to our knowledge, have investigated the antisuicidal effects of repeated infusions of ketamine beyond the acute phase of treatment, an important clinical consideration given that the period of increased suicide risk extends beyond the acute phase of treatment into the initial weeks following discharge from acute psychiatric care—a time window during which risk for completed suicide is especially high.[83]

The second major concern is the brief duration of the antidepressive effects of ketamine. This represents perhaps the most critical limitation of ketamine as an antidepressive treatment. Most patients who respond well to a single dose of ketamine may be expected to relapse within 2–3 weeks.[25,51–53] Even with more aggressive treatment using repeated short-term ketamine infusions administered for up to 2 weeks, relapses still occurred after 18–19 days, on average, following the last ketamine administration,[54,55] and 55–89% of patients may be expected to relapse within 1 month.[54,56,57]

All accepted antidepressive treatments are characterized by a reasonably clear means of sustaining clinical benefit over the longer term among those who initially respond well to the treatment.[84–86] By contrast, the safest and most effective methods of prolonging initial antidepressive responses to ketamine are unclear. Such strategies may eventually include treating acute depressive symptoms with ketamine and then substituting other medications that impact glutamatergic neurotransmission but have lower potential for psychomimetic adverse effects and abuse for longer-term maintenance treatment. Some controlled investigations have provided proof-of-concept for studying the antidepressive effectiveness of add-on riluzole and D-cycloserine following acute treatment with ketamine.[87,88] However, this evidence is only preliminary and, as reviewed recently, these and other NMDA receptor modulators have been tested individually for their acute antidepressive effects but have not been shown to be as consistently effective as ketamine for treating depression in adults.[42,49]

The administration of repeated ketamine infusions to sustain initial positive responses has some appeal, since it is analogous to the use of maintenance pharmacotherapy or ECT. For all practical purposes, these accepted practices represent the repeated administration of an effective and well-tolerated acute-phase treatment over the long term in order to prevent relapses. However, maintenance pharmacotherapy and ECT have become accepted practices after rigorous clinical investigation and, in some cases, years of clinical experience. As reviewed earlier, there are case reports and small case series describing successful maintenance of acute antidepressive responses to ketamine using repeated infusions, but the effectiveness of this or any practice cannot be established on the basis of anecdotal reports. Instead, continuation- and maintenance-phase studies of ketamine in patients with MDD or BP who responded well acutely are urgently needed. Until data from such studies become available, it must be concluded that there is no good evidence of the effectiveness of providing serial ketamine administrations for purposes of maintaining initial antidepressive benefits.

A third major concern deals with the uncertainty about ketamine's safety profile. The safety of ketamine for the acute treatment of MDD or BP depression is reassuring, based on the results of short-term trials that enrolled carefully selected subjects with MDD or BP depression, and perhaps on decades of its safe use as an

anesthetic.[89] But only a limited number of very short-term exposures to ketamine for depression have been studied. The largest meta-analysis of ketamine for depression that included a review of safety data involved 201 patients from nine short-term studies.[41] By comparison, the safety datasets for most approved antidepressants number several hundred to more than a thousand patients with months and in some cases a year or more of follow-up.[84,90] Such data make it possible to detect at least some infrequent but potentially severe adverse effects, as well as adverse effects that require a longer time to develop. Unfortunately, there are no safety datasets in the case of ketamine for depression that allow for the systematic evaluation of these types of potential adverse effects.

The striking lack of data on the long-term safety of ketamine for depression is particularly troubling from the perspective of early adoption of ketamine into routine clinical work. The potential long-term safety concerns with ketamine are not benign and include the development of ketamine abuse or dependence. Ketamine's addiction profile is characterized by physiological dependence, a withdrawal syndrome characterized by psychotic symptoms, and tolerance to its intoxicating effects that can lead to respiratory depression in overdose situations.[64,91,92] The abuse profile and the lack of a reassuring profile of safety in overdose with ketamine in settings of nonmedical use raise concerns that these worrisome effects may occur in the setting of poorly monitored repeated infusions of ketamine for treating depressed patients, particularly those with comorbid substance-use disorders. The risks of such outcomes may seem low based on an absence of reports of new-onset ketamine abuse or dependence from short-term trials; however, controlled trials of ketamine for depression provided single or only a few exposures to ketamine, and excluded persons with substance-use disorders. On that basis, the absence of such safety signals in patients who are at low baseline risk for developing ketamine-use disorders who received very few ketamine exposures may be falsely reassuring.

A fourth major concern is that, for the time being, little formal regulatory safety monitoring of ketamine for depression currently exists outside of clinical trials. As pointed out earlier, clinical trials of ketamine for depression were conducted under the auspices of protocol-driven informed consent and monitoring procedures, and accountability to institutional review boards. These safety features are standard practice for the conduct of clinical trials.[93] Outside of these settings, the safety monitoring of ketamine, still an investigational drug for depression, must instead rely on passive surveillance through the voluntary reporting of adverse events by patients and clinicians. Even in countries with established pharmacovigilance programs, adverse outcomes, including serious adverse events, are notoriously underreported.[94]

CONCLUSIONS

In our view, there is insufficient empirical support for the early adoption of ketamine into routine practice. Pragmatically, the early adoption of ketamine into routine practice has already arrived, whether or not the field is truly ready. Until more data from longer-term studies become available, the early adoption of ketamine for clinical use must be measured in clinical and patient expectations and with informed consent. There is currently no FDA approval of ketamine for depression. Therefore, the clinical use of ketamine for depression will be off-label with the potential for significant short-term benefit, as well as possible—but unknown—longer-term benefit in a high-risk population. Careful screening, management, and follow-up of severely depressed patients who receive ketamine therapy will be necessary, in addition to managing patient and caregiver expectations with attention to the potential for nonresponse and treatment-emergent adverse events. To help the field move forward in best designing and modifying ketamine therapy protocols for treatment-resistant depression, there may be merit in studying and publishing effectiveness and safety results of ketamine therapy for depression in naturalistic cohorts. This approach may also provide a means of generating preliminary longer-term safety data for ketamine when used as an antidepressive therapy. Such efforts would require the development of clinical protocols with standardized screening, clinical phenotyping, and follow-up procedures, as well as institutional review board approval.

REFERENCES

1. Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci 2006;7:137–151.
2. Altshuler LL, Frye MA, Gitlin MJ. Acceleration and augmentation strategies for treating bipolar depression. Biol Psychiatry 2003;53:691–700.
3. Abdallah CG, Averill LA, Krystal JH. Ketamine as a promising prototype for a new generation of rapid-acting antidepressants. Ann N Y Acad Sci 2015;1344:66–77.
4. Øye I. Ketamine analgesia, NMDA receptors and the gates perception. Acta Anaesthesiol Scand 1998;42:747–749.
5. Clements JA, Nimmo WA. Pharmacokinetics and analgesic effect of ketamine in man. Br J Anaesth 1981;52:27–30.
6. Geisslinger G, Hering W, Thomann P, et al. Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. Br J Anaesth 1993;70:666–671.
7. Reardon S. Rave drug tested against depression. Nature 2015;517:130–131.
8. Kellner CH, Greenberg RM, Ahle GM, Liebman LS. Electroconvulsive therapy is a standard treatment; ketamine is not (yet). Am J Psychiatry 2014;171:796.
9. Rasmussen KG. Has psychiatry tamed the "ketamine tiger?" Considerations on its use for depression and anxiety. Prog Neuropsychopharmacol Biol Psychiatry 2016;64:218–224.

10. Cusin C, Hilton GQ, Nierenberg AA, Fava M. Long-term maintenance with intramuscular ketamine for treatment-resistant bipolar II depression. Am J Psychiatry 2012;169:868–869.
11. Messer M, Haller IV. Maintenance ketamine treatment produces long-term recovery from depression. Primary Psychiatry 2010;17:48–50.
12. Messer M, Haller IV, Larson P, et al. The use of a series of ketamine infusions in two patients with treatment-resistant depression. J Neuropsychiatry Clin Neurosci 2010;22:442–444.
13. Segmiller F, Ruther T, Linhardt A, et al. Repeated S-ketamine infusions in therapy resistant depression: a case series. J Clin Pharmacol 2013;53:996–998.
14. Szymkowicz SM, Finnegan N, Dale RM. A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression. J Affect Disord 2013;147:416–420.
15. Schatzberg A. A word to the wise about ketamine. Am J Psychiatry 2014;171:262–263.
16. Lawrence J. The secret life of ketamine. Pharm J 2015;294:7854–7855. Available at: http://www.pharmaceutical-journal.com/news-and-analysis/features/the-secret-life-of-ketamine/20068151.article. Accessed on: December 29, 2015.
17. aan het Rot M, Zarate CA Jr., Charney DS, Mathew SJ. Ketamine for depression: where do we go from here? Biol Psychiatry 2012;72:537–547.
18. Rush AJ. Ketamine for treatment-resistant depression: ready or not for clinical use? Am J Psychiatry 2013;170:1079–1081.
19. Zarate CA Jr., Niciu MJ. Ketamine for depression: evidence, challenges and promise. World Psychiatry 2015;14:358–350.
20. Ketamine Advocacy Network. Available at: http://www.ketamine advocacynetwork.org/. Accessed on: December 29, 2015.
21. Hamilton J. Club drug ketamine gains traction as a treatment for depression. National Public Radio. Available at: http://www.npr.org/sections/health-shots/2015/09/28/443203592/club-drug-ketamine-gains-traction-as-a-treatment-for-depression. Accessed on: December 29, 2015.
22. Pollack A. Special K, a hallucinogen, raises hopes and concerns as a treatment for depression. The New York Times 2014. Available at: http://www.nytimes.com/2014/12/10/business/special-k-a-hallucinogen-raises-hopes-and-concerns-as-a-treatment-for-depression.html?_r=0. Accessed on: December 29, 2015.
23. Diazgranados N, Ibrahim L, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an NMDA antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 2010;71:1605–1611.
24. Price RB, Nock M, Charney DS, Matthew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry 2009;66:522–526.
25. Zarate C, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry 2012;71:939–946.
26. Ballard ED, Ionescu DF, Vande Voort JL, et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res 2014;58:161–166.
27. Murrough JW, Soleimani L, deWilde KE, et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med 2015;45:3571–3580.
28. Reinstatler L, Youssef NA. Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature. Drugs R D 2015;15:37–43.
29. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. STAR*D project results: a comprehensive review of findings. Curr Psychiatry Rep 2007;9:449–459.
30. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59(6):530–537.
31. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60(3):261–269.
32. Frye MA, Prieto ML, Bobo WV, et al. Current landscape, unmet needs, and future directions for treatment of bipolar depression. J Affect Disord 2015;169(Suppl 1):S17–S23.
33. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006;163:217–224.
34. Post RM, Leverich GS, Altshuler LL, et al. An overview of recent findings of the Stanley Foundation Bipolar Network, pt 1. Bipolar Disord 2003;5:310–319.
35. Gitlin MJ, Swendsen J, Heller TL, Hammen C. Relapse and impairment in bipolar disorder. Am J Psychiatry 1995;152:1635–1640.
36. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001;158:420–426.
37. Sylvia LG, Shelton RC, Kemp DE, et al. Medical burden in bipolar disorder: findings from the Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE). Bipolar Disord 2015;17:212–223.
38. Tondo L, Isacsson G, Baldessarini R. Suicidal behavior in bipolar disorder: risk and prevention. CNS Drugs 2003;17:491–511.
39. Griffiths JJ, Zarate CA, Rasimas JJ. Existing and noval biological therapeutics in suicide prevention. Am J Prev Med 2015;47(3S2):S195–S203.
40. Diamond PR, Farmery AD, Atkinson S, et al. Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. J Psychopharmacol 2014;28:536–544.
41. Xu U, Hackett M, Carter G, et al. Effects of low-dose and very low-dose ketamine among patients with major depression: a systematic review and meta-analysis. Int J Neuropsychopharmacol November 17, 2015. pii: pyv124. doi:10.1093/ijnp/pyv124. [Epub ahead of print].
42. Newport DJ, Carpenter LL, McDonald WM, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry 2015;172:950–966.
43. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med 2015;45:693–704.
44. Lee EE, Della Selva MP, Liu A, Himelhoch S. Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. Gen Hosp Psychiatry 2015;37:178–184.
45. Romeo B, Choucha W, Fossati P, Rotge JY. Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. Psychiatry Res 2015;230:682–688.
46. Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum Psychopharmacol 2015;30:152–163.
47. Parsaik AK, Singh B, Khosh-Chashm D, Mascarenhas SS. Efficacy of ketamine in bipolar depression: systematic review and meta-analysis. J Psychiatr Pract 2015;21:427–435.

48. Fond G, Loundou A, Rabu C, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology (Berl) 2014;231:3663–3676.
49. Caddy C, Giaroli G, White TP, Shergill SS, Tracy DK. Ketamine as the prototype glutamatergic antidepressant: pharmacodynamics actions, and a systematic review and meta-analysis of efficacy. Ther Adv Psychopharmacol 2014;4:75–99.
50. Murrough JW. Ketamine as a novel antidepressant: from synapse to behavior. Clin Pharm Ther 2012;91:303–309.
51. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47:351–354.
52. Zarate CA Jr, Singh JB, Carlson NE, et al. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006;63:856–864.
53. Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry 2010;67:793–802.
54. aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry 2010;67:139–145.
55. Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry 2012;74:250–256.
56. Rasmussen KG, Lineberry TW, Galardy CW, et al. Serial infusions of low-dose ketamine for major depression. J Psychopharmacol 2013;27:444–450.
57. Shiroma PR, Albott CS, Johns B, et al. Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. Int J Neuropsychopharmacol 2014;17:1805–1813.
58. Lai R, Katalinic N, Glue P, et al. Pilot dose-response trial of i.v. ketamine in treatment-resistant depression. World J Biol Psychiatry 2014;15:579–584.
59. Cusin C, Ionescu DF, Pavone KJ, et al. Ketamine augmentation for outpatients with treatment-resistant depression: preliminary evidence for two-step intravenous dose escalation. Aust N Z J Psychiatry February 18, 2016. pii: 0004867416631828. [Epub ahead of print].
60. Wan L-B, Levitch CF, Perez AM, et al. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. J Clin Psychiatry 2015;76:247–252.
61. Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep 1962;10:799–812.
62. Ghasemi M, Kazemi MH, Yoosefi A, et al. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. Psychiatry Res 2014;215:355–361.
63. McGirr A, Berlim MT, Bond DJ, et al. A systematic review and meta-analysis of randomized controlled trials of adjunctive ketamine in electroconvulsive therapy: efficacy and tolerability. J Psychiatr Res 2015;62:23–30.
64. Lodge D, Mercier MS. Ketmaine and phencyclidine: the good, the bad and the unexpected. Br J Pharmacol 2015;172:4254–4276.
65. Bobo WV, Miller SC. Ketamine as a preferred substance of abuse. Am J Addict 2002;11:332–334.
66. Schak KM, Vande Voort JL, Johnson EK, et al. Potential risks of poorly monitored ketamine use in depression treatment. Am J Psychiatry 2016;173:215–218.
67. Liu JX, Zerbo E, Ross S. Intensive ketamine use for multiple years: a case report. Am J Addict 2015;24:7–9.
68. Kalsi SS, Wood DM, Dargan PI. The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. Emerg Health Threats J 2011;4:7107. doi: 10.3402/ehtj.v4i0.7107.
69. Morgan CJ, Muetzelfeldt L, Curran HV. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. Addiction 2010;105:121–133.
70. Wood D. Ketamine and damage to the urinary tract. Addiction 2013;108:1515–1516.
71. Wang C, Zheng D, Xu J, Lam W, Yew DT. Brain damages in ketamine addicts as revealed by magnetic resonance imaging. Front Neuroanat 2013;7:23. doi:10.3389/fnana.201300023
72. Liao Y, Tang J, Fornito A, et al. Alterations in regional homogeneity of resting-state brain activity in ketamine addicts. Neurosci Lett 2012;522:36–40.
73. Murrough JW, Burdick KE, Levitch CF, et al. Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial. Neuorpsychopharmacology 2015;40:1084–1090.
74. Neuchterlein KH, Green MF, Kern RS, et al. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. Am J Psychiatry 2008;165:203–213.
75. Murrough JW, Wan LB, Iacoviello B, et al. Neurocognitive effects of ketamine in treamtent-resistant major depression: association with antidepressant response. Psychopharmacol (Berl) September 11, 2013. [Epub ahead of print].
76. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.
77. Duru G, Fantino B. The clinical relevance of changes in the Montgomery-Asberg Depression Rating Scale using the minimum clinically important difference approach. Curr Med Res Opin 2008;24:1329–1335.
78. Frye MA. Clinical practice. Bipolar disorder—a focus on depression. N Engl J Med 2011;364:51–59.
79. Lapidus KA, Levitch CF, Perez AM, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry 2014;76:970–976.
80. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 2013;170:1134–1142.
81. Sos P, Klirova M, Novak T, et al. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. Neuroendocrinol Lett 2013;34:287–293.
82. Frye MA, Blier P, Tye SJ. Concomitant benzodiazepine use attenuates ketamine response: implications for large scale study design and clinical development. J Clin Psychopharmacol 2015;35:334–336.
83. Qin P, Nordentoft M. Suicide risk in relation to psychiatric hospitalization: evidence based on longitudinal registers. Arch Gen Psychiatry 2005;62:427–432.
84. Borges S, Chen YF, Laughren TP, et al. Review of maintenance trials for major depressive disorder: a 25-year perspective from the US Food and Drug Administration. J Clin Psychiatry 2014;75:205–214.
85. Miura T, Noma H, Furukawa TA, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry 2014;1:351–359.
86. Rabheru K. Maintenance electroconvulsive therapy (M-ECT) after acute response: examining the evidence for who, what, when, and how? J ECT 2012;28:39–47.
87. Ibrahim L, Diazgranados N, Franco-Chaves J, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology 2012;37:1526–1533.

88. Kantrowitz JT, Halberstam B, Grangwisch J. Single-dose ketamine followed by daily D-cycloserine in treatment-resistant bipolar depression. J Clin Psychiatry 2015;76:737–738.
89. Radvansky BM, Puri S, Sifonios AN, Eloy JD, Le V. Ketmaine—a narrative review of its uses in medicine. Am J Ther April 24, 2015. [Epub ahead of print].
90. Gartlehner G, Thieda P, Hansen RA, et al. Comparative risk for harms of second-generation antidepressants : a systematic review and meta-analysis. Drug Saf 2008;31:851–865.
91. Critchlow DG. A case of ketamine dependence with discontinuation symptoms. Addiction 2006;101:1212–1213.
92. Lankenau SE, Sanders B, Bloom JJ, et al. Prevalence and patterns of prescription drug misuse among young ketamine injectors. J Drug Issues 2007;37:717–736.
93. Iltis AS, Misra S, Dunn LB, et al. Addressing risks to advance mental health research. JAMA Psychiatry 2013;70:1363–1371.
94. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006;29:385–396.