Ketamine and Depression: A Review

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Ketamine, via intravenous infusions, has emerged as a novel therapy for treatment-resistant depression, given rapid onset and demonstrable efficacy in both unipolar and bipolar depression. Duration of benefit, on the order of days, varies between these subtypes, but appears longer in unipolar depression. A unique property is reduction in suicidality although data are more limited. Strategies to extend duration, via multiple doses, maintenance treatment, or subsequent augmenting medications have yielded mixed results. There is a relative paucity of data regarding alternate methods of administration such as intramuscular, intranasal, and oral routes, though preliminary results are promising. Adverse effects most reliably incl ude dissociative and sympathomimetic effects, both transient and mild, and suggest good tolerability. Ketamine's unique effects may represent an opportunity for a paradigm shift in the pharmacologic treatment of depression.

Keywords: *Ketamine; treatment-resistant depression; suicide; NMDA; glutamate; rapid acting; review.*

Despite significant progress, depression remains a common and disabling condition that affects millions, leading to increased primary care visits and decreased productivity (Baune, Adrian, & Jacobi, 2007). Both psychotherapy and antidepressant pharmacotherapy are evidence-based treatments recommended by experts and treatment guidelines (Gelenberg et al., 2010). For those with more severe depression, pharmacotherapy is often required for recovery. However, inadequate response and lack of remission are common, and characterize treatment-resistant depression (TRD; Keitner and Mansfield, 2012). The current pharmacopoeia available to clinicians is primarily based on modulation of serotonergic, noradrenergic, and dopaminergic transmission in the brain, with first line agents primarily consisting of selective serotonin reuptake inhibitors (SSRIs; Keitner & Mansfield, 2012). As demonstrated by the STAR*D study, multiple trials of medications are frequently required to achieve remission, and despite this, about 35% of patients remain symptomatic after several successive interventions (Rush et al., 2006; Olin, Jayewardene, Bunker, & Moreno, 2012). When monoamine modulating antidepressant medications do work, there is typically a delay of weeks before response is achieved. In those first few weeks, antidepressant treatment may increase risk of suicidal behavior, and possibly including completed suicide (Björkenstam et al., 2013). With the lack of rapid response from existing medications, and indeed the apparent risk until such response, there is urgent need for development of rapid acting treatment alternatives for depression (Monteggia, Gideons, & Kavalali, 2013). For severe depression, electroconvulsive therapy (ECT) is the only somatic intervention with the potential for more rapid treatment effect, however concern over adverse effects limit use. Alternative approaches utilizing direct electrical modulation, including repetitive transcranial magnetic stimulation (rTMS), trigeminal nerve stimulation, and deep brain stimulation (Cook, Espinoza, & Leuchter, 2014) as well as magnetic seizure therapy and vagal nerve stimulation (Wani, Trevino, Marnell, & Husain, 2013) are promising in terms of efficacy, but have not been shown consistently to have a more rapid onset of effect than pharmacotherapy.

Studies suggest a role for the glutamate system in regulation of mood (Skolnick et al., 1996; Matthews, Henter, & Zarate, 2012; Machado-Vieira, Salvadore, Diazgranados, & Zarate, 2009), and particular promise

has been generated from studies looking at the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine for this novel indication (Artigas, 2013; Zarate et al., 2013; Mathew, Manji, & Charney, 2008). Ketamine was developed in 1963, first tested on humans in 1964, and FDA approved for roles in anesthesia in 1970 (Reich et al., 1989; JHP Pharmaceuticals, 2009). It was not until 2000 that ketamine was concretely demonstrated in the literature to have antidepressant properties (Berman et al., 2000). Ketamine has shown a large effect size, with onset on the order of hours, and duration of effect of approximately one week (Zarate et al., 2006). Reduction in suicidal thoughts is further described, similarly within hours of administration (Price et al., 2009; Price et al., 2014).

A significant limitation exists in that ketamine is only FDA-approved for intravenous (IV) or intramuscular (IM) use in induction or maintenance of anesthesia, making administration in less controlled settings difficult. While most studies on ketamine thus far have looked at longer IV infusions, other routes have shown promise for increasing patient access to ketamine (Larkin & Beautrais, 2011; Harihar, Dasari, & Srinivas, 2013; Lara, Bisol, & Munari, 2013; Lapidus et al., 2014; Iglewicz et al., 2014).

This article reviews the extant literature regarding use of ketamine as an antidepressant, highlighting its role as a rapid acting agent for unipolar and bipolar depression. We report on and analyze efficacy, with additional attention to durability of response, improvement in suicidality, routes of administration, dosing protocols, and safety. Different stereoisomeric forms of ketamine are also reviewed given the possibility that one form may be associated with fewer dissociative effects. We conclude with recommendations for future study design as well as potential off-label use in less structured settings. Detailed discussions on the history and neuropharmacology of ketamine, and the glutamate theory of depression are not included; the reader is referred to previous publications on these topics (Domino et al., 2010; Krystal, Sanacora, & Duman, 2013; Caddy. Giaroli, White, Shergill, & Tracy, 2014; Naughton, Clarke, Olivia, Cryan, & Dinan, 2014).

Materials and Methods

PubMed.gov was searched using the term "ketamine depression," with the filter of English language, through March 2015, yielding 1042 studies. Studies were excluded that did not investigate clinical use of ketamine in humans for treatment of depression, either unipolar or bipolar, or suicidality. Those utilizing ketamine as an anesthetic or augmenting agent for, or in combination with, ECT or rTMS were excluded, as were studies regarding the use of ketamine as an augmenting agent for psychotherapy, for purposeful alteration of consciousness, or in regards to ketamine misuse. The remaining articles were further reviewed for pertinent references. Data on depression response rates were combined and recalculated to include intent to treat (ITT) analysis, accounting for differences between rates reported in the studies and in this review. To assess for ongoing or planned studies a search of ClinicalTrials.gov was performed with the terms "ketamine depression."

Results

Using the above search criteria, a total of 61 publications from PubMed.gov and 96 from ClinicalTrials.gov were identified for inclusion in this review.

Study population and methodology

Of these 61 studies, 46 utilized the IV route of administration, accounting for over 450 patients in total. A further 18 studies utilized IM, oral, intranasal, sublingual, or subcutaneous treatment in over 100 patients. Nearly all publications reported use of racemic ketamine, with only 13 patients in total receiving *S*-ketamine (Denk, Rewerts, Holsboer, Erhardt-Lehmann, & Turck, 2011; Paul, Schaaf, Padberg, Moller, & Frodl, 2009; Segmiller et al., 2013; Paslakis, Gilles, Meyer-Lindenberg, & Deuschle, 2010). Most studies utilized only one administration of ketamine, though five open label investigations (OLI) and one randomized control trial (RCT) did assess multiple doses, from one to three times per week, for up to three weeks. The majority of publications reported on patients with unipolar depression, though bipolar depression was also represented in ten. Given the differences in presentation, etiology, and response between these two types of depression, these are considered separately. Save for a minority of case studies (Table 5; Suppl. Table 1), articles utilized one or more validated depression rating scales, including the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979), Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), or Clinical Global Impression scale (CGI; Guy et al., 1976). The only study to report on the pediatric population utilized

ratings scales more specific to that population (Papolos, Teicher, Faedda, Murphy, & Mattis, 2013). Studies of ketamine in hospice patients also utilized the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) (Table 5; Suppl. Table 1).

We focused on the categorical outcome of response—defined as >50% reduction—within 24 hours since this was most commonly the primary outcome measure referred to in the studies reviewed. Remission was not consistently reported, and was also variably defined. Notably, too, the majority of these studies were performed in patients with treatment resistance, and while definitions varied between studies, this typically was qualified by at least two, if not more, failed trials of adequate dose and duration antidepressant treatment. Some also included failure of ECT and only few described failure of adequate psychotherapy. To objectively assess such trials, many studies utilized the Antidepressant Treatment History Form (Sackeim, 2001). Unless otherwise specified below, we accept the authors' descriptions of TRD. Of the studies employing ketamine IV infusions, most utilized racemic ketamine 0.5mg/kg over 40 minutes, with several more varying the duration from 30 to 60 minutes. For the sake of brevity, we abbreviate this protocol as KET in the rest of this document.

Efficacy From Single Infusions

The eight RCTs investigating IV ketamine included six crossover studies, all with saline placebo, and two parallel group designs, both with active controls (Table 1). All but one utilized a single ketamine infusion. Six were done in patients with unipolar depression and the other two in patients with bipolar depression. The larger of the two active control and blinded RCTs utilized midazolam and included 72 patients in a 2:1 ratio of ketamine : midazolam, all with treatment-resistant unipolar depression, who were discontinued from any concomitant medications. In the ketamine group, 64% responded at 24 hour follow-up, compared to 28% in the midazolam group (Murrough, Perez, Mathew, & Charney, 2013). Response rate in the ketamine arm fell below 50% after day three. The other active control blinded RCT utilized ECT as the comparison condition, demonstrating a more rapid onset of action and greater response rates at 24 hours in the ketamine arm; KET elicited 78% response versus 11% with ECT (Ghasemi et al., 2013). The other placebo controlled studies in unipolar depression generally recruited fewer patients, and found 24 hours outcomes of 45% with KET versus 2% with saline; and 4 hour outcomes of 29% versus 7% (Figure 1).

Both studies of patients with bipolar depression were performed by the same group and found more rapid onset, but shorter duration, of benefit (Table 1). Response was 58% in the first four hours, but by day one, half of the cohort no longer met this criterion (Figure 2). While studies in unipolar depression generally discontinued psychotropic medications and provided a washout period, those in bipolar depression maintained patients on therapeutic levels of mood stabilizers, either lithium or valproic acid, which may have had an effect on outcome.

Limitations in blinding and control selection are prevalent in all but Murrough et al. (2013), who utilized midazolam as an active control. The trial with ECT as the active control (Ghasemi et al., 2013) did not appear to have had strict patient blinding, despite blinding of the treatment team. Valentine et al. (2011) was the opposite, with study personnel being aware of experimental conditions. Other studies utilized a saline placebo, but the apparent ease in recognition of dissociative effects likely sabotaged the blind.

Seventeen OLIs describe outcomes in unique depressed patients after KET, of which sixteen were principally in unipolar depression (Table 2). Nearly half of the over 250 unipolar depression patients, 95% of whom were categorized as TRD, responded within 4-6 hours after KET (Figure 3). At 24 hours, the overall response rate increased to 59% and then gradually declined with time. While 4 week outcomes were only available for 47 individuals, the 21% response rate after a single infusion is remarkable in light of the high degree of treatment resistance. Each open-label trial was focused on some aspect of KET besides acute antidepressant efficacy *per se*, with several valuable findings. Thakurta et al. (2012) demonstrated robust, but short-lived (< 3 days) antidepressant effects of standard dose KET in an Indian population. Ibrahim et al. (2011) demonstrated that a history of non-response to ECT was not associated with a reduced likelihood of response to KET in TRD. Machado-Vieira et al. (2009) did not detect change in peripheral blood brain-derived neurotrophic factor (BDNF) levels or correlation between BDNF and MADRS scores, in 23 TRD subjects over the first 4 hours after KET. Salvadore et al. demonstrated correlations between short-term antidepressant response

to KET and pretreatment signals in prefrontal cortex on magnetoenchephalography (2009, 2010) and proton magnetic resonance spectroscopy (2012). In support of this possibility, Cornwell et al. (2012) demonstrated that stimulus-evoked somatosensory cortical magneto-encephalographic responses were increased after ketamine infusion in responders, but not non-responders to KET. Phelps et al. (2009) identified another link to

Figure 1. Randomized, crossover, controlled trials, response rates in unipolar depression

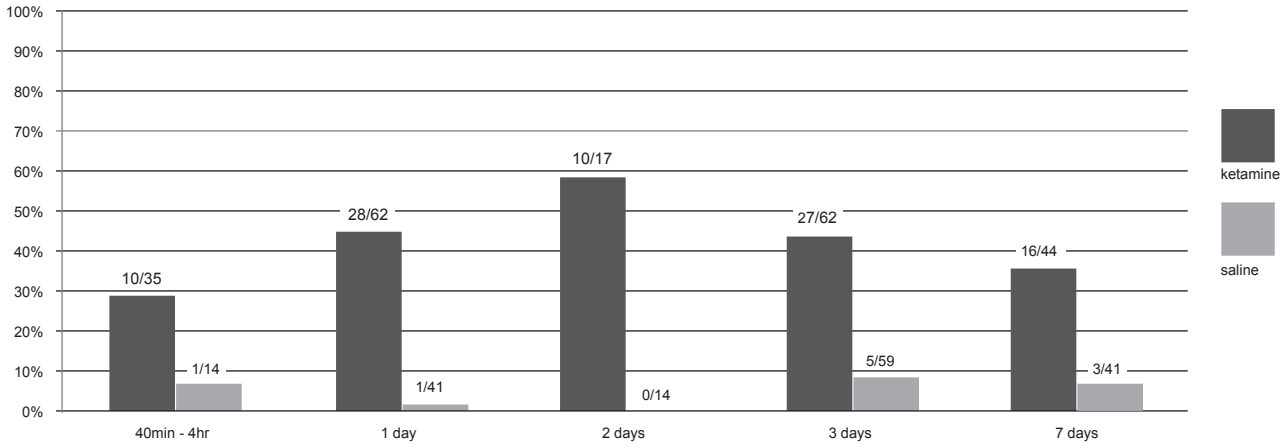


Figure 2. Randomized, crossover, controlled trials, response rates in bipolar depression

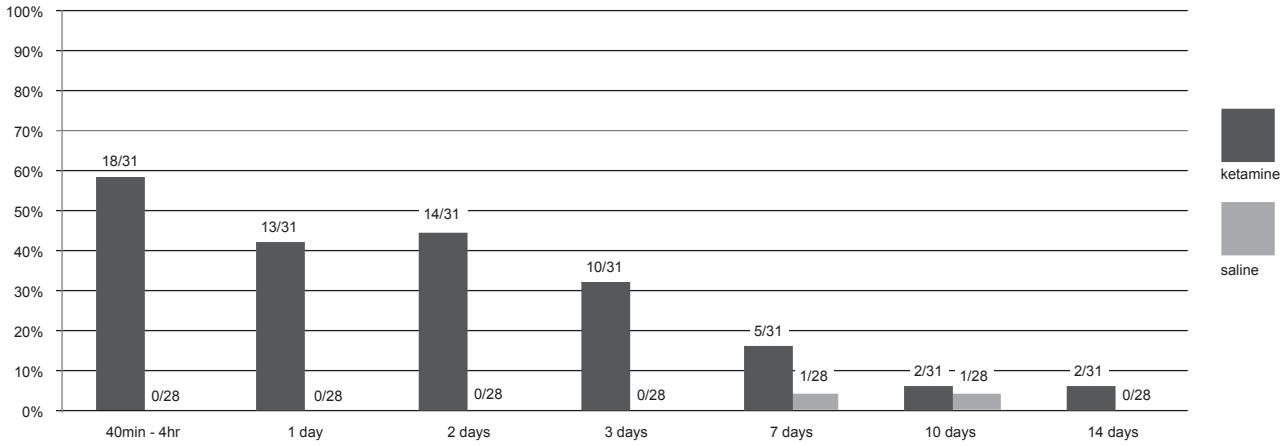
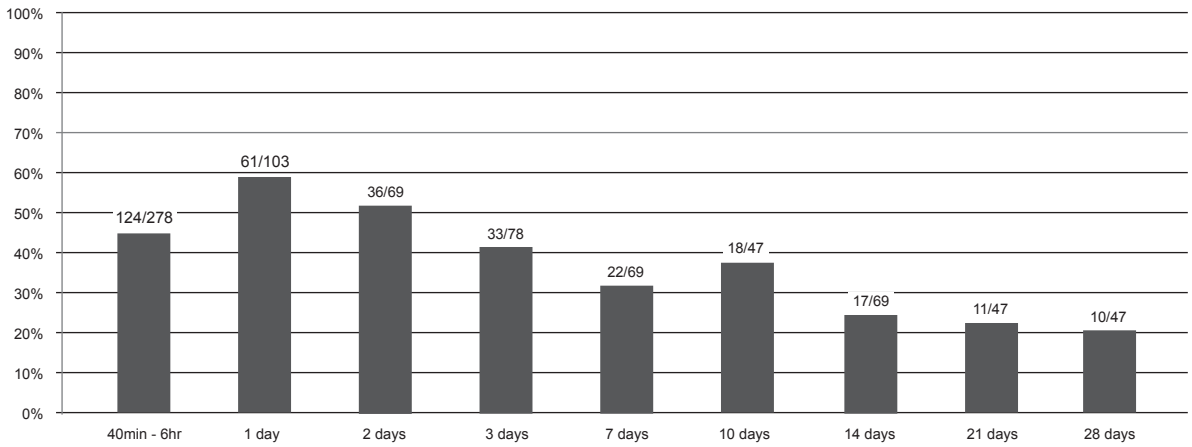


Figure 3. Open Label IV ketamine, response rates in unipolar depression



a potential biomarker, demonstrating that non-alcohol-dependent MDD subjects with a family history of alcoholism had a substantially greater likelihood of response to KET than those without. Luckenbaugh et al. (2012) reported similar findings from a post-hoc analysis of RCT data (Diazgranados et al., 2010a; Zarate et al., 2012). Both Mathew et al. (2010) and Ibrahim et al. (2012) failed to demonstrate benefits from randomization to riluzole over placebo during planned month-long follow-up treatment after response to open-label KET. Finally, Larkin and Beautrais (2011) found administration of a lower total ketamine dose (0.2 mg/kg), via IV bolus rather than slow infusion, permitted use in an emergency department setting by busy clinicians. While they reported cumulative remission of 71.4% in the first four hours, improved response in the subsequent two weeks must be interpreted in light of telephone follow up and naturalistic treatment, including inpatient care (this data omitted from the table).

The one OLI solely in patients with treatment-resistant bipolar depression demonstrated progressive decreases in mean HDRS score and increases in response (Rybakowski, Permoda-Osip, Skibinska, Adamski, & Bartkowska-Sniatkowska, 2013; Table 2). Response more than doubled from 24% at 1 day to 52% at 1 week, remaining stable for the duration of the two week long trial. Patients were maintained on a variety of mood stabilizing medications, although a limitation of the study is that subjects were tapered off of antidepressants as recently as 2 weeks prior to KET. This may potentially explain the large disparity in outcome data from the more rigorously designed RCTs.

Multidose Studies

One RCT and five OLIs assessed multiple sequential doses of IV ketamine (Table 3). Of these, three utilized a regimen of thrice weekly infusions for two weeks. Another utilized up to four infusions, at a rate of two per week over two weeks, stopping once patients achieved remission. Only one study directly compared two different schedules: once weekly versus twice weekly infusions over the course of three weeks (Diamond et al., 2014). All six noted either stable or increasing rates of response over subsequent infusions. The response rate for all subjects within 24 hours of their final infusion was 59%, though if the outlier is excluded (Diamond et al. 2014), this increases to 74%. The majority of these studies also reported time to relapse after the final infusion, monitoring subjects over the subsequent 4 weeks or longer, however criteria for relapse varied from liberal (aan het Rot et al., 2010) to conservative (Shiroma et al., 2014). Summing totals from these studies over each time point reveals 50% of patients no longer met response criteria between 7-10 days following the final infusion, which may potentially underestimate true benefit due to our conservative calculations (Figure 4).

The one RCT compared three ketamine infusions with three bilateral ECT treatments over one week, finding 89% response rate after three ketamine infusions versus 67% with ECT (Ghasemi et al., 2013). Regarding the five OLIs, all unique patients are represented in Murrough et al. (2013), Rasmussen et al. (2013), Shiroma et al. (2014), and Diamond et al. (2014). Response rates immediately after conclusion of the series of infusions were 71%, 60%, 79%, and 29%, respectively (ITT). Diamond et al. (2014) was again

Figure 4. Open label and RCT mutidose infusion, response rates in unipolar depression

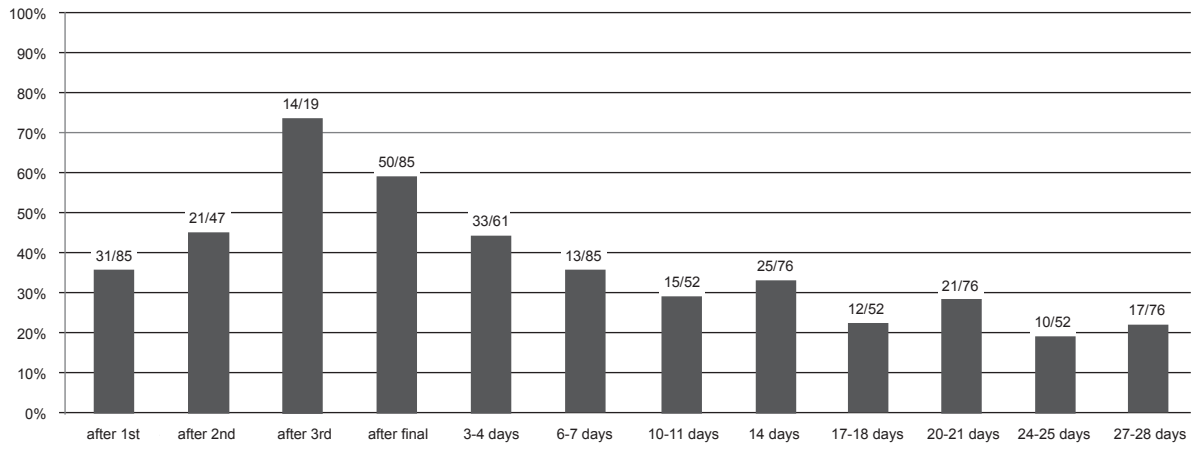


Table 1. Random controlled trials of ketamine efficacy for depression

	Study	Year	Design	Diagnosis	TRD	N	Gender	Age	Concom Meds	Interval	Response Measure	Arm	40mn-4hr ‡	1 days	2 days	3-4 days	7 days	10 days	14 days	21 days	28 days
Unipolar Depression	Berman et al. [1]	2000	double blind crossover	unipolar (8) bipolar (1)	no	9	4M 5F	37	no	72 hrs	HDRS 25 decr 50%	ketamine saline	1/8 (13%) *	2/8 (25%) *	* *	4/8 (50%) 1/8 13%					
	Zarate et al.	2006	double blind crossover	unipolar	yes	18	6M 2F	47	no	7 days	HDRS 21 decr 50%	ketamine saline	9/17 (53%) 1/14 7%	12/17 (71%) 0/14 (0%)	10/17 (59%) 0/14 (0%)	9/17 (53%) 2/14 14%	6/17 (35%) 0/14 (0%)		2/17 (12%)		
	Valentine et al. [1]	2011	single blind crossover	unipolar	no	10	4M 6F	42	no	7 days	HDRS 25 decr 50%	ketamine saline	0/10 (0%) *	4/10 (40%) *	* *	3/10 (30%) 1/10 (10%)	* *				
	Sos et al. [2]	2013	double blind crossover	unipolar	no	27	15M 15F [3]	43	yes	7 days	MADRS decr 50%	ketamine saline	* *	10/27 (37%) 1/27 (4%)	* *	11/27 (41%) 1/27 (4%)	10/27 (37%) 3/27 (11%)				
	Totals for Unipolar Depression % responding % responding											ketamine saline	10/35 (29%) 1/14 (7%)	28/62 (45%) 1/41 (2%)	10/17 (59%) 0/14 (0%)	27/62 (44%) 5/59 (8%)	16/44 36%) 3/41 (7%)		2/17 (12%)		
Bipolar Disorder	Diazgranados et al.	2010	double blind crossover	bipolar I and II	yes	22	7M 15F	48	yes	14 days	MADRS decr 50%	KET +Li/VPA saline +Li/VPA	9/17 (53%) 0/16 (0%)	7/17 (41%) 0/16 (0%)	9/17 (53%) 0/16 (0%)	8/17 (47%) 0/16 (0%)	2/17 (24%) 1/16 (6%)	1/17 (6%) 1/16 (6%)	1/17 (6%) 0/16 (0%)		
	Zarate et al.	2012	double blind crossover	bipolar I and II	yes	15	7M 8F	47	yes	14 day	MADRS decr 50%	KET +Li/VPA saline +Li/VPA	9/14 (64%) 0/12 (0%)	6/14 (43%) 0/12 (0%)	5/14 (36%) 0/12 (0%)	2/14 (14%) 0/12 (0%)	1/14 (7%) 0/12 (0%)	1/14 (7%) 0/12 (0%)	1/14 (7%) 0/12 (0%)		
	Totals for Bipolar Depression % responding % responding											KET +Li/VPA saline +Li/VPA	18/31 (58%) 0/28 (0%)	13/31 (42%) 0/28 (0%)	14/31 (45%) 0/28 (0%)	10/31 (32%) 0/28 (0%)	5/31 (16%) 1/28 (4%)	2/31 (6%) 1/28 (4%)	2/31 (6%) 0/28 (0%)		
Parallel Groups	Murrough et al. [4]	2013	parallel group	unipolar unipolar	yes yes	47 25	35M 37F	47 43	no no	7 days 7 days	MADRS decr 50% midazola 0.045mg/kg	ketamine midazola 0.045 mg/kg	* *	30/47 (64%) 7/25 (28%)	28/47 (60%) 6/25 (24%)	28/47 (60%) 5/25 (20%)	21/47 (45%) 4/25 (16%)	*17/47 (36%)* *4/25 (16%)*	*13/47 (28%)* *2/25 (8%)*	*9/47 (19%)* *0/25 (0%)*	*9/47 (19%)* *0/25 (0%)*
	Ghasemi et al. [5]	2013	parallel group	unipolar unipolar	yes yes	9 9	8M 10F	38	yes	1 day	HDRS 25 decr 50%	ketamine ECT	* *	7/9 (78%) 1/9 (11%)							
Intranasal	Lapidus et al. [6]	2014	double blind crossover	unipolar	yes	20	10M 10F	48	yes	7 days	MADRS decr 50%	ketamine 50 mg IN saline	6/18 (33%) 1/18 (6%)	8/18 (44%) 1/18 (6%)	4/18 (22%) 1/18 (6%)	6/18 (33%) 2/18 (11%)	1/18 (6%) 0/18 (0%)				

some studies did not report depression response at all time points. ‡ The highest of available scores was utilized for the 40min-4hr tine point.

[1] Response data from Valentine et al. 2011 and Berman et al. 2000 were later published in aan het Rot et al. 2012. All studies utilized single administration of racemic ketamine 0.5mg/kg IV infusion over 40 mins except [2] 0.54mg/kg over 30 mins, [5] the first of three infusions, done over 45 mins, [6] intranasal ketamine 50mg. [3] Three subjects dropped out before receiving ketamine, so were excluded from modified intent to treat analysis. [4] After 7 days measure was defined as loss of response, or MADRS>=20 maintained for two consecutive visits and meeting criteria for a major depressive episode for 1 week.

Table 2. Open label investigations of ketamine efficacy for depression

	Study	Year	Diagnosis	TRD	N	Gender	Age	Concomitant Medication	Interval	Response Measure	40mn-6hr	1 days	2 days	3 days	7 days	10 days	14 days	21 days	28 days
Unipolar or Mixed	Machado-Vieira et al.	2009	unipolar	yes	23 [1]	14M/9F	44	no	240 mins	MADRS decr 50%	11/23 (48%)								
	Phelps et al.	2009	unipolar	yes	26 [1]	14M/12F	44	no	230 minutes	MADRS decr 50%	11/26 (42%)								
	Ibrahim et al.	2011	unipolar	yes	42 [1]	24M/18F	47	no	230 minutes	MADRS decr 50%	21/42 (50%)								
	Cornwell et al.	2012	unipolar	yes	20, 0 unique [1]	15M/5F	46	no	230 minutes	MADRS decr 50%	9/20 (45%)								
	Ibrahim et al.	2012	unipolar	yes	42 2 unique [1]	26M/16F	47	no [2]	28 days	MADRS decr 50%, then returning above 25% decr	26/42 (62%)	10/21 (48%)	8/21 (38%)	8/21 (38%)	5/21 (24%)	4/21 (19%)	4/21 (19%)	3/21 (14%)	3/21 (14%)
	Salvadore et al.	2009	unipolar	yes	11 [3]	7M/4F	44	no	230 minutes	MADRS decr 50%	5/11 (45%)								
	Salvadore et al.	2010	unipolar	yes	15 8 unique [3]	?	51	no	230 minutes	MADRS decr 50%	6/15 (40%)								
	Salvadore et al.	2012	unipolar	yes	14 10 unique [3]	9M/5F	50	no	24 hours	MADRS decr 50%	2/14 (14%)	*							
	Mathew et al.	2010	unipolar	yes	26 [4]	16M/10F	48	no [2][5]	72hrs + 32 days	MADRS decr 50% and MADRS 1/2<=2; then relapse [5]	16/26 (62%)	17/26 (65%)	14/26 (54%)	14/26 (54%)	*14/26 (54%)*	*14/26 (54%)*	*12/26 (46%)*	*8/26 (31%)*	*7/26 (27%)*
	Larkin and Beautrais [6]	2011	unipolar	no	14	7M/7F	31	yes	4hrs	MADRS <=10	10/14 (71%)								
	Thakurta et al.	2012	unipolar	yes	22 [7]	10M/12F	50	no	14 days	HDRS 17 decr 50%	15/22 (68%)	17/22 (77%)	14/22 (64%)	7/22 (32%)	3/22 (14%)	*	1/22 (5%)		
	Murrough et al. [8]	2013	unipolar	yes	24 14 unique [4]	15M/9F	48	no	first infusion	MADRS decr 50%	16/24 (67%)	15/24 (63%)							
	Rasmussen et al. [9]	2013	unipolar, bipolar II	yes	10	4M/6F	47	yes	first infusion	MADRS decr 50%	2/10 (20%)	2/10 (20%)							
	Shiroma et al. [8]	2014	unipolar	yes	14	14M	54	yes	first infusion	MADRS decr 50%	3/14 (21%)								
	Diamond et al.	2014	unipolar (22) bipolar (6)	yes	28	16M/12F	47	yes	first infusion	BDI decr 50%	3/28 (11%)								
	Chilukuri et al.	2014	unipolar	yes	9	3M/6F	36	yes	3 days	HDRS 17 decr 50%	3/9 (33%)	*	*	4/9 (44%)					
	Totals for Unipolar or Mixed % responding [10]										124/278 (45%)	61/103 (59%)	36/69 (52%)	33/78 (42%)	22/69 (32%)	18/47 (38%)	17/69 (25%)	11/47 (23%)	10/47 (21%)
Bipolar	Rybakowski et al. [11]	2013	bipolar	yes	25	4M 21F	49	yes	14 days	HDRS 17 decr 50%	1/25 (4%)	6/25 (24%)	*	*	13/25 (52%)	*	13/25 (52%)		

* some studies did not report depression response at all time points.
[1][3][4] Studies with overlapping patients.
[2] Responders were randomized to daily riluzole or placebo, but upon subsequent analysis differences determined to non-significant.
[5] Subjects randomized to pretreatment with one time dose of either lamotrigine 300 mg or placebo, to assay if this would attenuate dissociative effects and improve antidepressant benefit. No significant effect was found. Relapse criteria was defined as MADRS≥20 and MADRS increased by 10 from day 3 score, both for two consecutive visits.
[7] Subjects overlap with Thakurta et al. 2012.
All studies utilized a single 0.5mg/kg IV infusion over 40 minutes except [11] over 45 minutes, [6] 0.2mg/kg IV over 1-2 minutes, [9] 1-4 such IV infusions over 100 minutes; 2x/wk for 2wks or remission, [8] 6 infusions; 3x/wk for 2 wks.
[10] Calculation excluded Cornwall et al. 2012 and Ibrahim et al. 2012 due to preponderance of non-unique subjects.

Table 3. Multidose ketamine efficacy for depression

	Study	Year	Diagnosis	TRD	N	Gender	Age	Con-com Meds	Doses	Interval	Response Measure	after 1st infusion	after 2nd infusion	after 3rd infusion	after final infusion	3-4 days	6-7 days	10-11 days	14 days	17-18 days	20-21 days	24-25 days	27-28 days
Open Label	aan het Rot et al.	2010	unipolar	yes	10 [1]	5M 5F	51	no	6; 3x/wk for 2wks	2wks of infusions + 4wks	MADRS decr 50%	9/10 (90%)	*	*	9/10 (90%)	7/10 (70%)	5/10 (50%)	5/10 (50%)	4/10 (40%)	3/10 (30%)	2/10 (20%)	3/10 (30%)	2/10 (20%)
	Murrough et al.	2013	unipolar	yes	24 14 unique [1]	15M 9F	48	no [2]	6; 3x/wk for 2wks	2wks of infusions + 12wks	MADRS decr 50%	16/24 (67%)	*	*	17/24 (71%)	16/24 (67%)	15/24 (63%)	10/24 (42%)	10/24 (42%)	7/24 (29%)	6/24 (25%)	5/24 (21%)	4/24 (17%)
	Rasmussen et al. [3]	2013	unipolar, bipolar II	yes	10	4M 6F	47	yes	1-4; 2x/ wk for 2wks or remission	0-2wks of infusions + 4wks	MADRS decr 50%	2/10 (20%)	6/10 (60%)	6/10 (60%)	6/10 (60%)	*	5/10 (50%)	*	3/10 (30%)	*	3/10 (30%)	*	3/10 (30%)
	Shiroma et al.	2014	unipolar	yes	14	14M	52	yes	6; 3x/wk for 2wks	2wks of infusions + 4wks	cumulative MADRS decr 50%	3/14 (21%)	*	*	11/14 (79%)	*	8/14 (57%)	*	7/14 (50%)	*	7/14 (50%)	*	5/14 (36%)
	Diamond et al.	2014	unipolar (22) bipolar (6)	yes	15	16M 12F	47	yes	3; weekly for 3wks	3wks of infusions + 6 months	BDI decr 50%	3/28 (11%)	5/15 (33%)	*	5/15 (33%)	5/15 (33%)	5/15 (33%)	4/15 (27%)	4/15 (27%)	4/15 (27%)	4/15 (27%)	4/15 (27%)	4/15 (27%)
					13				6; 2x/wk for 3wks			3/28 (11%)	3/13 (23%)	*	3/13 (23%)	3/13 (23%)	1/13 (8%)	1/13 (8%)	1/13 (8%)	1/13 (8%)	1/13 (8%)	1/13 (8%)	f1/13 (8%)
RCT	Ghasemi et al. [4]	2013	unipolar	yes	18	8M 10F	38	yes	3; 3x/wk for 1wk	1wk of infusions + 1 week	HDRS25 decr 50%	7/9 (78%)	7/9 (78%)	8/9 (89%)	8/9 (89%)	9/9 (100%)	9/9 (100%)						
	Totals for Opel Label and RCT % responding [10]														50/85 (59%)	33/61 (54%)	31/85 (36%)	15/52 (29%)	25/76 (33%)	12/52 (23%)	21/76 (28%)	10/52 (19%)	17/76 (22%)

* some studies did not report depression response at all time points.31/85 (36%) Response data was recalculated conservatively, accounting for differences from published data. Data from first infusions are also reported on tables 1 and 2 where appropriate.
[1] Patients overlap between studies.
[2] Three responders were started on venlafaxine as part of another study.
All studies utilized 0.5mg/kg IV over 40 minutes except [3] over 100 minutes. [4] over 45 minutes.
[5] Calculation excluded aan het Rot et al. given these subjects are represented in Murrough et al.

the outlier. Altogether, studies yielded a 22% response rate approximately a month after conclusion of the course. In Murrough et al. (2013), 17% remained responders over an additional 3 months follow-up, with only one receiving other medication in the interim. These authors also observed that initial non-responders (at 4 hours after the first infusion) were four times less likely than initial responders to achieve response at the end of 6 infusions. Additionally, several studies noted that patients required up to two infusions before successfully achieving response (Rasmussen et al., 2013; Diamond et al., 2014), suggesting that one infusion may be insufficient. Rasmussen et al. (2013) added to the literature by extending 0.5mg/kg infusions over 100 minutes (0.3 mg/kg/hr), the slower rate permitting use without presence of anesthesia personnel. Interestingly enough, the study with the lowest response rate was conducted in an ECT recovery room and found that several patients complained the setting was too noisy, chaotic, or distressing (Diamond et al., 2014). Also notable is that this is the only study to use the BDI, a patient rated scale, as an outcome measure. The other study that was conducted in an ECT recovery room had the next lowest response rate (Rasmussen et al., 2013). Diamond et al. (2014) is unique in that they assessed memory at baseline and after the treatment course, finding improvements in autobiographical, episodic, and subjective memory. This study was also the only one to directly compare different treatment regimens, though unexpectedly found better results with weekly versus twice weekly infusions.

Case Reports

The 17 published case studies (or judged equivalent) that utilized KET comprised just over 30 patients

and—save for one dose finding study and another comparing racemic versus *S*-ketamine—typically utilized multiple infusions (Suppl. Table 1). These reports on 1-3 patients describe dramatic improvement in depressive symptoms and functioning in patients with TRD (Kollmar, Markovic, Thuerauf, Schmitt, & Kornhuber, 2008; Liebrenz, Borgeat, Leisinger, & Stohler, 2007; Liebrenz, Stohler, & Borgeat, 2009); antidepressant effect of ketamine even when this was only arrived at serendipitously (Ostroff, Gonzales, & Sanacora, 2005); several descriptions of prolonged relief of depression with repeated dosing (Correll, 2006; Messer et al., 2010; Murrough et al., 2011); and safe use of ketamine in depressed patients with severe medical comorbidities or who were concomitantly treated with multiple other CNS-acting medications (Kollmar et al., 2008; Liebrenz et al., 2007, 2009; Stefanczyk-Sapieha, Oneschuk, & Demas, 2008). There were notable examples of rapid relief of intense dysphoria and crying in a terminally ill cancer patient on a palliative care unit (Stefanczyk-Sapieha et al., 2008). The cases of Yang, Zhou, Gao, Shi, and Yang (2013) demonstrated rapid relief of depression in young, drug-naïve men. Szymkowicz, Finnegan, and Dale (2013) administered between 16-34 repeated KET infusions to three TRD patients over a 12 month period, adjusting frequency depending on individual response. Their first patient remitted after the 2nd infusion, and was maintained so with periodic treatments over the subsequent 9 months. Their two other subjects suffered repeated relapses despite intermittent courses of repeat infusions. Lai et al. (2014) is unique in that it is the only dose finding study, comparing 0.1 to 0.4mg/kg of ketamine IV over 5 minutes and a saline control, but due to low enrollment and poor retention, was placed with the cases. Only one of the four individuals displayed a clear dose response relationship for antidepressant response, though dissociative effects were clearly dose related.

Alternate Routes of Administration

In contrast to most studies of IV infusion, studies into intramuscular, subcutaneous, intranasal, oral, and sublingual dosing have mostly utilized multiple administrations attempting to extend response (Table 5). Bioavailability of these different formulations ranges from ~20% for oral, ~30% for sublingual, 45% for intranasal, to 93% for intramuscular (Clements, Nimmo, & Grant, 1982). Dose, frequency, follow up interval, treatment setting, and response metrics varied greatly between publications. All patients had their existing medications continued, potentially biasing results. Onset of benefit was generally rapid in parenteral routes, and was successfully maintained with repeat dosing in several instances.

In regards to IM administration, one OLI and five case studies detailed effects in 25 patients. The OLI study (Chilukuri et al., 2014) was notable in that it directly compared outcomes from different routes of administration (0.5mg/kg IV over 40 minutes, 0.25mg/kg IM, and 0.5mg/kg IM) and found comparable response rates of 33-44% immediately and several days after administration. In contrast, in the case reports, doses ranged from 0.5mg/kg to 1.0mg/kg, from every 3-8 days, and from 2-68 treatments. The five patients with unipolar depression all met formal criteria for response by 24 hours. Glue, Gulati, Le Nedelec, and Duffull (2011) also performed a dose-response assessment finding greater improvements with higher doses; while 0.5mg/kg and 0.7mg/kg decreased MADRS scores, only 1.0mg/kg led to response. Zanicotti, Perez, and Glue (2012, 2013) described a woman with metastatic cancer and unipolar TRD who, after 1.0mg/kg, experienced remission of depression for 5-6 days, and pain for 24 hours. On a weekly outpatient regimen, response was largely maintained for 8 months. Two patients with bipolar depression experienced qualitative improvement within days to a week after 0.5mg/kg or 0.9mg/kg IM, that was maintained for 9-12 months by dosing at 3-4 day intervals, although one patient did require a dose increase after five months (Cusin, Hilton, Nierenberg, & Fava, 2012).

Three studies utilized intranasal administration, of which one was a double blinded crossover RCT that compared ketamine 50mg with saline (Lapidus et al., 2014). This study found significant differences in MADRS through two days, and a response rate of 44% at 24 hours, comparable to other RCTs that utilized ketamine infusions (Table 1; Figure 1). The second trial was a case series of 12 pediatric subjects (ages 6-19) with bipolar TRD that received a dose between 30-120mg. Onset of benefit was frequently within the hour, lasting for 3-4 days, and maintained for months with once to twice weekly dosing (Papolos et al., 2013). The final case describes successful long term maintenance of euthymia with twice weekly intranasal administration.

The one study on sublingual administration, in a mixed cohort of unipolar and bipolar depression, utilized a 10mg dose and found "rapid" improvements

Table 4. Suicidality

	Study	Year	Diagnosis	TRD	N	Gender	Age	Concom Meds	Number of infusions	Interval	Response Measure	Baseline	40mn-6hr	1 days	2 days	3 days
RCTs	Berman et al.	2000	unipolar (8) bipolar (1)	no	9	4M/5F	37	no	1	72 hours	HDRS-SI group mean	*	*	*	*	"significantly decreased" (p = 0.02)
	Zarate et al.	2006	unipolar	yes	18	6M/12F	47	no	1	7 days	HDRS-SI group mean	*	*	"significant effect" for ketamine	*	*
	DiazGranados et al.	2010	bipolar I and II	yes	18	6M/12F	48	yes	1	14 days	MADRS-SI group mean	*		not significant for any time point		
	Zarate et al.	2012	bipolar I and II	yes	15	7M/8F	47	yes	1	14 days	MADRS-SI group mean	2.3	0.25 (vs. 2.2 with saline, p < 0.001)	1.1 (vs. 2.2 with saline, p < 0.01)	1.1 (vs. 2.1 with saline, p < 0.01)	1.3 (vs. 2.3 with saline, p < 0.01)
	Price et.al.	2014	unipolar	yes	57 0 unique [1]	27M/30F	47	no	1	7 days	SSI < 4	27/57 (47%)	*	86% (vs. 62% with midazolam, p = 0.04)	*	*
Open Label Trials	Price et.al.	2009	unipolar	yes	26 0 unique [5]	16M/10F	48	no	1	24 hours	MADRS-SI <=1	7/26 (27%)	*	21/26 (81%)		
	aan het Rot et al.	2010	unipolar	yes	10 [5]	5M/5F	51	no	6; 3x/wk for 2wks	2 wks of infusions + 4 wks [6]	MADRS-SI <=1	2/10 (20%)	*	9/10 (90%)	*	*
	DiazGranados et al.	2010	unipolar	yes	33 [3]	20M/13F	46	no	1	230 minutes	SSI < 4	23/33 (70%)	32/33 (97%)			
	Larkin and Beautrais	2011	unipolar	no	14	7M/7F	31	yes	1	10 days	MADRS-SI group mean	3.9 (0.4)	0.6 (0.1) ("significantly lower than baseline")	*	*	*
	Thakurta et al.	2012	unipolar	yes	27 [2]	13M/14F	49	no	1	2 days	SSI group mean	4.85 ± 5.37	0.78±1.48 (p = 0.001)	~3.5 (p > 0.05)	4.41±4.8 (p = 0.53)	
	Ibrahim et al.	2012	unipolar	yes	42 2 unique [3]	26M/16F	47	no [4]	1	28 days	SSI group mean	2.55		no significant changes throughout study		
	Murrough et al.	2013	unipolar	yes	24 14 unique [5]	15M/9F	48	no	6; 3x/wk for 2wks	2 wks of infusions + 12wks [6]	MADRS-SI group mean	*	1.9±0.66 (p < 0.01)	*	*	*
	Rasmussen et al.	2013	unipolar	yes	10	4M/6F	47	yes	1-4; 2x/wk for 2wks	0-2 wks infusions + 4wks [7]	SSI group mean	3.7±1.95	*	1.6±1.65 (p=0.007)	*	*
	Diamond et al.	2014	unipolar (22) bipolar (6)	yes	28	16M/12F	47	yes	1-2x/wk for 3wks	3 wks of infusions + 6 months	HAMD-SI group mean	2.0 (SD=0.9)	*	0.7 (SD=1.1)	*	*

*some studies did not report depression response at all time points.
Suicidality was assessed as a secondary or post-hoc measure; trials were designed to assess response rates for depression as the primary outcome measure.
[1] Patients overlap with Murrough et al. 2013.
[2] Patients overlap with Thakurta et al. 2012.
[3] Patients overlap between these studies.
[4] Responders were randomized to riluzole or placebo, but upon analysis differences found to non-significant.
[5] Patients overlap between studies.
[6] Data reported is for after completion of first infusion.
[7] Data reported is for after completion of all infusions.

Table 5. Alternate routes of ketamine administration

	Study	Type	Year	Diagnosis	TRD	N	Gender	Age	Co-morbidities	Dose ‡	Number of doses	Frequency	Duration of study	Outcome measure	Depression response within 24 hours	Durability of benefit
Intramuscular	Glue et al.	case series	2011	unipolar	yes	2	2F	?	none reported	0.5, 0.7, and 1.0mg/kg	3	unclear	unclear, at least 3 days	MADRS	yes, 3/3 (100%), but only at 1.0mg/kg	not reported
	Zanicotti et al. [1]	case	2012, 2013	unipolar	yes	1	1F	36	metastatic ovarian cancer, pain	1.0mg/kg	7, 34	every 7-8 days	2 months, 8 months	MADRS	yes, remission at 1hr	remission after each dose for 3-7 days, largely maintained for 8 months
	Harihar et al.	case series	2013	unipolar	unclear	2	1M	23	obsessive-compulsive disorder	0.5mg/kg	2	every 3 days	1 month	HDRS	yes, remission at 2hr	remission through 1 month
							1M	21	none reported	0.5mg/kg	2	every 3 days	unclear, at least 3 days	HDRS	yes, remission at 2hr	>3 days
	Cusin et al	case series	2012	bipolar II	yes	2	1F	57	ADHD	50mg for 5mos, then 70mg for 4mos (55kg)	68+	every 4 days	9 months	clinical assessment	unclear	remission "within a few days", maintained for 9 months
							1F	48	ADHD, fibromyalgia, hypothyroid	50mg for 6 mos (120kg)	61+	every 3 days	12 months	clinical assessment	no	responded "after 1 week," maintained for 6 months
	Chilukuri et al.	open label	2014	unipolar	yes	9	1M/8F	32	n/a	0.25mg/kg		once	3 days	HDRS	yes, 3/9 (33%)	increased to 44% at 3 days
						9	2M/7F	42	n/a	0.5mg/kg		once	3 days	HDRS	yes, 4/9 (44%)	3 days
Intranasal	Papolos et al.	case series	2013	bipolar I, Fear of Harm phenotype	yes	12	10M/2F	6 - 19	unclear	30-120mg [2]	many	every 3-7 days	several months	CBQ	yes, 12/12 (100%) within 24hr, and many within 1hr	"several months,", 72-96hrs of benefit after each dose
	Clark	case	2014	unipolar	yes	1	1F	44	migraines	50mg	32	twice weekly	4 months	clinical assessment	no	"euthymic" by day 3, maintained >4 months
	Lapidus et al.	RCT, cross-over	2014	unipolar	yes	20	10M/10F	48	none reported	50mg		once	7 days	MADRS	yes, 8/18 (44%)	3 days
										saline		once	7 days	MADRS	1/18 (6%)	low throughout study
Sublingual	Lara et al.	case series	2013	unipolar (12), bipolar (14)	yes	26	8M/18F	22-83	various	10 mg (100 mg/mL) for 5 minutes	1-90	every 2-7 days	up to 6 months	custom 0-10 mood scale	unclear, 17/26 (65%) with "rapid" response	20/26 (77%) had response to at least one dose; 10/26 (38%) maintained response for "months"
Subcutaneous	Gálvez et al.	case	2014	unipolar, melancholic	yes	1	1F	62	HTN, hypothyroid, CVA	0.1mg/kg, then 0.2mg/kg	2	a month apart	9 months	MADRS	yes, only at higher dose	5 months
										0.2mg/kg [5]	12	approx. weekly	9 months	MADRS	no, not until 3rd treatment	10 weeks
O/S*	McNulty et al.	case	2012	unipolar	yes	1	1M	44	hospice	0.5mg/kg SC, then daily [6]	many	daily	11 weeks	clinical assessment	yes	11 weeks
Oral	Paslakis et al.	case series	2010	unipolar	no	4	?/1M/2F	36-57	melancholia, AvPD† alcohol abuse	*S*-ketamine 1.25mg/kg	12 to 14	split over three times daily	14 days	HDRS	no	2/4 (50%) responded at 7 days, maintained through 14 days
	Irwin et al.	case series	2010	unipolar	no	2 [3]	1M/1F	64,70	hospice: COPD, neoplasia	0.5mg/kg		once	several months	HDRS 17	yes, 1/2 (50%) patients responded by 120 min	1 month for initial responder; other responded at 8 days
	Irwin et al.	open label	2013	unipolar	no	14 12 unique [3]	?/1M/7F	?	hospice	0.5mg/kg	28	nightly	28 days	HDRS 17	no	unclear; mean time to response 14.4±19.1 days for 8/14 (57%) responders
	De Gioannis and Leo	case series	2014	bipolar, SI	yes	2	1F 1M	37 44	none chronic pain	0.5-1.5mg/kg[4] 0.5-3.0mg/kg[4]	6 or more 3 or more	monthly every 2-3 wks	>3 months >4 months	MADRS MADRS	yes yes	unclear unclear
	Iglewicz et al.	case series	2014	unspecified depression	no	31 [3]	11M 20F	68	hospice	0.5mg/kg	1 - 12 [7]	up to three times daily [7]	21 days	CGI	yes, 10/14 (71%) [7]	5/6 (83%) had response start to fade at day 2-3 [7]

*Oral and Subcutaneous. ‡ Doses administered are racemic ketamine unless otherwise noted. † Avoidant Personality Disorder.
All patients continued existing medications during treatment with ketamine.
[1] Includes follow-up publication on the same patient.
[2] Variable dose: 100 mg/mL solution via metered nasal spray pump bottle.
[3] Two patients overlap between these studies.
[4] Two patients received 0.5mg/kg orally, which was titrated up in 0.5mg/kg increments at follow-up sessions to final doses of 3.0mg/kg every 2-3 weeks and 1.5mg/kg monthly
[5] Patient received a second course of treatment after initial relapse.
[6] An initial one time 0.5mg/kg (40 mg) subcutaneous dose was followed by 0.5mg/kg (40 mg) daily oral maintenance.
[7] Of 31 subjects, 29 received ketamine orally, 1 received subcutaneous, and 1 received via both routes; 22 received 1 dose, 5 received 2 doses, and 4 received three times daily dosing for 3 days; time to first response and time to fading of response available for smaller sample.

in 17 of the 26 patients, though the time frame was not defined. Using repeat dosing, from every 2-7 days, ten patients were described as maintaining response over a period of months, based on a Likert scale (Lara et al., 2013).

Subcutaneous administration has also been reported on. McNulty et al. (2012) described a case of "dramatic relief" from depression in a hospice patient after initial subcutaneous administration of 0.5mg/kg, followed by the same amount by mouth daily, with maintenance for 11 weeks. Another case describes long term maintenance of response with repeated doses, notably at only 0.2mg/kg (Gálvez et al., 2014).

Oral, compared to parenteral, ketamine administration results in a higher blood norketamine to ketamine ratio because of extensive first pass metabolism. Norketamine is pharmacologically active as an NMDA antagonist and has analgesic and likely antidepressant effects. It has longer elimination half-life than ketamine itself. The clinical implications for treatment of depression are unclear (Blonk, Koder, van den Bemt, & Huygen, 2010). We found four case studies and a subsequent OLI that utilized oral administration. One case study (Irwin & Iglewicz, 2010) in two hospice patients with depression found response in both after a single dose of 0.5mg/kg, one within 120 minutes, the other at 8 days. The follow-up OLI included 12 additional patients and utilized daily dosing of 0.5mg/kg (Irwin et al., 2013), finding 57% response rate, mean time to response of 14.4 days, and maintenance of response for at least 28 days. Most recently the same authors published a retrospective chart review involving 31 patients finding 71% response at 24 hours after single oral doses of 0.5mg/kg (Iglewicz et al. 2014). It is unclear why this study displayed such rapid response, while the other did not. De Gioannis and Leo (2014) described use of oral ketamine outside the hospice setting, in two individuals with bipolar disorder and suicidality, demonstrating maintenance of response with escalating doses of oral ketamine every two to four weeks.

_S_-Ketamine

Ketamine exists as a racemic mixture of the *S*- and *R*- stereoisomers, and while most studies have employed the racemate, a minority has solely used the more potent *S*- stereoisomer. There may be differences between the two, both in terms of antidepressant response and dissociative effects, though results are conflicting. Studies with *S*-ketamine describe treatment in just over ten patients, all with unipolar depression (Table 5, Suppl. Table 1). No reports utilizing *R*-ketamine for treatment of depression exist. Only one publication, a case report, describes direct comparison between stereoisomeric forms of ketamine. Two patients were each given equianalgesic IV infusions of racemic ketamine 0.5mg/kg and *S*-ketamine 0.25mg/kg a week apart (Paul et al., 2009). Robust antidepressant response to both isoforms of ketamine was observed in one patient, while the other responded to neither. Further, both patients had mild dissociative/perceptual disturbances ("psychotomimetic") with the racemate but not *S*-ketamine. Paslakis et al. (2010) treated four individuals with *S*-ketamine using a total oral daily dose of 1.25mg/kg, bioequivalent to 0.25mg/kg IV, divided over three times daily and similarly found no dissociative effects, and a 50% response rate. Conversely, subsequent studies utilizing IV infusions of *S*-ketamine 0.25mg/kg, either one time or multiple, found comparable response rates soon after infusion, but did note strong dissociative effects (Denk et al., 2011; Segmiller et al., 2013).

Suicidality

The data regarding reduction of suicidality with ketamine is generally suggestive of benefit (Table 4). The majority of studies did not assess suicidality as a primary outcome measure, and also utilized group mean change in suicidality scales rather than more easily interpretable results such as percent of the cohort achieving lack of suicidality. In regards to unipolar depression, three RCTs and nine OLIs reported on suicidality, typically utilizing either the HDRS or MADRS suicide items, or the scale for suicide ideation (SSI; Beck, Kovacs, & Weismann, 1979). Of these, only one OLI reported lack of benefit. The others showed benefit at disparate time points ranging from the first four hours post dose to three days out. Time course data is present in only one study, with loss of significance after four hours. Four studies, however, reported categorical outcomes of percent of subjects attaining an SSI or MADRS-SI score below a certain threshold (resolution of suicidal thoughts). These "response rates" ranged from 81% to 90% within the first 24 hours. Another study found, at 4 hours, a 97% response rate in 33 previous ketamine responders, and a 100% response among the high suicidality subcohort (Diazgranados et al., 2010b). Price et al. (2014) reanalyzed data from the Murrough et al. (2013) RCT, finding decreases in both explicit suicidality as well as implicit associations ("Escape = Me"). Other case reports,

Table 6. Ongoing and planned studies, Part 1. Randomized and double blind control studies

Sponsor	Date initiated	Status	Study design	Diagnosis	TRD	Primary outcome	Route	Ketamine arm / dose	Placebo arm	Number of doses
NIMH	2004, July	recruiting	parallel	MDD or bipolar	yes	various	IV infusion / 40min	0.5mg/kg	unclear	unclear
Washington University School of Medicine	2010, August	recruiting	parallel	MDD	yes	HDRS	IV infusion / variable duration	infusion over 100 hours	ketamine infusion for 40 min, and saline infusion for 100 hours	single
The University of New South Wales	2011, Sept	unknown	crossover	MDD or bipolar	no	unspecified depression scales	IV, IM, and SC	variable 0.1-0.5mg/kg	saline or midazolam	weekly for 6 wks
Yale University	2012, March	recruiting	crossover	MDD or bipolar II, and alcohol dep.	no	HDRS	IV infusion / 40min	0.5mg/kg	saline	single
Columbia University	2012, March	recruiting	parallel	MDD	no	HDRS	IV infusion / 40min	0.1, 0.2, 0.3, 0.4, and 0.5mg/kg	saline	single
University Hospital, Grenoble	2012, March	unknown	parallel	MDD	no	MADRS	IV infusion / 40min	0.5mg/kg + venlafaxine orally	Saline + venlafaxine orally	single
Massachusetts General Hospital	2012, May	enrolling by invitation	parallel	MDD	yes	HDRS	IV infusion / 45min	0.25mg/kg	scopolamine 0.2ug/kg IV over 15 minutes	2x/wk for 3 wks
Janssen Research & Development	2012, June	completed (unpublished)	parallel	MDD	yes	MADRS	IV infusion / 40min	0.5mg/kg / variable frequency of doses	saline / variable frequency of doses	either 2x or 3x/wk for 4 wks
Massachusetts General Hospital	2012, August	ongoing, not recruiting	parallel	MDD and SI	yes	HDRS	IV infusion	unclear dose	saline	2x/wk for 3 wks
University of Alabama at Birmingham	2012, August	recruiting	parallel	SI	no	SSI	IV infusion	0.2mg/kg	saline	single
Mayo Clinic	2012, September	recruiting	parallel	Depression, advanced cancer	no	HADS-D, HADS-A	oral	0.5mg/kg	unclear	single
New York State Psychiatric Institute	2012, October	recruiting	parallel	MDD	no	unspecified SI scale	IV infusion / 40min	0.5mg/kg	0.02mg/kg midazolam	single
American British Cowdray Medical Center	2013, May	recruiting	parallel	MDD	yes	HDRS	IV infusion / 40min	0.5mg/kg	saline	single
University of Ottawa	2013, May	recruiting	crossover	MDD	yes	HDRS	IV infusion / 40min	0.5mg/kg	midazolam	single versus six infusions, then weekly for 3 wks
Mount Sinai School of Medicine	2013, June	recruiting	parallel	MDD	yes	MADRS	IV infusion / 40min	ketamine + lithium orally	ketamine + placebo orally	unclear
Massachusetts General Hospital	2013, August	recruiting	parallel	MDD	yes	HDRS	IV infusion	0.1, 0.2, 0.5, and 1.0mg/kg	midazolam	single
New York State Psychiatric Institute	2013, September	recruiting	parallel	bipolar	no	SSI	IV infusion / 40min	0.5mg/kg	midazolam	single
Janssen Research & Development	2013, September	recruiting	parallel	MDD	yes	SEP, MEP; unspecified depression scale	IV infusion / 40min	0.5mg/kg	unclear	single
New York University	2013, December	recruiting	parallel	MDD	no	MADRS	IV bolus	0.25mg/kg	diphenhydramine 25mg	single
Tel-Aviv Sourasky Medical Center	2014, January	ongoing, not recruiting	parallel	MDD or SA	yes	unspecified SI measure	oral	ketamine	unclear	daily for 21 days
University of Cincinnati	2014, July	not yet open	parallel	SI	no	MADRS, SSI	intranasal	0.2mg/kg	saline	given in one day over two doses
Massachusetts General Hospital	2014, November	not yet open	parallel	MDD and SI, age >65	yes	HDRS	intranasal	50mg	saline	2x/wk for 3 wks
Centre Hospitalier Universitaire de Nīmes	2014, November	not yet open	parallel	SI	no	SSI	IV infusion / 40min	0.5mg/kg	saline	twice over 3 days
Minneapolis Veterans Affairs	2015, Jan	not yet open	parallel	MDD	yes	MADRS	IV infusion / 40min	0.5mg/kg, 3x/wk for 2wks	5 midazolam infusions and 1 ketamine infusion	comparing one versus 6 infusions

utilizing IV infusions (Murrough et al., 2011; Zigman & Blier 2013), and a case series with IM administration (Harihar et al., 2013), all showed benefit. Conversely, one OLI of oral ketamine in 14 hospice patients found no such benefit (Irwin et al., 2013).

In bipolar depression, two RCTs and two case series report on suicidality. The two RCTs, both by the same group, conflict in finding significant benefit. Zarate et al. (2012) demonstrated significant differences in between-group MADRS-SI scores through three days. Diazgranados et al. (2010a), on the other hand, found no difference between IV ketamine and placebo, though these authors excluded patients with risk for suicide at baseline. One case series utilized IM administration and showed qualitative improvement (Cusin et al., 2012), while the other did so with oral doses every two to four weeks (De Gioannis & Leo, 2014).

Adverse Effects

During infusion, two adverse events with ketamine led to discontinuation in RCTs (Suppl. Table 2): hypotension and bradycardia, and hypertension unresponsive to beta-blockers (Murrough et al., 2013). Following infusion, four adverse events led to discontinuation: worsening mood in three patients (one with suicidal ideation), and increased anxiety in the other (Diazgranados et al., 2010a). Two placebo patients discontinued, one each during infusion and after infusion for elevated blood pressure (Valentine et al., 2011) and hypomania (Diazgranados et al., 2010a), respectively. In OLIs, only two adverse events led to treatment discontinuation out of nearly 300 individuals (Suppl. Table 3): elevated blood pressure unresponsive to beta-blockers during infusion (Murrough et al., 2013), and a panic attack (Diamond et al., 2014). In case reports, one subject receiving *S*-ketamine at 0.25mg/kg discontinued during infusion due to dissociation (Segmiller et al., 2013).

Tachycardia and transient elevations in blood pressure were commonly reported hemodynamic effects in RCTs and OLIs, though two cases of hypotension (Murrough et al., 2013; aan het Rot et al., 2010), one case of bradycardia (aan het Rot et al., 2010), and one vasovagal episode were also reported. Aan het Rot et al. (2010) also reported one patient with bradypnea, with oxygen desaturation to 94%. To date, no RCTs or OLIs have reported these effects persisting beyond four hours, save for one patient with mild, asymptomatic hypotension lasting until discharge at 24 hours (aan het Rot et al., 2010).

Dissociation, psychotomimetic effects, manic symptoms, and other psychiatric effects were assessed in most investigations. In RCTs and OLIs adverse effects

Table 6. Ongoing and planned studies, Part 2. Open label studies

Sponsor	Date initiated	Status	Study design	Diagnosis	TRD	Primary outcome	Route	Ketamine arm / dose	Number of doses
University Hospital, Geneva	2010, June	unknown	open label	MDD	yes	MADRS	IV infusion / 40min	0.5mg/kg	single
Massachusetts General Hospital	2012, April	ongoing, not recruiting	open label	MDD and SI	yes	HDRS	IV infusion / 45min	0.5mg/kg, then 0.75mg/kg for nonresponders	2x/wk for 3 wks
Jinling Hospital, Nanjing University School of Medicine	2012, April	unknown	open label	MDD or bipolar	yes	MADRS, HDRS, SSI	IV infusion / 40min	0.5mg/kg	single
New York State Psychiatric Institute	2013, April	recruiting	open label	bipolar	yes	unclear	IV infusion / 60min	0.5mg/kg + d-cycloserine orally	single
Nationwide Children's Hospital	2013, August	recruiting	open label	SA, age 12-18	no	QIDS-C, CGI	IV infusion / 15min	0.5mg/kg	single
University of Minnesota	2014, February	recruiting	open label	MDD, age 12-18	yes	CGI	IV infusion / 100min	0.5mg/kg	3x/wk for 2 weeks
Mayo Clinic	2014, March	recruiting	open label	MDD or bipolar, and SI	yes	MADRS	IV infusion / 100min	0.5mg/kg	3x/wk for 2wks, then weekly for 4wks
NIMH	2014, April	recruiting	open label, parallel [1]	MDD	yes	MADRS	IV infusion / 40min	0.5mg/kg	single
UCLA	2014, June	recruiting	open label	MDD	yes	MADRS, HDRS	IV infusion / 40min	0.5mg/kg	single
Sheba Medical Center	2014, August	not yet open	open label	MDD	yes	MADRS	IV infusion	0.5mg/kg	unclear
Yale University	2014, November	not yet open	open label	MDD or bipolar	yes	Extinction Learning Task performance	IV infusion	unclear	2x/wk for 2 wks, with CBT for 8 wks

[1] Study will compare outcomes between those with and without family history of alcoholism.

as measured by Clinician Administered Dissociative Symptom Scale (CADSS; Bremner et al., 1998), Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) or Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) revealed significant increases compared with control/baseline, that generally resolved by 80 min to four hours.

In the four OLIs utilizing repeat dosing, changes in CADSS and BPRS were similar after each infusion, with no progressive increase with multiple infusions. Similarly, hemodynamic and respiratory effects did not worsen with repeat administrations. Dose dependent increases in dissociative symptoms were reported in one ascending dose study, in which rapid IV infusions over two to five minutes were used (Lai et al., 2014). Transient tachycardia and asymptomatic premature ventricular contractions were described in one patient, and nausea and vomiting in another (aan het Rot et al., 2010; Shiroma et al., 2014). One suicide attempt occurred during the washout period before ketamine infusion (Murrough et al., 2013). One report of mania was found in a patient who received 34 doses of ketamine at variable intervals over a 1 year period (Liebrenz et al., 2009), and another reported a "mild" hypomanic episode in a patient after his third infusion (Diamond et al., 2014). Niciu et al. (2013) analyzed data from three NIMH RCTs of IV ketamine infusion in bipolar depression, finding transient increases in YMRS scores lasting no more than a day after infusion, and no cases of full blown mania or hypomania. They also reported that within the YMRS elevations, none of the patients had specific elevations in the elevated mood item (Suppl. Table 2).

Adverse effects in case reports were consistent with those of RCTs and OLIs. Events uniquely described in the case reports include the following: less pronounced dissociation on a second dose compared to the first (Liebrenz et al., 2009; Clark et al., 2014), hypomania in one patient (Szymkowicz et al., 2013), "delirium" for 5-8 minutes following 0.5mg/kg bolus (Yang et al., 2013), and in a report of two patients, psychotomimetic effects during racemic but not *S*-ketamine infusions (Szymkowicz et al., 2013).

Intramuscular reports noted effects similar to those of IV, without mention of hemodynamic changes. In one case, decrease in dizziness and derealization occurred over repeat (41 total) injections (Zanicotti et al., 2013), whereas in another a dose of 1.0mg/kg resulted in intolerable dissociative effects necessitating a dose decrease to 0.5mg/kg (Cusin et al., 2012). In one intranasal study of 12 pediatric patients, transient (60 minutes) dissociative effects similar to IV were reported, as well as mild palpitations and moderate respiratory distress (Papolos et al., 2013), whereas in another intranasal case report the patient described feeling "high," but only during the first few of more than thirty administrations (Clark et al., 2014). Sublingual dosing in 26 patients resulted in no euphoria, psychotic, or dissociative symptoms. Lightheadedness (mild, transient, and improving on repeat dosing) and one report of tachycardia (<30 minutes) occurred. Mouth numbness was the only novel effect reported (Lara et al., 2013). In the 50 patients that received oral ketamine, essentially no adverse effects, including vital sign changes, were reported (Paslakis et al., 2010; Irwin & Iglewicz, 2010; Irwin et al., 2013), save for disorientation and hallucinations in a minority of a medically ill hospice population (Iglewicz et al., 2014). In fact, there were improvements in BPRS and adverse symptom checklists (Irwin & Iglewicz, 2010). Only diarrhea, trouble sleeping, and "trouble sitting still" occurred (one each) in a study of 14 patients (Irwin et al., 2013). The only study of oral *S*-ketamine, divided over three times daily, found essentially no side effects in all four patients.

Ongoing and Planned Studies

A review of ClinicalTrials.gov yielded five OLIs and twenty RCTs (Table 6). Add-on oral medication as a potential method for extension of benefit is being investigated in a total of four studies: lithium, venlafaxine, minocycline, and d-cycloserine. Multiple dose regimens are being studied in nine trials, and suicidality is being studied in five. Four are assaying escalating doses, variable number of infusions, or increasing duration of infusion. The majority utilize ketamine IV infusions, while three are using intramuscular, intranasal, oral, or subcutaneous methods of administration. In only one study did we find a plan to include more than one route of administration. All studies utilize racemic ketamine.

Discussion

Discussion is divided into consideration of antidepressant and antisuicidal effects, adverse effects, ketamine's stereoisomers, further clinical issues, and recommendations for future research.

Antidepressant and antisuicidal effects

Ketamine appears to have remarkably robust efficacy in short-term relief of severe and treatment-resistant depression, with onset in hours, and duration

of at least a few days. While this has been observed in both unipolar and bipolar depressed populations, in the latter, duration appears slightly shorter and there are fewer supporting studies. Similarly, in cases of non-TRD, this effect seems to hold, though relative efficacy is unclear. Ketamine's effectiveness in relief of acute suicidal ideation is also a highly valuable finding, though with less support. This benefit appears unique to ketamine among available treatment options, although comparisons with other active treatments are lacking. Furthermore, there are conflicting findings as to whether reductions in suicidality are specific, or rather related to overall reductions in depression (Price et al., 2009; Diazgranados et al., 2010b; Rasmussen et al., 2013; Murrough et al., 2013). Studies for the most part have excluded individuals with recent suicidality, and instead performed post-hoc reanalyses of suicidality subscales, though future studies are enrolling high risk individuals for targeted therapy with ketamine (Table 6). To date there are no data on suicide attempts, completed suicide, or other long-term effects, nor on parasuicidal behavior. Despite the limited amount of data, this is fertile ground for further research given the great potential benefit to treat emergent suicidality or avert hospitalization. Ketamine deserves consideration for use in select patients who otherwise would continue to suffer severely, if only as a temporizing measure to give clinicians time to identify and implement alternative treatments.

The largest challenge with this promising agent remains the extension of benefit for the longer term, which is pertinent to the vast majority of depressed patients who have failed to benefit sufficiently from psychotherapy, psychosocial interventions, and the initial tiers of somatic intervention. Repeated ketamine infusions have shown some promise, and there may be a cumulative dose effect similar to ECT, where a series of treatments are required to induce full response or remission (aan het Rot et al., 2010; Murrough et al., 2013; Rasmussen et al., 2013). Indeed, several studies concluded patients require more than one infusions before being considered non-responders. The comparison to ECT is tempting, and certainly makes for a good argument against those who would dismiss the potential for ketamine in depression because of the only short-term benefit of single infusions. It is far from clear what the optimum dose, frequency, and number of infusions will be, and how this might be individualized, though future studies will be revealing. It also worth noting that some patients do not benefit from ketamine, despite multiple treatments (Szymkowicz, Finnegan, & Dale, 2014).

Alternatives to IV infusion, such as intramuscular (IM), intranasal(IN), oral, sublingual (SL), and subcutaneous (SC) routes, have been ástudied to a lesser extent, but do appear to work, with the trade-off of potentially lower response rates with all routes other than the IM, which results in ketamine bioavailability similar to IV administration. A significant limitation is lack of high quality prospective studies: of these alternate routes, our review found only one RCT, which utilized IN administration (Lapidus et al., 2014). Compared with IV administration, IM, IN, and SL routes are similarly rapid acting, with conflicting and weaker data for SC and oral administrations. Duration of benefit is similar to IV infusions, on the order of days, but has been successfully prolonged with repeated dosing, which is notably easier given the relatively low resource requirements with such administrations. Several cases describe treatment in an office-based setting, with patients returning to the office anywhere from multiple times a week to once a month, and maintaining response on the order of months. It is unclear if such response eventually fades, or rather if it could be continued indefinitely, though several cases describe maintenance for nearly a year (Zanicotti et al., 2013; Cusin et al., 2012). Oral dosing, while used mostly in hospice populations, appears to have slower onset of benefit, though an initial loading dose via a rapid acting route of administration could be combined with more convenient maintenance daily oral administration, as in one case report (McNulty et al., 2012).

Adverse effects

Ketamine appears to be well tolerated, the most commonly reported adverse effects being transient dissociative and psychotomimetic experiences. As noted in several studies, patients appear to become tolerant to such effects after several subsequent administrations, and yet maintain a similar antidepressant response (Berman et al., 2000; Paul et al., 2009; Luckenbaugh et al., 2014). Occasionally, hemodynamic effects, typically transient and mild, have led to treatment discontinuation although in every case these have responded to conservative management. There does not appear to be a correlation between hemodynamic effects and antidepressant response (Luckenbaugh et al., 2014). In our review, sublingual, intranasal, and especially oral administration generally resulted in fewer adverse effects

than seen after IV administration, and may be due to a slower increase in blood levels (Lara et al., 2013; Paslakis et al., 2010; Irwin & Iglewicz, 2010; Irwin et al., 2013; Iglewicz et al., 2014). Supporting this possibility, Lai et al. (2014), found extensive dissociative symptoms with IV administration over 2 minutes, leading them to mitigate this issue by extending administration over five minutes. The safety profile of short-term ketamine, particularly in closely monitored settings, is reassuring.

There is however a relative paucity of data on ketamine's adverse effects in the long-term treatment of depression. Long-term exposure in abuse populations, where dose and frequency far exceed those used in clinical protocols, does suggest potentially serious sequelae. In such populations, both short- and long-term neurocognitive adverse effects have been reported (Curran & Monaghan, 2001; Morgan, Monaghan, & Curran, 2004). Conversely, data from studies utilizing ketamine for treatment of depression indicate that it may actually improve neurocognitive outcomes, most likely by reversing the "pseudo-dementia" seen in severe depression (Permoda-Osip, Kisielewski, Bartkowska-Sniatkowska, & Rybakowski, 2015; Shiroma et al., 2014). Lower urinary tract symptoms (LUTS) appear to be a not infrequent problem in long-term abusers of ketamine, and include urinary frequency, urge incontinence, dysuria, urgency, and hematuria (Chu et al., 2008; Shahani, Streutker, Dickson, & Stewart, 2007). Severe sequelae have been reported including interstitial cystitis, papillary necrosis, and irreversible renal failure. In chronic pain patients and abusers, LUTS have been reported as early as five months, although symptoms may begin in as little as nine days (Chu et al., 2008; Storr & Quibell, 2009; Grégoire, Maclellan, & Finley, 2008). One large prospective cohort study surveyed 3,806 recreational users, 1,285 of whom had used ketamine in the year prior. LUTS was reported in 340 (26.6%) in a dose and frequency related pattern. Resolution with abstinence occurred in 51% of cases, and continued deterioration occurred in 3.8% (Wein, 2013). Mechanisms for these effects are unknown. In our review, only one complaint of urinary tract symptoms was found, cystitis, and judged to be caused not by ketamine, but rather sexual activity (Diamond et al., 2014). Another setting in which ketamine's rapid onset of antidepressant—in addition to analgesic—effects has been used with success is the inpatient palliative care setting (Prommer et al., 2012, Iglewicz et al., 2014), though concern has been raised that in the cancer patients, ketamine's mTor upregulation could accelerate tumor growth (Yang, Zhou, & Yang, 2011). In treatment of bipolar depression, another important adverse effect to monitor for is induction of mania or cycle acceleration. As noted in the Niciu et al. (2014) review of three larger NIMH trials, this was not found to be a serious concern, however long-term data in this area are completely lacking.

Ketamine's Stereoisomers

Ketamine exists as a racemic mixture of the *S*- and *R*- stereoisomers, yet these appear to have subtly different effects. *S*-ketamine has long been known to have approximately 2-3 times greater potency in terms of analgesia and anesthesia (Kohrs & Durieux, 1998), and 3-4 times greater affinity for the PCP binding site of the NMDA receptor, but only negligible binding to the sigma receptor. *R*-ketamine on the other hand, has greater, although still weak, sigma receptor binding, but the significance of this is unclear (Vollenweider, Leenders, Oye, Hell, & Angst, 1997). Observations from the anesthesia literature initially noted that in equianalgesic doses, *S*-ketamine has a lower incidence of psychotomimetic side effects than either the racemate or *R*-stereoisomer (Raeder et al., 2000), leading some to investigate it for depression. Both the racemate and *S*-ketamine appear to have antidepressant effects, but data regarding psychotomimetic effects of the component stereoisomers are more contradictory. A separate series of trials may perhaps explain this; one pilot study of healthy individuals found that the dose of *S*-ketamine required to induce psychosis is 60% of that of the racemate, suggesting the *S*-enantiomer is responsible for such effects (Vollenweider et al., 1997). These authors found psychotomimetic effects in *S*-ketamine versus "a state of relaxation" in *R*-ketamine (Vollenweider et al., 1997). Animal studies assessing equimolar equivalents of each stereoisomer found both to provide a rapid and long lasting antidepressant effect, but ultimately a longer durability of effect with the *R*-enantiomer, leading them to speculate the *R*- form may be a good candidate for future study (Zhang, Li, & Hashimoto, 2014; Hashimoto et al., 2014). Further research directly comparing *S*-, *R*-, and racemic ketamine is needed to clarify if one indeed exhibits fewer dissociative effects while still maintaining antidepressant efficacy.

Further Clinical Issues

There is no uniform definition of treatment resistance in the literature reviewed, although patients

with or without treatment resistance, however defined, respond similarly. In assessing improvements in depression, the most commonly used measures—the MADRS and HDRS—may not adequately assess change over a time scale on the order of hours. Several questions, for example regarding sleep and appetite, cannot reflect change over the course of a 40 minute infusion; some studies have gotten around this by carrying forward prior subscores (Rasmussen et al., 2013). The issue of concomitant medications—or their discontinuation—is another confound which will need to be carefully managed in the design of future long term studies.

Several potential predictors of response have received attention. Our review suggests that both bipolar and unipolar depressed patients may exhibit short term response to ketamine. Besides the potential for pharmacologic differences between the *S*- and *R*-enantiomers discussed above, ketamine is hepatically metabolized to norketamine, which also has neurotrophic effects and psychopharmacologic properties. The importance of this is unclear; Sos et al. (2013) found no correlation between blood levels of ketamine or norketamine and antidepressant response. Several authors have suggested that the melancholic subtype of major depression may augur a greater likelihood of response, but this not been studied prospectively (Paslakis et al., 2010; Atigari & Healy, 2013; Gálvez et al., 2014). Multiple studies found a greater likelihood of antidepressant response in TRD patients with a family history of alcoholism, compared to those without, although no relationship to personal history of alcoholism was seen (Phelps et al., 2009; Niciu et al., 2014). Ionescu, Luckenbaugh, Niciu, Richards, & Zarate (2014) found greater response in anxious versus non-anxious unipolar depression, but in a separate post-hoc analysis in bipolar depression found no difference between the anxious and non-anxious subtypes. At least in bipolar depression, this is notable because those with the anxious subtype are frequently poorer responders to conventional treatment. To this end, in studies of conditions previously classified as anxiety disorders, such as post-traumatic stress disorder and obsessive-compulsive disorder, ketamine has also shown benefit (Feder et al., 2014; Rodriguez et al., 2013).

To date, other agents directed at the neurochemical system most frequently held to account for ketamine's antidepressant effect—NMDA receptor antagonism—have been disappointing in terms of extending ketamine's short-term benefits (Ibrahim et al., 2012; Mathew et al., 2010; Zarate et al., 2006; Heresco-Levy et al., 2006). Additional trials are underway to explore this strategy, although infusion of a specific NMDA antagonist, AZD6765, was not effective (Zarate et al., 2013). Alternative mechanisms, such as ketamine's effects on seizure threshold, are worth considering (Atigari & Healy, 2013).

An obvious question is how dissociative and antidepressant effects might be related. Our review found that the time course of these effects differs substantially, and antidepressant effects can occur in patients who do not experience even transient dissociative effects and vice-versa. One post-hoc analysis found that magnitude of acute dissociative symptoms partially correlated with later antidepressant response (Luckenbaugh et al., 2014). Thus, the dissociative effects are not necessarily part of the antidepressant effects *per se*. On the other hand, it is worth considering that this dissociation is part of the unique effect of ketamine that is not shared by conventional antidepressants: an altered sense of self that can also lead to a new state of contentment. This could explain why recent trials with non-psychoactive NDMA antagonists have not demonstrated antidepressant efficacy, and may in fact represent an as yet unexplored aspect of mood regulation—what might be called the eudaimonic dimension (or "well-being," from Aristotle)—that ketamine has given the field an opening to better explore. Companion articles in this current issue expand on this notion in much more depth. It is also worth noting that nitrous oxide and classic hallucinogens, share similar dissociative/psychotomimetic and antidepressant effects with ketamine (Nagele et al., 2014; Baumeister, Barnes, Giaroli, & Tracy, 2014). Similarly, ketamine and the classic hallucinogens have each been employed in end of life care, either for depression or anxiety, but perhaps with a similar mechanism (Iglewicz et al., 2014; Gasser et al., 2014; Grob et al., 2011). It may be the case, as with classic hallucinogens, which were originally termed psychotomimetic, that these altered states are less "psychotic mimicking" and more psychedelic, or "mind manifesting." In the case of classic hallucinogens, concerns over these effects led their potential antidepressant benefit to be ignored for many years (Baumeister et al., 2014).

A corollary issue pertinent to ketamine's unique effects is what has been called "set and setting" (Johnson, Richards, & Griffiths, 2008). That is, the mind sets of the provider and the patient, and the

environmental setting in which the treatment session occurs, may have particularly important impact on treatment outcome. Consistent with this, two studies conducted in noisy, crowded, high intensity medical settings had the poorest outcomes among the studies of multiple ketamine infusions (Rasmussen et al., 2013; Diamond et al., 2014). Conversely, recent studies of MDMA-assisted psychotherapy for post-traumatic stress disorder (Mithoefer et al., 2013) and psilocybin for end of life anxiety (Grob et al., 2011) used carefully designed protocols to optimize these aspects of the interventions. It is possible that similar optimization of ketamine treatment would improve antidepressant outcomes.

Several unanswered questions remain in the clinical use of ketamine for depression. Is the presence of an anesthesiologist required? By extending the duration of the ketamine infusion to 100 minutes anesthesiology monitoring was determined to be unnecessary (Rasmussen et al., 2013). Another study reports infusions were performed by a psychiatrist with Basic Life Support training and code team backup (Zigman & Blier, 2013). A further question, as alluded to in discussion of alternate routes, is whether ketamine could be used in an office-based setting: the RCT using intranasal ketamine amended their protocol after demonstrated safety, and began discharging individuals four hours after receiving their doses (Lapidus et al., 2014). Furthermore, several case reports utilizing IM and other methods of administration describe successful long-term treatment in an office-based setting. Ultimately, more rigorous studies in such settings are needed.

Ketamine has not yet been formally promoted for general clinical use but has seen growing use among psychiatrists in private practice and academic centers. Providers hoping to utilize ketamine for treatment of depression should take care to offer full informed consent as well as communicate that this use is off-label from FDA approved indications of ketamine. There is a relative paucity of data on both the effectiveness and safety in the outpatient setting, though case reports suggest this can successfully be done. Existence of an abuse population must also be considered when expanding ketamine use to this setting. Further, there are serious safety concerns from the abuse and pain management literature, as noted above. Our review provides strong suggestive support for the use of more "user friendly" alternatives to IV infusion, but caution is warranted.

Recommendations for future research

Based on this review, the following specific recommendations stand out:

1) Trials to further assess if benefit seen in TRD extends to non-treatment refractory depression.
2) Direct comparisons between various routes of administration, both in acute and maintenance treatment, as well as to both placebo or standard agents.
4) Trials to specifically assess anti-suicidal effects, in both acute and maintenance treatment.
5) Dose-response relationships for each route of administration, including monitoring of levels of both ketamine and norketamine levels.
6) Examination of optimal dosing frequencies for all routes of administration, with the goal of extending duration of response
7) Systematic monitoring of psychotomimetic and dissociative effects with long-term treatment, and correlations with responses to treatment, including whether tachyphylaxis to these effects may occur.
8) Systematic monitoring of neuropsychological functions, urinary tract related symptoms, suicidal behavior, and at least in bipolar subjects, mood switching, during long term treatment.
9) Careful analysis of ketamine's "eudaimonic" effects as they relate to antidepressant, dissociative, psychotomimetic, and antisuicidality effects.
10) Additional trials to follow-up on the suggested benefits of ketamine in other disorders such as PTSD and OCD; and as a transpersonal agent for those with life threatening illness and at the end-of life.

Conclusion

A thorough review of the literature utilizing ketamine for treatment refractory depression reveals rapid onset of action in the first several hours, often lasting several days to a week, after a single infusion. We acknowledge a common criticism raised about the limited time frame of efficacy from a single dose of ketamine, however this does not distinguish it from any other treatment of depression, including psychotherapy, medication, or ECT. Furthermore, multiple dosing studies and alternate routes of administration have safely and successfully extended the antidepressant benefit of ketamine, with select cases demonstrating maintenance for nearly a year. These findings are all

the more impressive when viewed from the perspective of an already treatment-resistant population. While the existing paradigm of 40 minute IV infusions has proven limitedly effective, much less resource intensive protocols such as intranasal, intramuscular, oral, and subcutaneous methods of administration represent a potential revolution in the use of ketamine. These routes of administration have the advantage of expanding ketamine research to the outpatient setting. We did not find evidence of serious neurocognitive adverse effects in clinical use, in contrast to what has been reported with ketamine abuse. This is an area in which ketamine may distinguish itself from ECT as an alternative for TRD. Similarly, we did not find evidence of LUTS, but this has not been systematically investigated. The frequency and seriousness of LUTS in the abuse population makes it an important adverse effect to monitor in future long term studies.Dissociative effects are common, time limited, generally well tolerated, and appear to subside in intensity with repeat dosing. These and other unique effects, distinguish it from currently used monoaminergic antidepressants and warrant further study in terms of their ability to advance understanding of depression and its treatment. Significant hemodynamic effects requiring intervention are possible but uncommon, and do require careful monitoring. Potential contraindications do exist, including psychosis, abuse liability, and hemodynamic instability, but with care in patient selection unwanted outcomes can be minimized. Ketamine is clearly a very promising agent. While we must urge caution in wide spread clinical application before further research is completed, our review of the risks and benefits supports its use in carefully selected cases who have not benefited from other treatments.

Abbreviations Key

ADHD, Attention Deficit Hyperactivity Disorder
BDI, Beck Depression Inventory
BDI-SI, Beck Depression Inventory Suicide Item
BDNF, brain-derived neurotrophic factor
BPRS, Brief Psychiatric Rating Scale
CADSS, Clinician Administered Dissociative States Scale
CBQ, Childhood Bipolar Questionnaire
COPD, Chronic Obstructive Pulmonary Disease
DS, Demoralization Scale
ECT, Electroconvulsive Therapy
HDRS, Hamilton Depression Rating Scale
HDRS-SI, Hamilton Depression Rating Scale Suicide Item
HTN, Hypertension
ITT, intent to treat
LUTS, lower urinary tract symptoms
MADRS, Montgomery-Åsberg Depression Rating Scale
MADRS-SI, Montgomery-Åsberg Depression Rating Scale Suicide Item
MEP, motor evoked potentials
NMDA, *N*-methyl-D-aspartate
OAS, Overt Aggression Scale
QIDS, Quick Inventory of Depressive Symptoms
QIDS-SR Quick Inventory of Depressive Symptoms-Self Report
rTMS, repetitive transcranial magnetic stimulation
SEP, sensory evoked potentials
SI, Suicidal Ideation
SSF, Suicide Status Form
SSI, Scale for Suicide Ideation
SSRI, selective serotonin reuptake inhibitor
TRD, Treatment-resistant depression
YBOCS, Yale Brown Obsessive-Compulsive Scale
YMRS, Young Mania Rating Scale

IV, intravenous
IM, intramuscular
t, time of first administration
mg, milligrams
kg, kilograms
mL, milliliters
hr, hours
min, minutes
mos, months
wk(s), weeks

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About the Journal

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Supplemental Table 1. Cases with IV administration of ketamine, Part 1. *S*-ketamine

Study	Year	Diagnosis		N		Age	Comorbidities	Medication Status	Formulation	Dose	No. of doses	Frequency	Duration of study	Measure	Depression response within 24 hours	Durability of benefit
Paul et al. [1]	2009	unipolar	yes	2	1M 1F	51, 58	1) nicotine dependence, HTN 2) none	continued	racemic	0.5mg/kg over 40 min	1	weekly	2 weeks	HDRS	yes; 1/2 (50%)	3 days
									S-ketamine	0.25mg/kg over 40 min	1	weekly	2 weeks	HDRS	no; 0/2 (0%), though had near-response	n/a
Denk et al.	2011	unipolar	yes	1	F	56	none	unclear	*S*-ketamine	0.25mg/kg over 40 min	1	n/a	100 minutes		yes, remission immediately after infusion	n/a
Segmiller et al. [2]	2013	unipolar	yes	6	?	?	unclear	continued	*S*-ketamine	0.25mg/kg over 40 min	6	1-2x/wk for 4 wks	4 weeks	HDRS	yes; though after 1st, 3/6 (50%), and 3rd, 4/6 (68%), infusions	not reported

[1] Two subjects received 0.5mg/kg racemic ketamine and 0.25mg/kg *S*-ketamine over 40 minutes in this open-label crossover study.
[2] Some data not available.

Supplemental Table 1. Cases with IV administration of ketamine, Part 2. Racemic ketamine

Study	Year	Diagnosis	TRD	N	Gender	Age	Comorbidities	Medication Status	Formulation	Dose	No. of doses	Frequency	Duration of study	Measure	Depression response within 24 hours	Durability of benefit
Ostroff et al.	2005	unipolar	yes	1	F	47	schizo-affective disorder	off for 1 day	racemic	0.5mg/kg bolus (for ECT induction)	2	every 48 hours	5 days	custom scale	yes; mood rating improved from 2/10 to 7/10	5 days
Correll and Futter	2006	unipolar	yes	2	F	39	none	continued	racemic	0.27mg/kg/hr for 5 days	1	n/a	6 months	HDRS	no; remission via first HDRS time point at 5 days	12+ months
		unipolar	yes	2	M	33	none	continued	racemic	0.3mg/kg/hr for 5 days	3	2.5 and 7.5 months later	8 months	HDRS	no; remission via first HDRS time point at 5 days	"several weeks"
Liebrenz et al [1]	2007, 2009	unipolar	yes	1	M	55	alcohol, benzodiazepine, and nicotine dependence	ativan continued, off antidepressants for 1 week	racemic	0.5mg/kg over 50min	2	35 days later	14 days, 7 days	HDRS	no; 1st infusion, response at 48hrs; 2nd infusion near response at 48hrs	1st infusion maintained for 14 days, 2nd infusion maintained 1 day
Kollmar et al.	2008	unipolar	yes	1	F	47	none	unclear	racemic	0.5mg/kg over 40 min	2	2 wks later	6 months	HDRS	yes, remission within 24 hours after each infusion	4 days
Stefanczyk-Sapieha et al.	2008	unipolar	yes	1	M	50	metastatic prostate cancer	methylphenidate held day of infusion	racemic	0.5mg/kg over 60min	2	10 days later	13 days	HDRS, BDI	no, near-response within first 6 hrs	6 hrs each time
Messer et al.	2010	unipolar	yes	2	M	50	obesity, sleep apnea	unclear	racemic	0.5mg/kg over 40 min	6	every other day	12 days	BDI	no, only after 2nd infusion	relapse at 29 days
		unipolar	yes	2	M	45	history of alcohol abuse, hypertension	unclear	racemic	0.5mg/kg over 40 min	2	weekly	12 days	BDI	yes, after 1st infusion	relapse at 18 days
Murrough et al.	2011	unipolar	yes	1	F	45	none	off	racemic	0.5mg/kg over 40min	6	three times a week	12 months	MADRS	yes, remission within 24 hrs	remission over 3 months via QIDS-SR
Zigman and Blier	2013	unipolar	yes	1	F	37	prior pituitary adenoma resection, B12 deficiency, and hypothyroidism	continued	racemic	0.5mg/kg over 40 min	1	once	1 month	custom scale	yes, dysphoria from 10/10 to 3/10 at 40min	mood remained improved for 8 days
Yang et al.	2013	unipolar	no	3	3M	19-31	none	off	racemic	0.5mg/kg over 3 min	1	once	120 minutes	group mean MADRS	yes; halved at 120min	n/a
Szymkowicz et al.	2013	unipolar and bipolar II	yes	3	?	?	1) panic disorder, 2) none, 3) bulimia, bipolar II, cluster C	continued	racemic	0.5mg/kg over 40 min	16 - 31	varied, from every other day to every 2 months	12 months	MADRS	yes; though after 2nd, 3rd, or 10th infusions	12 months in one patient
Szymkowicz et al.	2014	unipolar	yes	4	3M 1F	72	1) GAD, parkinsons, dementia 2) GAD, dementia, 3) GAD	continued	racemic	0.5mg/kg over 40 min	2 - 6	unclear	unclear	MADRS	no	n/a
Aligeti et al	2014	bipolar II	no	1	M	32	alcohol dependence	off	racemic	0.5mg/kg IV push	1	once	6 months	HDRS7, MADRS	yes	through 5 days, unclear afterwards
Lai et al. [2]	2014	unipolar	yes	4	2M 2F	51	1) - 3) melancholic depression	continued	racemic	saline	1	weekly	5 weeks	MADRS	no, 0/4 (0%)	n/a
										0.1mg/kg over 2-5 min					yes, 2/4 (50%)	1-3 days
										0.2mg/kg over 205 min					no, 0/4 (0%)	n/a
										0.3mg/kg over 2-5 min					no, 0/4 (0%)	n/a
										0.4mg/kg over 2-5 min					yes, 1/4 (25%)	1 day

[1] Includes follow-up publication on the same patient.

[2] Subjects received ascending doses of ketamine, from 0.1 - 0.4mg/kg, interspersed with a saline treatment. Patients were blinded to the order.

Supplemental Table 2. Random controlled trials adverse effects

	Study	Year	Design	Diagnosis	TRD	N	Gender	Age	CADSS, ket vs. PBO	BPRS, ket vs. PBO	YMRS, ket vs. PBO	Hemodynamic, Respiratory, EKG; more common with ketamine	Subjective adverse effects more common with ketamine	Subjective adverse effects more common in placebo	Adverse event leading to discontinuation	Miscellaneous
Unipolar Depression	Berman et al.	2000	double blind crossover	unipolar(8) bipolar(1)	n	9	4M 5F	37	not reported	Significantly greater BPRS scores. Non-significant by 80 min. Resolved at 110min	not reported	not reported	not reported	not reported	none reported	Changes in BPRS or VAS-high scores did not correlate with percent decreases observed in HDRS scores
	Zarate et al.	2006	double blind crossover	unipolar	y	18	16M 12F	47	not reported	Significantly greater BPRS positive symptoms subscale scores compared to placebo, only at 40 min	YMRS scores higher at 40 min only	"elevations in blood pressure,"	perceptual disturbances, confusion, euphoria, dizziness, and increased libido. The majority of adverse effects ceased within 80 min after the infusion. Reports of derealization or depersonalization ceased by 110min.	Gastrointestinal distress, increased thirst, headache, metallic taste, and constipation	none reported	A) Inverse relationship trend noted between the percentage change in HDRS score at day 1 and the peak percentage change in BPRS positive symptoms subscale score. B) "No serious adverse events occurred during the study."
	Valentine et al.	2011	single blind crossover	unipolar	n	10	4M 6F	42	Significantly greater dissociation at 20min; non-significant by 60min	Non-significant greater BPRS positive symptom scores at 20minutes to 80minutes.	not reported	Significantly elevated SBP at 10-95 min mean, peak 40min of 14.1+/-13.4mmHG. Trend toward increased DBP. No effect on heart rate	not reported	not reported	Elevated blood pressure during placebo infusion	-
	Sos et al.	2013	double blind crossover	unipolar	n	27	15M 15F	43	not reported	BPRS score change did not achieve statistical significance as a covariate (p=0.10)	not reported	"mild" increases in BP	"Typical effects" dissociation/perceptual disturbances, confusion, emotional blunting, euphoria. All resolved at 60 min.	worsening depression	Worsening depression in two receiving only KET	BPRS scores were significantly correlated with change in MADRS score at day 7 (P=0.04), and trended toward significance at days 1 and 4 (p=0.06 and <0.07, respectively).
	Murrough et al. (Continued below)	2013	parallel group	unipolar	y	47/25	35M 37F	47/43	Significantly greater dissociation at 40min	No significant difference in BPRS or BPRS positive scale	Mean YMRS <1 for both groups at 40min (only data available).	Elevated blood pressure, mean of 19 systolic and 9.1 diastolic, resolved at 240min. Midazolam decreased mean blood pressure. Hypotension in one patient.	Day of infusion: A) occurring in > 10% of patients: Nausea/vomiting, dry mouth, dizziness, palpitations, sweating, headache, poor coordination, tremor, blurred vision, poor concentration, restlessness, anxiety, decreased energy, and fatigue. B) Considered distressing in > 10%: Dizziness, blurred vision, and poor concentration. Day 1-7 after infusion: A) Nausea/vomiting, diarrhea, dizziness on standing, perspiration, dry skin, rash, dizziness, headache, blurred vision, poor concentration, restlessness, anxiety, fatigue, and malaise. B) Considered distressing in > 10%: Poor concentration, restlessness, anxiety, decreased energy, and fatigue. Day 1-7 after infusion: A) Nausea/vomiting, diarrhea, dizziness on standing, perspiration, dry skin, rash, dizziness, headache, blurred vision, poor concentra-	Day of Infusion: A) Occurring at > 10% incidence: General malaise B) Considered distressing in > 10%: Poor coordination. Day 1-7 after infusion: A) Palpitations and decreased energy. B) Considered distressing in > 10%: General malaise and fatigue . Day 1-7 after infusion: A) Palpitations and decreased energy. B) Considered distressing in > 10%: General malaise and fatigue .	Ketamine (2): Hypertension unresponsive to beta-blockers. Hypotension and bradycardia.	Two serious adverse events during study. Hypotension and bradycardia during venipuncture considered vasovagal, resolved. Suicide attempt during washout period prior to administration of ketamine or midazolam.

Supplemental Table 2 (cont'd). Random controlled trials adverse effects

	Study	Year	Design	Diagnosis	TRD	N	Gender	Age	CADSS, ket vs. PBO	BPRS, ket vs. PBO	YMRS, ket vs. PBO	Hemodynamic, Respiratory, EKG; more common with ketamine	Subjective adverse effects more common with ketamine	Subjective adverse effects more common in placebo	Adverse event leading to discontinuation	Miscellaneous
Unipolar Depression	Murrough et al. (Continued from above)	2013											tion, restlessness, anxiety, fatigue, and malaise. B) Considered distressing in > 10%: Poor concentration, restlessness, anxiety, decreased energy, and fatigue.			
	Ghasemi et al.	2013	parallel group	unipolar	y	9/9	8M 10F	38	not reported	not reported	not reported	Non-significant change in either group. Non-significant elevation in SBP and HR in three ketamine patient on 2nd and 3rd administration, transient.	not reported	not reported	not reported	not reported
	Lapidus et al.	2014	double blind crossover	unipolar	y	20	10M 10F	48	"small increases at 40 minutes" in KET group	"small increases at 40 minutes" in KET group	not reported (though in study design)	Mean increase of 7.6 in SBP. 3 pts > 130 SBP. No pts >100 DBP. No pts over 110 BPM	In > 1 patient: Feeling strange or unreal (8/18). Poor memory. Weakness/fatigue. Dizziness. Poor concentration. Decreased sexual arousal/orgasm/interest. Poor coordination. Numbness/tingling. All resolved by 240 minutes.	Trouble sleeping at 240 minutes and 240minutes to 24 hrs post. At 240 min to 24hrs, sleep disturbance/nightmares and "overall" adverse effect.	None. 2 withdrew prior to any treatment.	Among subjects who responded to ketamine, the increase in CADSS score at +40 min was 1.75 +/- 4.17 compared with 1.09 +/- 1.76 in subjects who did not respond to ketamine.
	Lai et al.	2014	single blind crossover	unipolar	y	4	2M 2F	51	unclear	unclear	unclear	unclear	dose related increase in psychotimimetic side effects.	n/a	none	dose dependent increase in psychotimimetic side effects
Bipolar Disorder	Diaz-grandos et al.	2010	double blind cross-over	bipolar I and II	y	18	6M 12F	48	not reported	not reported	not reported	Tachycardia and increased blood pressure. Resolved minutes after infusion.	Adverse events associated only with ketamine (≥10% of subjects) included dissociation; feeling strange, weird, or bizarre; dry mouth	unclear	Ketamine (4); anxiety, three with worsening mood (one worsening suicidal ideation). Placebo (1): Hypomania	A) "No serious adverse events occurred during the study." B) No adverse event was significantly different from placebo at 80 min or thereafter.
	Zarate et al.	2012	double blind cross-over	bipolar I and II	y	15		47	Significantly greater dissociation at 40min	No significant difference in BPRS or BPRS positive subscale noted.	Non-significant lower YMRS score	Tachycardia in one patient	Dry mouth, headache, breast pain/swelling, leg cramp, dizziness or faintness, difficulty falling asleep, decrease body temp, flatulance, concentration difficulty, drowsy/sleepiness, woozy, loopy, early morning awkening, interrupted sleep, vivid dreams, difficulty speaking, skin irritation, sweating, noise sensitivity, fearfulness, cough, increased thirst, diarrhea, increaed appetite, stool discoloration, increased libido, tremor and menstrual irregularity.	Irritability, muscle, bone, or joint pain, increased body temp, "slowed", and decreased libido.	none reported	A) "No serious adverse events occurred during the study." B)No adverse event was significantly different from placebo at 80 min or thereafter.

Supplemental Table 3. Open label investigations adverse effects

Study & Year (diagnosis)	TRD	N (gender)	Age	CADSS Results	BPRS Results	YMRS Results	Hemodynamic, Respiratory and EKG Effects	Subjective Adverse Effects	Adverse Event Leading to Ending Treatment	Miscellaneous
Machado-Vieira et al.2009 (unipolar)	yes	23 (14M/9F)	44	not reported	not reported	not reported	not reported	not reported	none reported	not reported
Phelps et al. 2009 (unipolar)	yes	26 (14M/12F)	44	Those with positive family history of alcohol (FHP) had significantly higher scores at 40minutes compared to group with family history negative (FHN).	Positive symptoms elevated in FHP and FHN groups at 40 minutes. Baseline by 80 minutes. FHP had significantly fewer dysphoric symptoms at 120 and 230 minutes.	not reported	not reported	not reported	none reported	not reported
Price et al. 2009 (unipolar)	yes	26 0 unique (16M/10F)	48	not reported	not reported	not reported	not reported	not reported	none reported	not reported
Salvadore et al. 2009 (unipolar)	yes	11 (7M/4F)	44	not reported	Significant decrease in psychotic symptoms after 230 minutes.	not reported	not reported	not reported	none reported	not reported
Diazgranados et al. 2010 (unipolar)	yes	33 (20M/13F)	46	Inadequate inter-rater reliability	Inadequate inter-rater reliability	not reported	not reported	Mild perceptual disturbances were observed in most patients only in the first hour after infusion.	none reported	"No serious adverse events occurred during the study"
Salvadore et al. 2010 (unipolar)	yes	15 8 unique (?)	51	not reported	Significant decrease in positive subscale after 230 minutes	not reported	not reported	not reported	none reported	not reported
Mathew et al. 2010 (unipolar)	yes	26 (16M/10F)	48	not reported	Nonsignificant changes in positive symptoms at 240 minutes	"significant main effect of time" on item 1. No effect of pretreatment.	Elevated blood pressure during infusion (mean 19.8 +/- 10.9 systolic mmHg, 13.4 +/- 7.7 diastolic mmHg) and pulse (mean 10.9 +/- 11.9 bpm). Baseline at 40-80 minutes.	Most common: blurry vision, diminished mental/sharpness, dizzy/faint, drowsy/sleepy, feeling strange/unreal, headache, numbness/tingling, ringing in ears/trouble hearing, and slurred speech.	none reported	"There were no serious adverse events, and no treatment-emergent mania or suicidality"
aan het Rot et al. 2010 (unipolar) [1]	yes	10 0 unique (5M/5F)	51	Significantly increased at 40 minutes, normal by 2 hours	Nonsignificant mean increase, baseline at 2 hours.	not reported	"A) Tachycardia and hypertension reported in two patients, resolved 5minutes after infusion. B) Bradycardia in one patient on initial and repeat infusions, resolved by 2hrs. C) Asymptomatic, mild hypotension (80/55) developed in one patient with baseline of 107/48, lasting until discharge at 24hours, and on two repeat infusions. D) Asymptomatic premature ventricular contractions reported in one patient on repeat infusions 4 and 5, resolved at 2hrs. E) Bradypnea noted in one patient on several infusions and one time"	6	three times a week	12 months
Larkin and Beautrais 2011 (unipolar)	no	14 (7M/7F)	31	not reported	no significant elevation at first time point of 40min	no significant elevation at first time point of 40min	not reported	mild positive psychotomimetic symptoms in two patients, resolving within 40 min; mild unpleasant dissociative symptoms in two patients, resolving within 30 min	none	n/a
Ibrahim et al. 2011 (unipolar)	yes	42 (24M/18F)	47	Significantly increased at 40 minutes, normal by 80 minutes	not reported	not reported	not reported	not reported	none noted	not reported
Salvadore et al. 2012 (unipolar)	yes	14 11 unique (9M/5F)	50	not reported	not reported	not reported	not reported	not reported	not reported	not reported

[1] 6 infusions total, 3x/wk for 2 wks

Supplemental Table 3 (cont'd). Open label investigations adverse effects

Study & Year (diagnosis)	TRD	N (gender)	Age	CADSS Results	BPRS Results	YMRS Results	Hemodynamic, Respiratory and EKG Effects	Subjective Adverse Effects	Adverse Event Leading to Ending Treatment	Miscellaneous
Thakurta et al. 2012 (unipolar)	yes	27 (13M/14F)	49	not reported	Significant increase in positive subscale at 40minutes only.	not reported	Non-specific elevation of blood pressure reported	Generally reported: elevated blood pressure, euphoria, headache,increased thirst, and dizziness occurring with ketamine administration ceased within 60 minutes.	none reported	"No serious adverse events occurred during the study"
Cornwell et al. 2012 (unipolar)	yes	20 0 unique (15M/5F)	46	Significantly increased at 40 minutes, not at later intervals	Significant decrease in positive subscale at 80minutes, 120minutes and 230minutes.	not reported	not reported	not reported	none reported	Referred to Ibrahim et al. 2012
Ibrahim et al. 2012 (unipolar) [2]	yes	42 2 unique (26M/16F)	47	Significant decrease to 28 days. First measurement post infusion at 230minutes.	No significant improvement in positive symptoms found after multiple comparison adjustments.	Non-specific improvement in all ketamine patients after day 1.	Elevations in blood pressure and pulse, resolved within 80min. No clinically meaningful EKG changes. No clinically meaningful changes in respiratory effects.	Generally reported: perceptual disturbances, drowsiness, confusion, and dizziness occurred during infusion, resolved within 80min.	none reported	not reported
Thakurta et al. 2012 (unipolar)	yes	22 (10M/12F)	50	not reported	Significant decrease in psychotic symptoms after 230 minutes.	not reported	not reported	not reported	none reported	not reported
Rybakowski et al. 2013 (bipolar, unspecified)	yes	25 (4M/21F)	49	not reported	not reported	not reported	not reported	not reported	none reported	not reported
Rasmussen et al. 2013 (unipolar and biploar) [3]	yes	10 (4M/6F)	47	not reported	No significant change in positive subscale or total BPRS noted at 2hours or one day.	Isolated symptoms. No mania.	No clinically significant elevation in blood pressure during the infusions. No arrhythmia. No patients required respiratory support.	Of 10 patients: Vertigo reported by one, dizziness by three, visual hallucinations by one, drowsiness by three, dysmegalopsia/anxiety and diplopia by one, and no adverse effects reported by three.	none reported	not reported
Murrough et al. 2013 (unipolar) [1]	yes	24 14 unique (15M/9F)	48	Significant increase from a mean of 0.3 ±0.5 pre-infusion to 7.8±12.0 at the peak of the infusion, and baseline by 240minutes.	Significant increase of positive symptoms subscale from a mean of 4.0±0.1 pre-infusion to 4.5±0.9 at the peak of the infusion, and baseline by 240minutes.	Elevated mood measured by the YMRS-1, baseline by 240minutes.	Elevated blood pressure and/or heart rate (33%).	The most common effects were reported with prevalence: 58.3% of patients reported feeling unreal/strange. 54.2% reported abnormal sensations, 50% blurred vision, 45.8% reported feeling drowsy/sleepy. Largely resolved prior to subsequent infusions.	Maximum blood pressure 180/115 during infusion. Unsatisfactory response to anti-hypertensives. Stabilized upon discontinuation.	16.7% reported that any side effect impaired functioning at any time. No serious adverse events occurred during the study,There was no trend towards increasing dissociative or psychotomimetic effects over the course of the trial.
Shiroma et a. 2014 (unipolar) [1]	yes	14 (14M)	54	Significant increase from a mean of 0 before infusion to 8.60±6.49 at the end of the infusion, returned to baseline by 120minutes.	Significant increase in positive subscale from a mean of 4.0±0 before infusion to 4.6±1.9 at the end of the infusion, returned to a mean by 120 minutes.	not reported	Elevation from normotensive to hypertensive blood pressure in one patient (180/92) that rapidly responded to 10mg labetalol. No arrhythmia. No patients required respiratory support.	"Patient with gastroesophageal reflux disease had nausea and	none	all well enough to return home at 4hrs

[1] 6 infusions total, 3x/wk for 2wks;
[2] Reported over 28 days and compared between post treatment with riluzole or placebo.
[3] up to 4 infusions total, 2x/wk for 2 wks or until remission.

Supplemental Table 3 (cont'd). Open label investigations adverse effects

Study & Year (diagnosis)	TRD	N (gender) [dose]	Age	CADSS Results	BPRS Results	YMRS Results	Hemodynamic, Respiratory and EKG Effects	Subjective Adverse Effects	Adverse Event Leading to Ending Treatment	Miscellaneous
Chilukuri et al. 2014 (unipolar)	yes	27 (9/9/9)	37	not reported	not reported	not reported	No change in mean SBP or DBP for all pts combined. Max 160 SBP, max 90			
	yes	9 (3M/6F) [0.5mg/ kg IV]	36	not reported	not reported	not reported	No change in mean SBP or DBP for all pts combined. Max 160 SBP, max 90	sedation/drowsy 22%, heavy head 11%	none	all well enough to return home at 24 hrs
	yes	9 (2M/7F) [0.5mg/ kg IM]	42	not reported	not reported	not reported	No change in mean SBP or DBP for all pts combined. Max 160 SBP, max 90	sedation/drowsy 22%, lightness of body 22% heavy head 11%	none	all well enough to return home at 4 hrs
	yes	9 (1M/8F) [0.25mg/ kg IM]	32	not reported	not reported	not reported	no change in mean SBP or DBP for all pts combined. Max 160 SBP, max 90	sedation/drowsy 33%	none	alll well enough to return home at 4 hrs
Diamond et al. 2014 (unipolar and bipolar)	yes	28 (16M/12F)	47	not reported	protocol mentioned BPRS, no result	not reported	One patient withdrew during their first treatment due to a panic attack nine minutes into the infusion, experiencing tachycardia and tachypnoea. One patient was withdrawn due to concurrent upper respiratory tract infection. One participant had a 10 minute vasovagal episode (bp 77/47, pulse 45 bpm, reduced level of consciousness) 11 minutes into his first infusion, resolved by 1 hour.	"Most patients" reported some transient effects, including perceptual	none reported	"No serious adverse events occurred during the study"