Ketamine and Depression: A Review

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Despite significant progress, depression remains a common and disabling condition that affects millions, leading to increased primary care visits and decreased productivity (Baune et al., 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 and 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 et al., 2012). When monoamine modulating antidepressant medications do work, there is a delay of typically 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 et al., 2013).

For severe depression, electroconvulsive therapy (ECT) is the only somatic inter-

vention 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 et al., 2014) as well as magnetic seizure therapy and vagal nerve stimulation (Wani et al., 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 et al., 2012; Machado-Vieira et al., 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 et al., 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 FDA-approved only 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 and Beautrais, 2011; Harihar et al., 2013; Lara et al., 2013; Lapidus et al., 2014; Iglewicz et al. 2014; Loo et al., 2016).

This chapter 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 et

al., 2013; Caddy et al., 2014; Naughton et al. 2014). In this review, we build upon a less extensive article previously published elsewhere (Ryan et al., 2014).

Materials and Methods

PubMed.gov was searched using the term "ketamine depression," with the filter of English language, through April 2016, yielding 1274 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, 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. Data from randomized controlled trials were weighed more heavily over open label investigations, which in turn were weighed more heavily than individual cases or case series. At least three areas of research pertinent to ketamine treatment of depression were not reviewed in depth for this manuscript due to space limitations: biomarkers for response, neurocognitive effects, and neuroimaging correlates.

Results

Study population and methodology

Using the above search criteria, a total of 77 publications were included in this review. Of these, 56 utilized the IV route of administration, accounting for over 500 patients in total. A further 20 studies utilized IM, oral, intranasal, sublingual, or subcutaneous treatment in over 150 patients. Nearly all publications reported use of racemic ketamine, with only 13 patients in total receiving *S*-ketamine (Denk et al., 2011; Paul et al., 2009; Segmiller et al., 2013; Paslakis et al., 2010). Most studies utilized only one administration of ketamine, though six open label investigations (OLI), two randomized control trials (RCT), and 35 case studies/series assessed multiple doses, from one to three times per week, for up to four weeks. The majority of publications reported on patients with unipolar depression, though bipolar depression was also represented in 14 publications. 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 et al., 1961), or Clinical Global Impression scale (CGI) (Guy et al. 1976). The only study to report on the pediatric population utilized rating scales more specific to that population (Papolos et al., 2013). Studies of ketamine in hospice patients also utilized the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) [**table 5; suppl. table 1**].

We focused on the categorical outcome of response—defined as >50% reduction—within 24 hours because 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 a 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. In studies utilizing alternate routes of administration, the dose and protocol varied widely, and the majority utilized multiple ketamine administrations.

Efficacy from single doses (RCT and OLI data)

The nine RCTs reporting outcomes from single doses of ketamine included six crossover studies, all with saline placebo, and three parallel group designs, all with either lower ketamine doses or active controls **[table 1].** Only one utilized a non-IV route of administration; the majority utilized a single ketamine infusion. Seven 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 et al., 2013). Response rate in the ketamine arm fell below 50% after day 3. 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). Li et al. (2016) notably compared 0.2mg/kg to 0.5mg/kg of ketamine, though only reported response in the initial four hours: 44% and 38%, respectively. The other placebo controlled studies in unipolar depression generally recruited fewer patients, and found 24-hour outcomes of 45% with KET versus 2% with saline; and four-hour outcomes of 34% versus 13% [**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.

Eighteen OLIs describe outcomes in unique depressed patients after KET, of which 17 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 four to six hours after KET **[figure 3].** At 24 hours, the overall response rate increased to 59% and then gradually declined with time. While four-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 nonresponse 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 four 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 magnetoencephalographic responses were increased after ketamine infusion in responders, but not non-responders to KET.

Phelps et al. (2009) identified another link to 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., 2010b; 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 monthlong follow-up treatment after response to open-label KET. 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 et al., 2013)[**table 2**]. Response more than doubled from 24% at one day to 52% at one week, remaining stable for the duration of the two-week 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 two weeks prior to KET. This may potentially explain the large disparity in outcome data from the more rigorously designed RCTs.

Efficacy from multiple doses (RCT and OLI data)

Generally, the highest quality data describing the effects of multiple doses of ketamine draws from studies utilizing the IV route of administration. Two RCTs and six OLIs assessed multiple sequential doses of IV ketamine [**table 3**]. Of these, three utilized a regimen of thrice-weekly infusions for two weeks. Two others utilized twice-weekly infusions, one of which stopped infusions when patients achieved remission (Rasmussen et al., 2013), and the other of which increased the dose after the third infusion (Cusin et al., 2016). Two studies directly compared different dosing schedules of infusions, ranging from one to three times weekly over the

course of three to four weeks (Diamond et al., 2014; Singh et al., 2016). All eight multidose studies 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 57%, though if the outliers are excluded (Diamond et al. 2014, Cusin et al., 2016), this increases to 74%. The majority of these studies also reported time to relapse after the final infusion, monitoring subjects over the subsequent four 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 seven to ten days following the final infusion, though this may potentially underestimate true benefit due to our conservative calculations [figure 4].

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). The other RCT compared two-times-a-week to three-times-a-week infusions, finding both conditions to be significantly better than saline placebo (Singh et al., 2016). They found no significant difference in response between the two ketamine conditions, and in fact slightly better outcomes with the less frequent dosing condition, suggesting two times a week dosing may be just as efficacious as three time a week. Regarding the six OLIs, all unique patients are represented in Murrough et al. (2013), Rasmussen et al. (2013), Shiroma et al. (2014), Diamond et al. (2014), and Cusin et al. (2016). Response rates immediately after conclusion of the series of infusions were 71%, 60%, 79%, 29%, and 36%, respectively (ITT). Altogether, studies yielded a 20% response rate approximately a month after conclusion of the course. In Murrough et al. (2013), 17% remained responders over an additional three months' follow-up, with only one receiving other medication in the interim. These authors also observed that initial nonresponders (at four hours after the first infusion) were four times less likely than initial responders to achieve response at the end of six 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). Cusin et al. (2016) had poorer outcomes perhaps due to a highly treatment resistant population, despite escalating the dose to 0.75mg/kg mid way through the series of infusions. Diamond et al. (2014) also assessed memory at baseline and after the treatment course, finding improvements in autobiographical, episodic, and subjective memory. Both this study and Singh et al. (2016) were the only to directly compare different treatment frequencies, and found better results with the lower frequency arms.

Case reports, intravenous route

We report data from case reports separately from RCTs and OLIs. The 22 published case studies (or judged equivalent) that utilized ketamine infusions (KET) comprised 40 patients and—save for one dose-finding study and another comparing racemic versus *S*-ketamine—mostly utilized multiple infusions [**suppl. table 1**]. These reports on one to three patients describe dramatic improvement in depressive symptoms and functioning in patients with TRD (Kollmar et al., 2008; Liebrenz et al., 2007, 2009); geriatric TRD patients (Srivastava et al., 2015; Hassamal et al., 2015); antidepressant effect of ketamine even when this was only arrived at serendipitously (Ostroff et al., 2005); several descriptions of prolonged relief of depression with repeated dosing (Correll, 2006; Messer et al., 2010; Murrough et al., 2011; Hassamal et al, 2015); 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 et al., 2008). Hassamal et al. (2015) described a woman who was treated successfully with three separate series of infusions over the course of more than a year, each providing benefit for four to eight months. There was a notable case 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 et al. (2013) demonstrated rapid relief of depression in young, drug-naïve men. Uniquely, da Frota Ribeiro et al. (2015) described two cases of severe psychotic depression refractory to other treatments who were responsive to ketamine IV infusions with improvement in both psychosis and depression, suggesting psychosis may not necessarily be a contraindication to ketamine. Gowda et al. (2016) reported on a grieving man who experienced remission for three months after a single infusion, focusing on the phenomenological experience as integral to his improvement.

Szymkowicz et al. (2013) administered between 16 and 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 second infusion, and was maintained so with periodic treatments over the subsequent nine months. Their two other subjects suffered repeated relapses despite intermittent courses of repeat infusions. Lai et al. (2014) is a dose-finding study, which compared 0.1 to 0.4mg/kg of ketamine IV over five minutes with a saline control; however, due to low enrollment and poor retention, just four individuals received ketamine. Of those, only one displayed a clear dose response relationship for antidepressant response, though dissociative effects were clearly dose-related.

Efficacy from 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 et al., 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 with parenteral routes, and was successfully maintained with repeat dosing in several instances.

One unique dose- and route-finding study divided its 15-patient cohort into three arms and varied the route of administration: four patients via IV push, five patients via IM, and six patients via SC (Loo et al., 2016). Patients in each arm received 0.1–0.5mg/kg doses, in an ascending design, along with a midazolam control, finding that doses under 0.5mg/kg were effective in some patients, and no significant differences in outcome existed between the various routes of administration.

In regard to IM administration, one RCT, one OLI, and six case studies detailed effects in 31 patients. The one RCT by Loo et al. (2016) found a 60% response rate in the five subjects, versus 0% with the midazolam control. 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 0.3mg/kg to 1.0mg/kg, from every two to eight days, and from two to 68 treatments. All but one patient with unipolar depression met formal criteria for response

by 24 hours, and this outlier experienced an affective switch into mania (Banwari et al., 2015). Glue et al. (2011) also performed a dose-response assessment, finding greater improvements with higher doses; although 0.5mg/kg and 0.7mg/kg decreased MADRS scores, only 1.0mg/kg led to response. Zanicotti et al. (2012, 2013) described a woman with metastatic cancer and unipolar TRD who, after 1.0mg/kg, experienced remission of depression for five to six days, and pain for 24 hours. On a weekly outpatient regimen, response was largely maintained for eight 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 nine to 12 months by dosing at three-to-four-day intervals, although one patient did require a dose increase after five months (Cusin et al., 2012).

Three studies utilized intranasal administration, of which one was a double blind 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 (Clark et al., 2014).

Two studies utilized sublingual administration, one in a mixed cohort of unipolar and bipolar depression (Lara et al., 2013). This study utilized a 10mg dose and found "rapid" improvements in 17 of the 26 patients, though the time frame was not defined. Using repeat dosing, from every two to seven days, ten patients were described as maintaining response over a period of months, based on a Likert scale. The other study with sublingual (transmucosal) ketamine is a chart review of 17 patients who were prescribed 0.5–1.0mg/kg every seven to 14 days, and found a 76% response rate, typically within 24 hours. This is likely an overestimate of true response, as responder classification was by chart review and refill history (Nguyen et al., 2016).

Subcutaneous (SC) administration has also been reported. The RCT by Loo et al. (2016) found 100% response in the six subjects treated by SC ketamine, versus 17% with the midazolam control. McNulty et al. (2012) describes 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).

We found four other case studies and a subsequent OLI that utilized oral administration. One case study (Irwin and 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 eight 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. More 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.

There have been relatively few investigations of doses other than the standard 0.5mg/kg; Loo et al. (2016) reported response to 0.1–0.5mg/kg via IV bolus, IM injection, and SC injection. A trial of 20 patients by Lenze et al. (2016), in contrast, tried a 96-hour ketamine infusion and found that, during eight weeks of follow-up, efficacy was no greater than for a 40-minute infusion.

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 10 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

Data regarding reduction of suicidality with ketamine is 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, four RCTs and nine OLIs reported on suicidality, typically utilizing either the HDRS or MADRS suicide items, or the scale for suicide ideation (SSI) (Beck et al., 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 two studies, with one suggesting loss of significance after four hours. Murrough et al. (2015b) found statistically significant differences between ketamine and midazolam, losing significance by three days. 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 sub-cohort (Diazgranados et al., 2010a). 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, utilizing IV infusions (Murrough et al., 2011; Zigman and 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, three RCTs and two case series report on suicidality. Two of the RCTs 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. (2010b), on the other hand, found no difference between IV ketamine and placebo, though these authors excluded patients with risk for suicide at baseline. Murrough et al. (2015) recruited both unipolar and bipolar subjects, and found benefit through two days follow-up. One case series uti-

lized 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 and Leo, 2014).

Adverse effects

During infusion, five different adverse events with ketamine led to discontinuation in RCTs [**suppl. table 2**]: hypotension and bradycardia, hypertension unresponsive to beta-blockers (Murrough et al., 2013), anxiety and paranoia in one patient, palpitations in another patient, and a combination of anxiety, dizziness, hypoesthesia, and feeling cold in a third (Singh et al., 2016). Following infusion, four adverse events led to discontinuation: worsening mood in three patients (one with suicidal ideation), and increased anxiety in another (Diazgranados et al., 2010b). Three placebo patients discontinued, for elevated blood pressure during infusion (Valentine et al., 2011), hypomania (Diazgranados et al., 2010b), and disc degeneration (Singh et al., 2016). 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).

Although clinically significant hemodynamic changes were rare, tachycardia and transient elevations in blood pressure were commonly reported across the various routes of administration in RCTs and OLIs [**suppl. tables 2 and 3**]. 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. In regard to pulmonary effects, aan het Rot et al. (2010) 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 as measured by Clinician Administered Dissociative Symptom Scale (CADSS) (Bremner et al., 1998), Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1970) or Young Mania Rating Scale (YMRS) (Young et al., 1979) revealed significant increases compared with control/baseline, that generally resolved by 80 min to four hours, and was rarely reported as distressing.

We evaluated the adverse effects in multiple dose studies separately. Of the two RCTs utilizing repeat dosing, Singh et al. (2016) noted diminishing intensity of dissociative symptoms with repeat dosing. In the six OLIs utilizing repeat dosing, elevations in CADSS and BPRS were either similar or diminished across multiple infusions, with no progressive increase over multiple infusions. Cusin et al. (2016) administered three infusions at 0.5mg/kg followed by three more infusions at 0.75mg/kg, finding decreasing dissociative effects despite the dose increase. Similarly, hemodynamic and respiratory effects did not worsen with repeat administrations. Dose-dependent increases in dissociative symptoms were reported in two dose-finding studies, one with rapid IV infusions over two to five minutes (Lai et al., 2014) and the other with rapid administration via IV, IM, or SC routes (Loo et al., 2016). 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 one-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**].

We evaluated the adverse effects in the non-IV alternate routes of administration separately. Intramuscular reports noted effects similar to those of IV, but with less intense dissociative effects and hemodynamic changes (Loo et al., 2016). 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 30 administrations (Clark et al., 2014). The only RCT utilizing intranasal administration found a similar side effect profile (Lapidus et al., 2014). Sublingual dosing was evaluated in 43 patients across two studies, and resulted in no euphoria,

psychotic, or dissociative symptoms (Lara et al., 2013; Nguyen et al., 2015). 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 51 patients that received oral ketamine, essentially no adverse effects, including vital sign changes, were reported (Paslakis et al., 2010; Irwin and 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 and 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. Loo et al. (2016) directly compared IV, IM, and SC administration and found the lowest side effect profile with SC dosing.

Lower urinary tract symptoms (LUTS) are common adverse effects in the ketamine abuse population. We looked systematically at the published data reviewed in previous sections of this chapter, and report the following: most RCTs (Berman et al., 2000; Zarate et al., 2006; Diazgranados et al., 2010b; Valentine et al., 2011; Sos et al., 2013; Ghasemi et al., 2013; Lenze et al., 2016; Loo et al., 2016; Singh et al., 2016) and OLIs (Machado-Viera et al., 2009; Phelps et al., 2009; aan het Rot et al., 2010; Mathew et al., 2010; Ibrahim et al., 2011; Cornwell et al., 2012; Savadore et al., 2009, 2010, 2012; Larkin & Beautrais, 2011; Thakurta et al., 2012; Rasmussen et al., 2013; Rybakowski et al., 2013; Chilukurti et al., 2014; Niciu et al., 2014; Shiroma et al., 2014a, 2014b) involving intravenous ketamine for treatment-resistant unipolar or bipolar depression, did not specifically report on the presence or absence of LUTS), with follow-up periods varying from 1 to 14 days. In Murrough et al. (2013), some urinary symptoms) were reported within the first day after infusion in two of the 26 patients, with such symptoms occurring in the subsequent week after serial infusions in one patient. In their large, two-site RCT comparing ketamine to midazolam, Murrough et al. (2013b) found during the one-to-seven-day period after infusion that four of the 47 ketamine patients (9%) reported frequent urination, three patients (6%) reported painful urination, and 1 patient (2%) reported difficulty urinating; in contrast, none of the 25 midazolam treated patients had urinary complaints. The study by Ibrahim et al. (2012) compared riluzole to placebo after a single open-label ketamine infusion. They found increased urinary frequency in three of 42 patients during the first several hours after infusion, and a combined five of 42 during the 28-day follow-up period (one of 20 in the riluzole

group, and four of 22 in the placebo group). After six infusions, Diamond et al. (2014) described development of persistent cystitis in one of the 28 patients, which was attributed by the patient to sexual activity, and that resolved with antibiotics. No other patients reported cystitis or developed abnormalities on urine dipstick testing. Cusin et al. (2016) reported difficulty urinating in one of 14 subjects during treatment with thrice-weekly ketamine infusions at 0.5mg/kg, but none during subsequent treatment at 0.75 mg/kg. Lapidus et al. (2014) reported that there was no difference in the incidence of urinary urgency between subjects randomized to intranasal ketamine or placebo. Finally, in case studies involving repeated ketamine administrations and variable duration of follow-up, ranging from two to 36 infusions and 12 days to 18 months, "no adverse effects" was reported, but LUTS) was not specifically addressed (Messer et al., 2010; Cusin et al., 2012; Segmiller et al., 2013; Szymkowitz et al., 2013; Hassamal et al., 2015; Srivastava et al., 2015).

Discussion

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 there are fewer studies on the matter. This benefit appears unique to ketamine, 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, 2010a; Rasmussen et al., 2013; Murrough et al., 2013; Ballard et al., 2014; Murrough et al., 2015). Up until recently, most studies have excluded individuals with recent suicidality, and instead performed *post-hoc* re-analyses of suicidality subscales; Murrough et al. (2015) notably treated suicidal patients with ketamine, finding significant improvements. To date, however, there are still no data on suicide attempts, completed suicide, or other long-term effects, nor on parasuicidal behavior; this is fertile ground for further research given the great potential benefit for treating emergent suicidality or averting 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 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; Singh et al., 2016). Indeed, several studies concluded patients require more than one infusion before being considered non-responders, and response rate appears to correlate with number of infusions [figure 3]. 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, duration, and number of infusions is, and how this might be individualized, though future studies will be revealing. The existing paradigm of the 0.5mg/kg dose is quite arbitrary, though several studies have assessed lower doses with success; it is not clear what the minimum effective dose is for antidepressant benefit, and if this could be a pathway to mitigate unwanted side effects. It also worth noting that some patients do not benefit from ketamine, despite multiple treatments (Szymkowicz et al., 2014), and tolerance has been reported (Bonnet et al., 2015). On the other hand, in loss of response after an initial series of infusions, repeat courses were shown to be effective and provide months more remission (Hassamal et al., 2015).

Alternatives to IV infusion, such as intramuscular (IM), intranasal (IN), oral, sublingual (SL), and subcutaneous (SC) routes, have been studied to a lesser extent, but do appear to work. The trade-off is potentially lower response rates with routes other than the IM, which results in ketamine bioavailability similar to, IV administration. These alternate routes offer a potentially greater benefit to risk ratio, given the more favorable side effect profile. Loo et al. (2016) did compare different routes of administration, finding non-IV routes were better tolerated. A significant limitation is lack of high-quality prospective studies: of these alternate routes, our review found only one robust 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 re-

source requirements with such administrations (Cooper et al., 2016). 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 a year or more (Zanicotti et al., 2013; Cusin et al., 2012). Several series of infusions spaced out over the course of a year proved to be effective in one case, suggesting that a block of six infusions could be repeated after relapse (Hassamal et al., 2015). Oral dosing has thus far been used mostly in hospice populations, and of the various routes of administration likely produces the mildest dissociative side effect profile, but with a slower onset of antidepressant benefit. One case report mitigated this limitation through an initial single loading dose via a rapid acting route, followed by more convenient oral daily maintenance dosing (McNulty et al., 2012). Oral ketamine administration, compared to parenteral, 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, along with longer elimination half-life than ketamine itself. The clinical implications for treatment of depression, however, are unclear (Blonk et al., 2010). Sos et al. (2013), however, found no correlation between blood levels of ketamine or nor-ketamine and antidepressant response.

Adverse effects

Ketamine appears to be well tolerated by the majority of individuals who receive it for short-term treatment of depression. The most commonly reported adverse effects are dissociative and psychotomimetic experiences, which are transient and typically resolve within an hour. Occasionally hemodynamic effects, also typically transient and mild, have led to treatment discontinuation, although in every case these have responded to conservative management. Even at doses as high as 4–6mg/kg used for sedation in an emergency room setting, ketamine proved to be safe (Isbister et al., 2016). Assessment of hemodynamic effects and antidepressant response revealed no correlation (Luckenbaugh et al., 2014), though such a correlation may exist between dissociative symptoms and antidepressant response, as we later explore. Intramuscular, sublingual, subcutaneous, intranasal, and especially oral administration generally resulted in fewer adverse effects than seen after IV administration, possibly due to a slower increase in blood levels (Lara et al., 2013; Paslakis et al., 2010; Irwin and Iglewicz, 2010; Irwin et al., 2013; Iglewicz et al.,

2014; Loo et al., 2016). Supporting this theory are data from Lai et al. (2014) that found extensive dissociative symptoms with IV administration over two minutes, and decreases in such symptoms with extension of administration over five minutes. Overall, the safety profile of short-term treatment with ketamine, particularly in closely monitored settings, is reassuring.

Conversely, there is a relative paucity of data on adverse effects from chronic repeated administrations of ketamine when used for 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 and Monaghan, 2001; Morgan et al., 2004). Conversely, data from studies utilizing ketamine for treatment of depression indicate it may actually improve neurocognitive outcomes, most likely by reversing the "pseudo-dementia" seen in severe depression (Permoda-Osip et al., 2015; Shiroma et al., 2014). In further support of a benign cognitive safety profile, Murrough et al. (2015) found no neurocognitive impairments one week after ketamine when compared with midazolam. In chronic recreational use of ketamine, ulcerative cystitis has been identified as an important adverse effect (Shahani et al., 2007). Since initial discovery, the syndrome of lower urinary tract symptoms (LUTS)) has been well characterized in this population and recognized by urologists as a new and serious medical condition (Chu et al., 2008; Tan et al., 2014; Middela and Pearce, 2011; Winstock et al., 2012; Yek et al., 2015; Wu et al., 2016). It occurs in 20–30% of chronic recreational ketamine users (Chu et al., 2008; Winstock et al., 2012), with incidence and severity proportional to cumulative dose and duration of use. Symptoms include increased frequency of urination (progressing to hourly or more frequent), painful urination, and ulceration of the bladder epithelium leading to bleeding. As the syndrome progresses, the bladder wall may thicken and stiffen, limiting drainage from the kidneys, eventually leading to hydronephrosis and renal failure. In the early stages, damage is reversible with abstinence from ketamine (Wein et al., 2013), though progresses to irreversible with continued use, eventually requiring urinary diversion or bladder replacement (Wu et al., 2016). Infection is not typical—there is sterile pyuria, with white blood cells reflecting inflammation—nor is malignancy, although this is still under study. Clinically, LUTS) have been reported in monitored pain treatment programs utilizing high doses of daily oral ketamine: after months at >80mg in three palliative care patients (Storr and Ouibell, 2009), and after nine days of 8mg/kg/d in an adolescent with neuropathic pain (Grégoire et al., 2008). Other reviewers, found,

as we did, a lack of systematic data on the occurrence of LUTS) in clinical use of ketamine for depression treatment, though this is certainly warranted (Katalinic et al., 2013; Bobo et al., 2015; Coyle and Laws, 2015). In regard to dissociative symptoms, several clinical studies have noted subjects develop tolerance to these effects with repeat dosing, but not to antidepressant benefit; that is, with serial infusions, tolerability appears to improve and antidepressant effect grows (Cusin et al., 2016; Singh et al., 2016).

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 et al., 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. (2015) review of three larger NIMH trials, this was not found to be a serious concern. Alternatively, Banwari et al. (2015) reported a case of mania induction in a unipolar patient.

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 two to three times greater potency in terms of analgesia and anesthesia (Kohrs and Durieux, 1998), and three to four 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 et al., 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. In humans, 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 at al 1997). These authors found psychotomimetic effects in *S*-ketamine versus "a state of relaxation" in *R*-ketamine (Vollenweider at al 1997). Similarly, a study in rodents reported minimal dissociative effects after *R*-

ketamine (Yang et al., 2015). 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 et al., 2014; Hashimoto et al., 2014; Yang et al., 2015). Further research directly comparing *S*-, *R*-, and racemic ketamine in humans 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 needs to be carefully managed in the design of future studies.

Several potential predictors of response have received attention. Our review suggests that patients with either unipolar or bipolar depression exhibit at least short term response to ketamine, likely more so in those with unipolar depression. Some 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 and Healy, 2013; Gálvez et al., 2014). At least two studies found a greater likelihood of antidepressant response in 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., 2015). The presence of an anxiety component to depression predicted greater response in unipolar depression, but not bipolar depression (Ionescu et al., 2014; Ionescu et al., 2014). 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). Additionally, several other factors have been found to predictor antidepressant response to ketamine: slow processing speed (Murrough et al., 2015), reduced attention (Shiroma et al., 2014), small hippocam-

pal volume (Adballah et al., 2015), pre-infusion standardized uptake values on PET imaging of the prefrontal cortex (Li et al., 2016), and MRI fractional anisotropy measurements of the cingulum and forceps (Vasavada et al., 2016).

To date, other agents directed at the neurochemical target 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; McCloud et al., 2015). Additional trials are underway to explore this strategy, although infusion of a specific NMDA antagonist, AZD6765, was not effective (Zarate et al., 2013). Another open label trial examined the combination of a single ketamine infusion followed by daily pyridoxine and D-cycloserine, the latter of which is an NMDA receptor antagonist at higher doses, and found remission in four of the eight subjects (Kantrowitz et al., 2015). Alternative mechanisms, such as ketamine's effects on seizure threshold, are also worth considering (Atigari and Healy, 2013).

An obvious question is how dissociative and antidepressant effects might be related. Our review found the time course of these effects differs substantially. 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 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. In support of this, a review by McCloud et al. (2015) found no benefit from memantine and cytidine, both NMDA receptor antagonists without reported dissociative/psychotomimetic effects. In this context it is worth noting that nitrous oxide and classical hallucinogens, which share similar dissociative/psychotomimetic effects with ketamine, may have antidepressant properties (Nagele et al., 2015; Baumeister et al., 2014; Carhart Harris et al., 2016). When used in combination with quinidine, dextromethorphan, which can also have dissociative effects (Morris et al., 2014), was found incidentally to have antidepressant effects (Pioro et al., 2010). Similarly, ketamine and the classic hallucinogens have

each been employed in grief and end of life care, either for depression or anxiety, but perhaps with a similar mechanism (Gowda et al., 2016; 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 et al., 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 (Mithoefer et al., 2016). 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 other specific clinical issues deserve further exploration. One study found a single dose of ketamine to accelerate the onset of benefit with escitalopram from an average of 26.5 days to 6.4 days, suggesting a clinical application for ketamine to accelerate treatment response, another important limitation of current medications (Hu et al., 2016). To date, studies in TRD have excluded psychotically depressed patients. However, da Frota Ribeiro et al. (2016) reported two cases of successful ketamine treatment in severe psychotic depression with remission from both depressive and psychotic symptoms, suggesting this contraindication for ketamine may not be necessary. 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 and 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. Alternate routes of administration could benefit not only the cost and availability compared to IV administration, but have been shown to mitigate the side effects of ketamine (Cooper et al., 2016). Ultimately, more rigorous studies in such settings are needed.

Conclusion

Recommendations for future research

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

1) Direct comparisons between various routes and durations of administration, both in acute and maintenance treatment, as well as to active placebo or standard agents. Less resource intensive routes of administration including intramuscular, intranasal, sublingual, subcutaneous, and oral routes should be studied as they offer potential advantages, including expansion of ketamine research to the outpatient setting.

2) Dose-response relationships for each route of administration, including monitoring of levels of both ketamine and nor-ketamine levels, in part to find the minimum effective dose for each route.

3) Examination of serial ketamine administrations and optimal dosing frequencies for each route of administration, or with augmenting agents, with the goal of extending the duration of response and long term maintenance of benefit.

4) Trials that prospectively assess anti-suicidal effects as a primary study end point, in both acute and maintenance treatment, perhaps as a way to avert or shorter inpatient psychiatric admission.

5) Trials to further assess if benefit seen in treatment resistant depression extends to non-treatment resistant depression, and if ketamine is a viable treatment strategy in this population.

6) Systematic monitoring of psychotomimetic and dissociative effects with long-term treatment, and correlations with responses to treatment, including assessments of tachyphylaxis to these effects.

7) Systematic monitoring of neuropsychological functions, urinary tract related symptoms, suicidal behavior, and at least in bipolar sub-

jects, mood switching, during long term treatment.

8) Careful analysis of ketamine's "eudaimonic" effects as they relate to antidepressant, dissociative, psychotomimetic, and antisuicidality effects.

9) 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 or at the end-of life.

Recommendations for clinical use

A thorough review of the literature utilizing ketamine for treatment of refractory depression reveals rapid onset of action within 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. 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 clinical use. Dissociative effects are common, time-limited, generally well tolerated, and appear to subside in intensity with repeat dosing. At doses used for treatment of depression, significant hemodynamic effects requiring intervention are possible but uncommon, and do warrant monitoring. Other potential contraindications exist, such as abuse liability, but with care in patient selection unwanted outcomes can be minimized. Ketamine is clearly a very promising agent. While we currently urge caution in widespread clinical adoption for treatment of depression, our review of the risks and benefits supports its acute—and potentially repeated—use in carefully selected cases who have not benefited from other treatments. Our review provides strong suggestive support for the use of more "user friendly" non-IV alternate routes of administration, but the evidence base is not as robust. While the existing and

somewhat arbitrary paradigm of 40-minute IV infusions has proven effective, much less-resource-intensive protocols such as intramuscular, intranasal, sublingual, subcutaneous, and oral methods of administration represent a potential revolution in the use of ketamine. These routes of administration have the advantage of expanding use of ketamine to the outpatient setting, along with corresponding cost reductions. Ketamine has not reached the status of being formally promoted for wider clinical use, although we acknowledge that it 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.

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
IN, intranasal
SL, sublingual
SC, subcutaneous
t, time of first administration
mg, milligrams
kg, kilograms
mL, milliliters
hr, hours
min, minutes
mos, months
wk(s), weeks

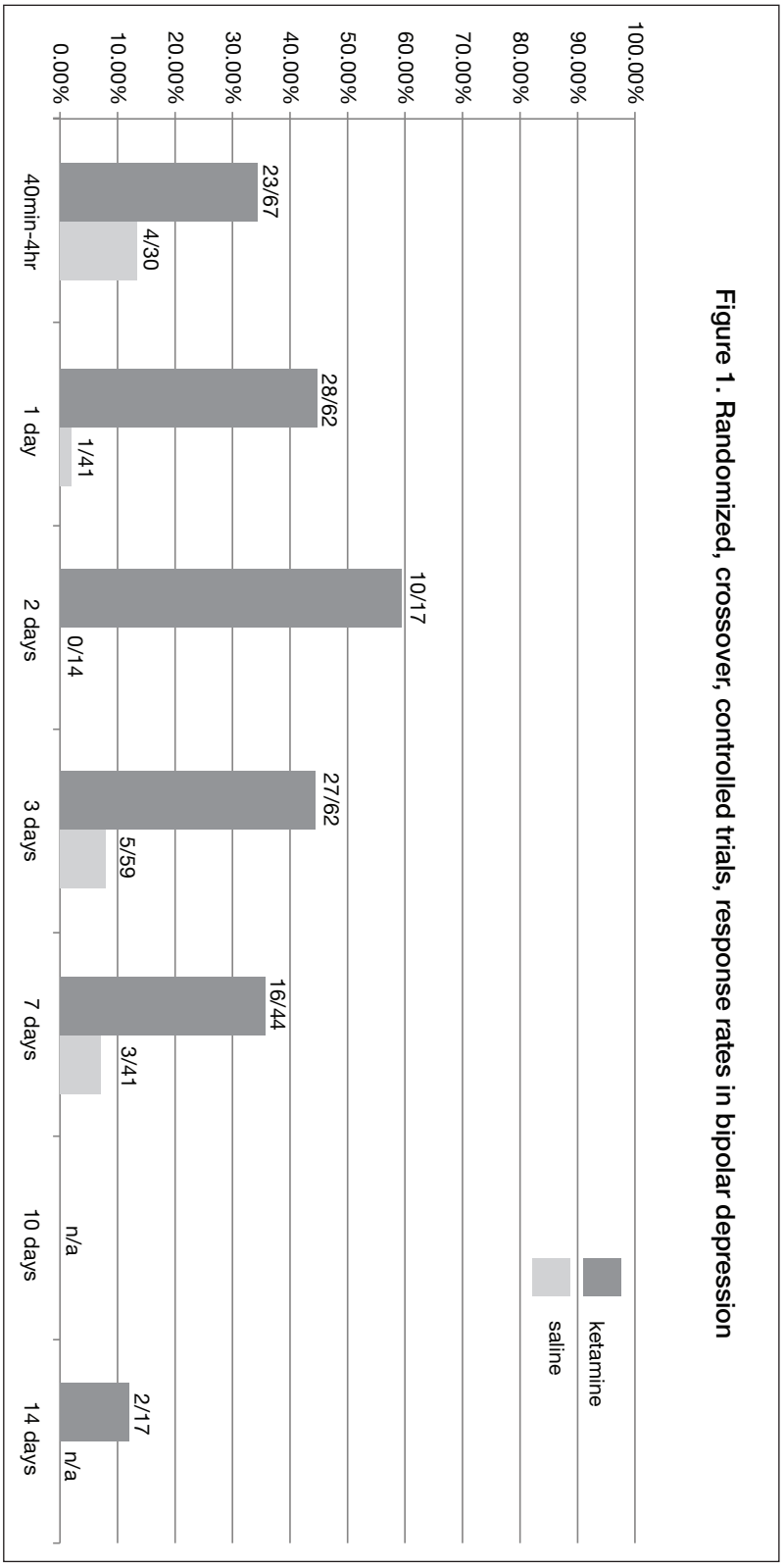

Figure 1. Randomized, crossover, controlled trials, response rates in bipolar depression

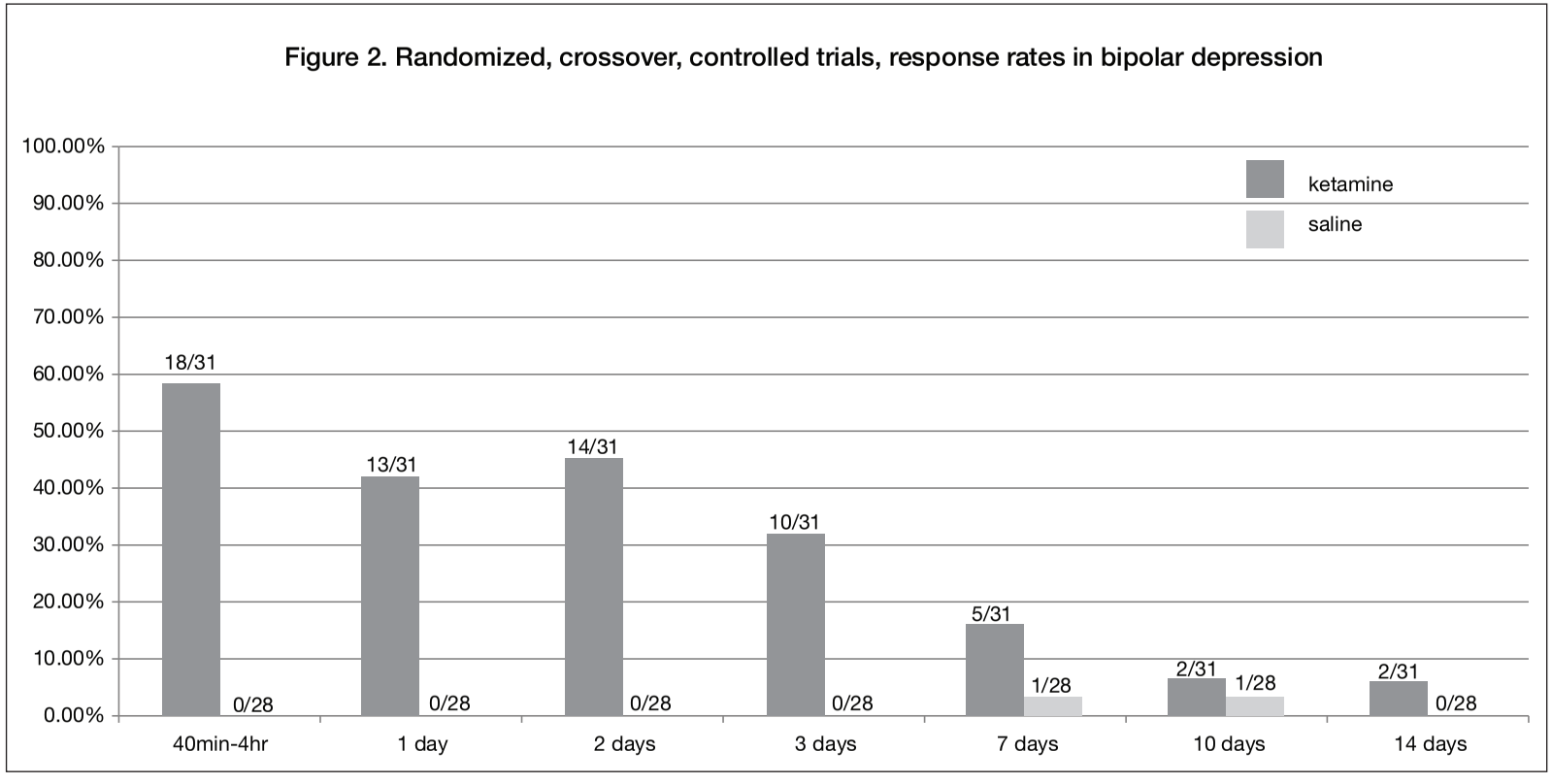
Figure 2. Randomized, crossover, controlled trials, response rates in bipolar depression
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50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
ketamine
saline
18/31
0/28
13/31
0/28
14/31
0/28
10/31
0/28
5/31
1/28
2/31
1/28
2/31
0/28
40min-4hr
1 day
2 days
3 days
7 days
10 days
14 days

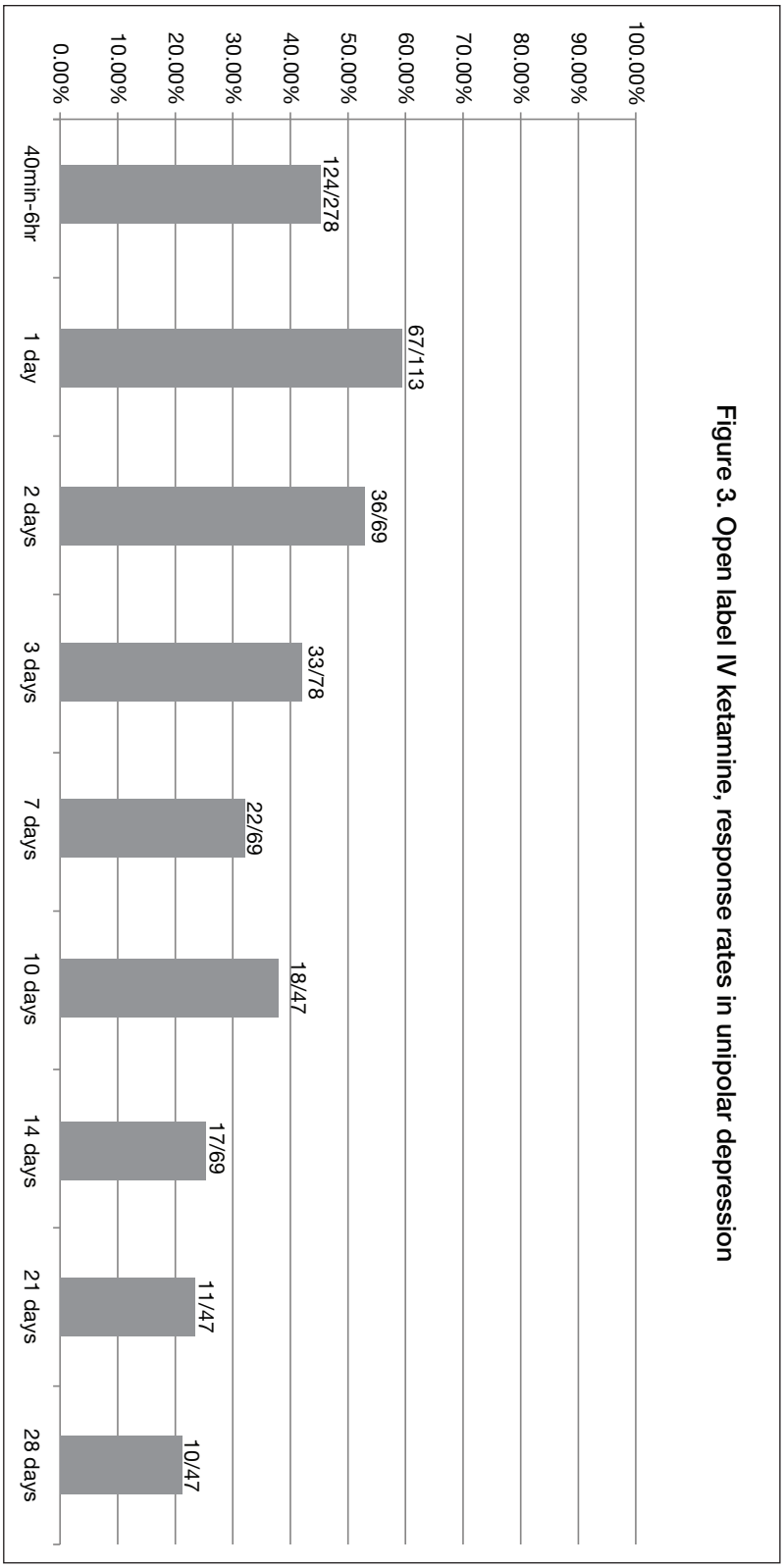

Figure 3. Open label IV ketamine, response rates in unipolar depression

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

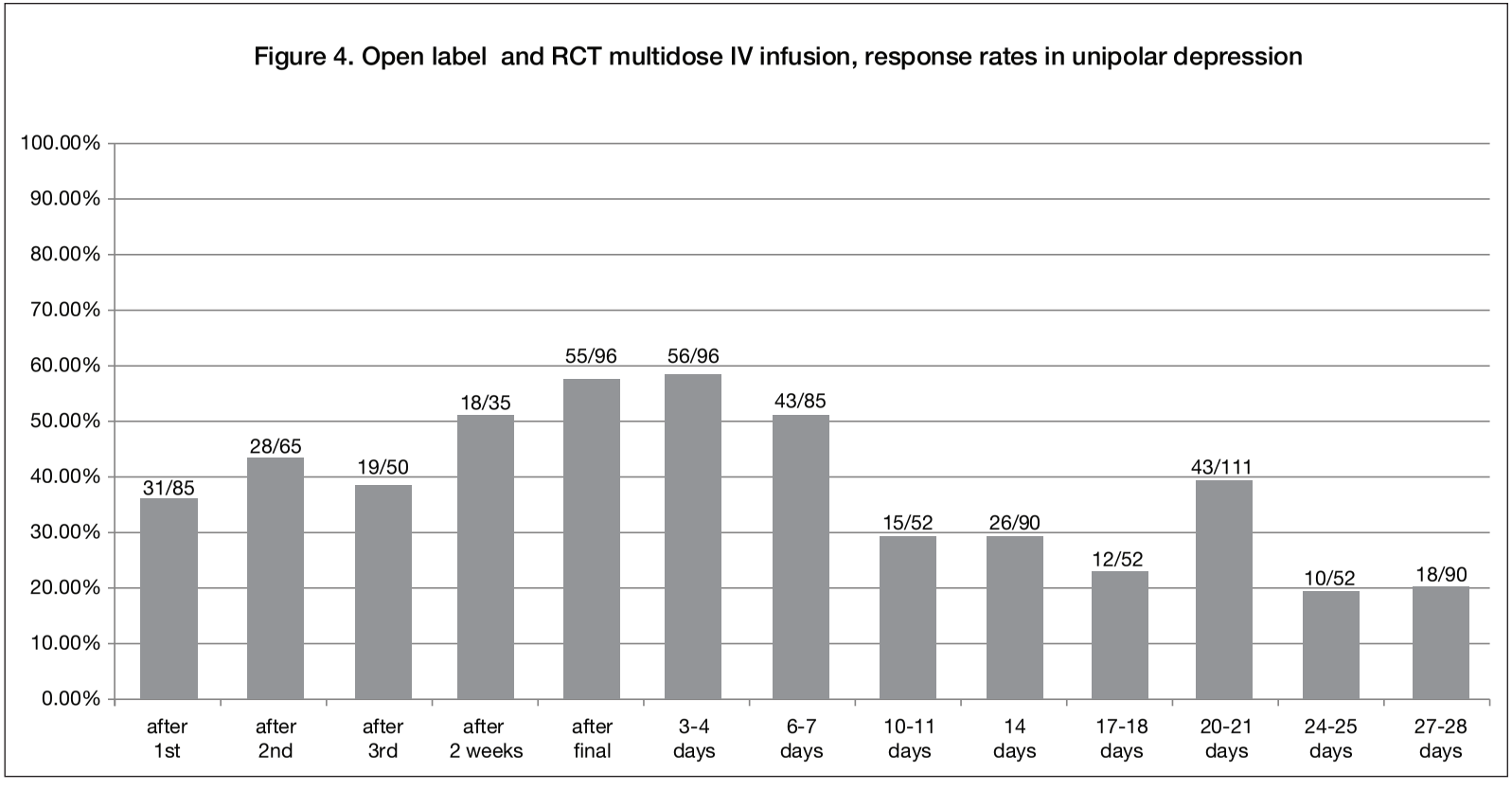

Table 1. Efficacy in random controlled trials of ketamine for depression

	Study	Year	Design	Diagnosis	TRD	N	Gender	Age	Concomitant Medication	Interval	Response Measure:
Unipolar Depression	Berman et al. [1]	2000	double blind crossover	unipolar(8) bipolar(1)	no	9	4M/5F	37	no	72 hours	HDRS 25 decr 50%
	Zarate et al.	2006	double blind crossover	unipolar	yes	18	6M/12F	47	no	7 days	HDRS 21 decr 50%
	Valentine et al. [1]	2011	single blind crossover	unipolar	no	10	4M/6F	42	no	7 days	HDRS 25 decr 50%
	Sos et al. [2]	2013	double blind crossover	unipolar	no	27	15M/15F [3]	43	yes	7 days	MADRS decr 50%
	Li et al.	2016	parallel group	unipolar	yes	16/ 16/ 16	13M/35F	46	yes	4 hours	HDRS 17 decr 50%
										totals	KET saline
Bipolar Disorder	Diazgranados et al.	2010	double blind crossover	bipolar I and II	yes	22	7M/15F	48	yes	14 days	MADRS decr 50%
	Zarate et al.	2012	double blind crossover	bipolar I and II	yes	15	7M/8F	47	yes	14 day	MADRS decr 50%
										totals	KET +Li/VPA saline + Li/VPA
Active Controls	Murrough et al. [4]	2013	parallel group	unipolar	yes	47/ 25	35M/37F	47/43	no	7 days	MADRS decr 50%
	Ghasemi et al. [5]	2013	parallel group	unipolar	yes	9/9	8M/10F	38	yes	1 day	HDRS 25 decr 50%
Intranasal	Lapidus et al. [6]	2014	double blind crossover	unipolar	yes	20	10M/10F	48	yes	7 days	MADRS decr 50%

* Some studies did not report depression response at all time points.
The highest of available scores was utilized for the 40 min-4hr time 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 minutes, except [2] 0.54mg/kg over 30 minutes, [5] the first of three infusions, done over 45 minutes, [6] intranasal ketamine 50 mg.
[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.

Arm	40min -4hr	1 day	2 days	3–4 days	7 days	10 days	14 days	21 days	28 days
ketamine	1/8 (13%)	2/8 (25%)	*	4/8 (50%)					
saline	*	*	*	1/8 (13%)					
ketamine	9/17 (53%)	12/17 (71%)	10/17 (59%)	9/17 (53%)	6/17 (35%)		2/17 (12%)		
saline	1/14 (7%)	0/14 (0%)	0/14 (0%)	2/14 (14%)	0/14 (0%)				
ketamine	0/10 (0%)	4/10 (40%)	*	3/10 (30%)	*				
saline	*	*	*	1/10 (10%)	*				
ketamine	*	10/27 (37%)	*	11/27 (41%)	10/27 (37%)				
saline	*	1/27 (4%)	*	1/27 (4%)	3/27 (11%)				
0.5mg/kg ket	6/16 (38%)								
0.2mg/kg ket	7/16 (44%)								
saline	3/16 (19%)								
% responding	**23/67 (34%)**	**28/62 (45%)**	**10/17 (59%)**	**27/62 (44%)**	**16/44 (36%)**		**2/17 (12%)**		
% responding	**4/30 (13%)**	**1/41 (2%)**	**0/14 (0%)**	**5/59 (8%)**	**3/41 (7%)**				
KET +Li/VPA	9/17 (53%)	7/17 (41%)	9/17 (53%)	8/17 (47%)	2/17 (24%)	1/17 (6%)	1/17 (6%)		
saline + Li/ VPA	0/16 (0%)	0/16 (0%)	0/16 (0%)	0/16 (0%)	1/16 (6%)	1/16 (6%)	0/16 (0%)		
KET +Li/VPA	9/14 (64%	6/14 (43%)	5/14 (36%)	2/14 (14%)	1/14 (7%)	1/14 (7%)	1/14 (7%)		
saline + Li/ VPA	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)		
% responding	**18/31 (58%)**	**13/31 (42%)**	**14/31 (45%)**	**10/31 (32%)**	**5/31 (16%)**	**2/31 (6%)**	**2/31 (6%)**		
% responding	**0/28 (0%)**	**0/28 (0%)**	**0/28 (0%)**	**0/28 (0%)**	**1/28 (4%)**	**1/28 (4%)**	**0/28 (0%)**		
ketamine	*	30/47 (64%)	28/47 (60%)	28/47 (60%)	21/47 (45%)	17/47 (36%)	13/47 (28%)	9/47 (19%)	9/47 (19%)
midazolam 0.045mg/kg	*	7/25 (28%)	6/25 (24%)	5/25 (20%	4/25 (16%)	4/25 (16%)	2/25 (8%)	0/25 (0%)	0/25 (0%)
ketamine	*	7/9 (78%)							
ECT	*	1/9 (11%)							
ketamine 50 mg IN	6/18 (33%)	8/18 (44%)	4/18 (22%)	6/18 (33%)	1/18 (6%)				
saline	1/18 (6%)	1/18 (6%)	1/18 (6%)	2/18 (11%)	0/18 (0%)				

Table 2. Efficacy in open label investigations of ketamine for depression

	Study	Year	Diagnosis	TRD	N	Gender	Age	Concomitant Medication	Interval
Unipolar or Mixed	Machado-Vieira et al.	2009	unipolar	yes	23 [1]	14M/9F	44	no	240 minutes
	Phelps et al.	2009	unipolar	yes	26 [1]	14M/12F	44	no	230 minutes
	Ibrahim et al.	2011	unipolar	yes	42 [1]	24M/18F	47	no	230 minutes
	Cornwell et al.	2012	unipolar	yes	20, no unique [1]	15M/5F	46	no	230 minutes
	Ibrahim et al.	2012	unipolar	yes	42, 2 unique [1]	26M/16F	47	no [2]	28 days
	Salvadore et al.	2009	unipolar	yes	11 [3]	7M/4F	44	no	230 minutes
	Salvadore et al.	2010	unipolar	yes	15, 8 unique [3]	?	51	no	230 minutes
	Salvadore et al.	2012	unipolar	yes	14, 10 unique [3]	9M/5F	50	no	24 hours
	Mathew et al.	2010	unipolar	yes	26 [4]	16M/10F	48	no [2][5]	72hrs + 32 days
	Larkin and Beautrais [6]	2011	unipolar	no	14	7M/7F	31	yes	4hrs
	Thakurta et al.	2012	unipolar	yes	22 [7]	10M/12F	50	no	14 days
	Murrough et al. [8]	2013	unipolar	yes	24, 14 unique [4]	15M/9F	48	no	first infusion
	Rasmussen et al. [9]	2013	unipolar, bipolar II	yes	10	4M/6F	47	yes	first infusion
	Shiroma et al. [8]	2014	unipolar	yes	14	14M	54	yes	first infusion
	Diamond et al.	2014	unipolar (22), bipolar (6)	yes	28	16M/12F	47	yes	first infusion
	Chilukuri et al.	2014	unipolar	yes	9	3M/6F	36	yes	3 days
	Vasavada et al.	2015	unipolar	no	10	8M/2F	48	yes	24 hours
									totals
Bipolar	Rybakowski et al. [11]	2013	bipolar	yes	25	4M/21F	49	yes	14 days

* 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.

Response measure	40min-6h	1 day	2 days	3 days	7 days	10 days	14 days	21 days	28 days
MADRS decr 50%	11/23 (48%)								
MADRS decr 50%	11/26 (42%)								
MADRS decr 50%	21/42 (50%)								
MADRS decr 50%	9/20 (45%)								
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%)
MADRS decr 50%	5/11 (45%)								
MADRS decr 50%	6/15 (40%)								
MADRS decr 50%	2/14 (14%)	*							
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%)
MADRS <=10	10/14 (71%)								
HDRS 17 decr 50%	15/22 (68%)	17/22 (77%)	14/22 (64%)	7/22 (32%)	3/22 (14%)	*	1/22 (5%)		
MADRS decr 50%	16/24 (67%)	15/24 (63%)							
MADRS decr 50%	2/10 (20%)	2/10 (20%)							
MADRS decr 50%	3/14 (21%)								
BDI decr 50%	3/28 (11%)								
HDRS 17 decr 50%	3/9 (33%)	*	*	4/9 (44%)					
MADRS decr 50%	*	6/10 (60%)							
% responding [10]	**124/278 (45%)**	**67/113 (59%)**	**36/69 (52%)**	**33/78 (42%)**	**22/69 (32%)**	**18/47 (38%)**	**17/69 (25%)**	**11/47 (23%)**	**10/47 (21%)**
HDRS 17 decr 50%	1/25 (4%)	6/25 (24%)			13/25 (52%)		13/25 (52%)		

[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 2wks.
[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	Concomitant Medication	Doses	Interval	Response Measure
Open Label	aan het Rot et al.	2010	unipolar	yes	10 [1]	5M/ 5F	51	no	6; 3x/wk	2wks of infusions + 4wks	MADRS decr 50%
	Murrough et al.	2013	unipolar	yes	24, 14 unique [1]	15M/ 9F	48	no [2]	6; 3x/wk	2wks of infusions + 12wks	MADRS decr 50%
	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%
	Shiroma et al.	2014	unipolar	yes	14	14M	52	yes	6; 3x/wk	2wks of infusions + 4wks	cumulative MADRS decr 50%
	Diamond et al.	2014	unipolar (22) bipolar (6)	yes	15	16M/ 12F	47	yes	3; 1x/wk	3wks of infusions + 6 months	BDI decr 50%
					13				6; 2x/wk		
	Cusin et al. [6]	2016	unipolar	yes	14	3M/ 11F	50	yes	6; 2x/wk	3wks of infusions + 3 months	HDRS28 decr 50%
RCT	Ghasemi et al. [4]	2013	unipolar	yes	9/9	8M/ 10F	38	yes	3; 3x/wk	1wk of infusions + 1 week	HDRS25 decr 50%
									3; 3x/wk	1wk of ECT	
	Singh et al.	2016	unipolar	yes	17/18/ 16/17	23M/ 45F	44	yes	8; 2x/wk saline	4wks of infusions + 3wks	MADRS decr 50%
									8; 2x/wk ketamine		
									12; 3x/wk saline		
									12; 3x/wk ketamine		
										totals	% responding to ketamine [5]

* Some studies did not report depression response at all time points.
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 and available.
[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, [6] 0.5mg/kg IV over 45 minutes for the first 3 infusions, then increased to 0.75mg/kg after.
[5] Calculation excluded aan het Rot et al. given these subjects are represented in Murrough et al. Calculations also exclude control results.

after 1st infusion	after 2nd infusion	after 3rd infusion	after 2 weeks	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
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%)
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%)
2/10 (20%)	6/10 (60%)	6/10 (60%)		6/10 (60%)	*	5/10 (50%)	*	3/10 (30%)	*	3/10 (30%)	*	3/10 (30%)
3/14 (21%)	*	*		11/14 (79%)	*	8/14 (57%)	*	7/14 (50%)	*	7/14 (50%)	*	5/14 (36%)
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%)
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%)	1/13 (8%)
*	*	1/14 (7%)	*	5/14 (36%)	*	*	*	1/14 (7%)	*	*	*	1/14 (7%)
7/9 (78%)	7/9 (78%)	8/9 (89%)		8/9 (89%)	9/9 (100%)	9/9 (100%)						
1/9 (11%)	2/9 (22%)	6/9 (67%)		6/9 (67%)	8/9 (89%)	8/9 (89%)						
*	1/17 (6%)	*	2/17 (12%)	*	*	*	*	*	*	*		
*	7/18 (39%)	*	11/18 (61%)	*	13/18 (72%)	*	*	*	*	10/18 (56%)		
*	*	0/16 (0%)	1/16 (6%)	*	*	*	*	*	*	*		
*	*	4/17 (24%)	7/17 (41%)	*	10/17 (59%)	*	*	*	*	12/17 (71%)		
31/85 (36%)	**28/65 (43%)**	**19/50 (38%)**	**18/35 (51%)**	**55/96 (57%)**	**56/96 (58%)**	**43/85 (51%)**	**15/52 (29%)**	**26/90 (29%)**	**12/52 (23%)**	**43/111 (39%)**	**10/52 (19%)**	**18/90 (20%)**

Table 4. Suicidality

	Study	Year	Diagnosis	TRD	N	Gender	Age	Concomitant Medication	Number of infusions
Open Label Trials	Berman et al.	2000	unipolar (8), bipolar (1)	no	9	4M/5F	37	no	1
	Zarate et al.	2006	unipolar	yes	18	6M/12F	47	no	1
	DiazGranados et al.	2010	bipolar I and II	yes	18	6M/12F	48	yes	1
	Zarate et al.	2012	bipolar I and II	yes	15	7M/8F	47	yes	1
	Price et.al.	2014	unipolar	yes	36/21, no unique [1]	27M/30F	47	no	1
	Murrough et al.	2015b	unipolar (13), bipolar (7), PTSD (3), Borderline (1)	no	12/12	8M/16F	42	yes	1
RCTs	Price et.al.	2009	unipolar	yes	26, no unique [5]	16M/10F	48	no	1
	Aan Het Rot et al.	2010	unipolar	yes	10 [5]	5M/5F	51	no	6; 3x/wk for 2wks
	DiazGranados et al.	2010	unipolar	yes	33 [3]	20M/13F	46	no	1
	Larkin and Beautrais	2011	unipolar	no	14	7M/7F	31	yes	1
	Thakurta et al.	2012	unipolar	yes	27 [2]	13M/14F	49	no	1
	Ibrahim et al.	2012	unipolar	yes	42, 2 unique [3]	26M/16F	47	no [4]	1
	Murrough et al.	2013	unipolar	yes	24, 14 unique [5]	15M/9F	48	no	6; 3x/wk for 2wks
	Rasmussen et al.	2013	unipolar	yes	10	4M/6F	47	yes	1-4; 2x/wk for 2wks
	Diamond et al.	2014	unipolar (22) bipolar (6)	yes	28	16M/12F	47	yes	1-2x/wk for 3wks

* Some studies did not report data or 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.

Interval	Outcome Measure	Baseline	40min-6h	1 day	2 days	3 days
72 hours	HDRS-SI group mean	*	*	*	*	"significantly decreased" (p=0.02)
7 days	HDRS-SI group mean	*	*	"significant effect" for ketamine	*	*
14 days	MADRS-SI group mean	*		not significant for any time point		
14 days	MADRS-SI group mean	2.3	0.25 (v.s. 2.2 with saline, p<0.001)	1.1 (v.s. 2.2 with saline, p<0.01)	1.1 (v.s. 2.1 with saline, p<0.01)	1.3 (v.s. 2.3 with saline, p<0.01)
7 days	SSI < 4	27/57 (47%)	*	86% (v.s. 62% with midazolam, p=0.04)	*	*
7 days	BSI / MADRS-SI	"Ketamine: 17.5 / 35.2 Midazolam: 17.9 / 34.3"	*	not significant / significant	significant / not significant	not significant / not significant
24 hours	MADRS-SI <=1	7/26 (27%)	*	21/26 (81%)		
2 wks of infusions + 4 wks [6]	MADRS-SI <=1	2/10 (20%)	*	9/10 (90%)	*	*
230 minutes	SSI < 4	23/33 (70%)	32/33 (97%)			
10 days	MADRS-SI group mean	3.9 (0.4)	0.6 (0.1) ("significantly lower than baseline")	*	*	*
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	
28 days	SSI group mean	2.55		no significant changes throughout study		
2 wks of infusions + 12wks [6]	MADRS-SI group mean	*	1.9±0.66 (p<0.01)	*	*	*
0-2 wks infusions + 4wks [7]	SSI group mean	3.7±1.95	*	1.6±1.65 (p=0.007)	*	*
3 wks of infusions + 6 months	HAMD-SI group mean	2.0 (SD=0.9)	*	0.7 (SD=1.1)	*	*

[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	Comorbidities	Dose (racemic, unless noted)
Intramuscular	Glue et al.	case series	2011	unipolar	yes	2	2F	?	none reported	0.5, 0.7, and 1.0mg/kg
	Zanicotti et al. [1]	case	2012, 2013	unipolar	yes	1	F	36	metastatic ovarian cancer, pain	1.0mg/kg
	Harihar et al.	case series	2013	unipolar	unclear	2	M	23	obsessive-compulsive disorder	0.5mg/kg
							M	21	none reported	0.5mg/kg
	Cusin et al	case series	2012	bipolar II	yes	2	F	57	ADHD	50mg for 5mos, then 70mg for 4mos (55kg)
							F	48	ADHD, fibromyalgia, hypothyroid	50mg for 6mos (102kg)
	Chilukuri et al.	open label	2014	unipolar	yes	9	1M/8F	32	n/a	0.25mg/kg
						9	2M/7F	42	n/a	0.5mg/kg
	Banwari et al.	case	2015	unipolar to bipolar	yes	1	M	52	none reported	0.3mg/kg
Intranasal	Papolos et al.	case series	2013	bipolar I, Fear of Harm phenotype	yes	12	10M/2F	6 - 19	unclear	30-120mg [2]
	Clark	case	2014	unipolar	yes	1	1F	44	migraines	50mg
	Lapidus et al.	RCT, crossover	2014	unipolar	yes	20	10M/10F	48	none reported	50mg saline
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
	Nguyen et al.	chart review	2015	unipolar	yes	17	2M/15F	24-66	various	0.5-1.0mg/kg

Number of doses	Frequency	Duration of study	Outcome Measure	Depression response within 24 hours	Durability of benefit
3	unclear	unclear, at least 3 days	MADRS	yes, 3/3 (100%), but only at 1.0mg/kg	not reported
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
2	every 3 days	1 month	HDRS	yes, remission at 2hr	remission through 1 month
2	every 3 days	unclear, at least 3 days	HDRS	yes, remission at 2hr	>3 days
68+	every 4 days	9 months	clinical assessment	unclear	remission "within a few days", maintained for 9 months
61+	every 3 days	12 months	clinical assessment	no	responded "after 1 week", maintained for 6 months
	once	3 days	HDRS	yes, 3/9 (33%)	increased to 44% at 3 days
	once	3 days	HDRS	yes, 4/9 (44%)	3 days
3	every 2 days	1 year	HDRS	unclear	n/a
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
32	twice weekly	4 months	clinical assessment	no	"euthymic" by day 3, maintained >4 months
	once	7 days	MADRS	yes, 8/18 (44%)	3 days
	once	7 days	MADRS	1/18 (6%)	low throughout study
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"
unclear	Every 7-14 days	up to 6 months	clinical assessment	unclear	76% responded, lasting from 1-2 weeks

continued next page

Table 5. Alternate routes of ketamine administration *continued*

	Study	Type	Year	Diagnosis	TRD	N	Gender	Age	Comorbidities	Dose (racemic, unless noted)
Subcutaneous	Galvez et al.	case	2014	unipolar, melancholic	yes	1	1F	62	HTN, hypothyroid, CVA	0.1mg/kg, then 0.2mg/kg
										0.2mg/kg [5]
IV, intramuscular, and subcutaneous	Loo et al. [8]	RCT	2016	unipolar	yes	4 (IV)	2M/2F	53	none reported	IV 0.1-0.5mg/kg
						5 (IM)	4M/1F	46		IM 0.1-0.5mg/kg
						6 (SC)	5M/1F	48		SC 0.1-0.5mg/kg
						15	11M/4F	49		midazolam
Oral and subcutaneous	McNulty et al.	case	2012	unipolar	yes	1	M	44	hospice	0.5mg/kg SC, then daily [6]
Oral	Paslakis et al.	case series	2010	unipolar	no	4	?/1M/2F	36-57	melancholia; avoidant personality disorder, alcohol abuse	S-ketamine 1.25mg/kg
	Irwin et al.	case series	2010	unipolar	no	2 [3]	1M/1F	64,70	hospice: COPD, neoplasia	0.5mg/kg
	Irwin et al.	open label	2013	unipolar	no	14,12 unique [3]	?/1M/7F	?	hospice	0.5mg/kg
	De Gioannis and Leo	case series	2014	bipolar, SI	yes	2	1F	37	none	0.5 - 1.5 mg/kg [4]
							1M	44	chronic pain	0.5 - 3.0 mg/kg [4]
	Iglewicz et al.	case series	2014	unspecified depression	no	31 [3]	11M/20F	68	hospice	0.5mg/kg

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

Number of doses	Frequency	Duration of study	Outcome Measure	Depression response within 24 hours	Durability of benefit
2	a month apart	9 months	MADRS	yes, only at higher dose	5 months
12	approx. weekly	9 months	MADRS	no, not until 3rd treatment	10 weeks
1-5	weekly	7 weeks	MADRS	unclear	75% response, 9 days (mean) 60% response, 12 days (mean) 100% response, 35 days (mean)
1					13% response
many	daily	11 weeks	clinical assessment	yes	11 weeks
12 to 14	split over three times daily	14 days	HDRS	no	2/4 (50%) responded at 7 days, maintained through 14 days
	once	several months	HDRS 17	yes, 1/2 (50%) patients responded by 120 min	1 month for initial responder; other responded at 8 days
28	nightly	28 days	HDRS 17	no	unclear; mean time to response 14.4±19.1 days for 8/14 (57%) responders
6 or more	monthly	>3 months	MADRS	yes	unclear
3 or more	every 2-3 weeks	>4 months	MADRS	yes	unclear
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]

[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.
[8] Utilized an ascending dose design in 0.1mg/kg increments, from 0.1 to 0.5mg/kg, with a midazolam control inserted randomly

Supplemental Table 1. Cases with IV administration of ketamine

	Study	Year	Diagnosis	TRD	N	Gender	Age	Comorbidities	Medication Status	Formulation
Racemic	Ostroff et al.	2005	unipolar	yes	1	F	47	schizoaffective disorder	off for 1 day	racemic
	Correll and Futter	2006	unipolar	yes	2	F	39	none	continued	racemic
			unipolar	yes	2	M	33	none	continued	racemic
	Liebrenz et al [1]	2007, 2009	unipolar	yes	1	M	55	alcohol, benzodiazepine, and nicotine dependence	ativan continued, off antidepressants for 1 week	racemic
	Kollmar et al.	2008	unipolar	yes	1	F	47	none	unclear	racemic
	Stefanczyk-Sapieha et al.	2008	unipolar	yes	1	M	50	metastatic prostate cancer	methylphenidate held day of infusion	racemic
	Messer et al.	2010	unipolar	yes	2	M	50	obesity, sleep apnea	unclear	racemic
			unipolar	yes	2	M	45	history of alcohol abuse, hypertension	unclear	racemic
	Murrough et al.	2011	unipolar	yes	1	F	45	none	off	racemic
	Zigman and Blier	2013	unipolar	yes	1	F	37	prior pituitary adenoma resection, B12 deficiency, and hypothyroidism	continued	racemic
	Yang et al.	2013	unipolar	no	3	3M	19-31	none	off	racemic
	Szymkowicz et al.	2013	unipolar and bipolar II	yes	3	?	?	1) panic disorder, 2) none, 3) bulimia, bipolar II, cluster C	continued	racemic
	Szymkowicz et al.	2014	unipolar	yes	4	3M/1F	72	1) GAD, parkinsons, dementia 2) GAD, dementia, 3) GAD	continued	racemic
	Aligeti et al	2014	bipolar II	no	1	M	32	alcohol dependence	off	racemic
	Lai et al. [2]	2014	unipolar	yes	4	2M/2F	51	1) - 3) melancholic depression	continued	racemic

Dose	Number of Doses	Frequency	Duration of study	Measure	Depression Response within 24 hours	Durability of benefit
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
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
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"
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
0.5mg/kg over 40 min	2	2 wks later	6 months	HDRS	yes, remission within 24 hours after each infusion	4 days
0.5mg/kg over 60min	2	10 days later	13 days	HDRS, BDI	no, near-response within first 6 hrs	6 hrs each time
0.5mg/kg over 40 min	6	every other day	12 days	BDI	no, only after 2nd infusion	relapse at 29 days
0.5mg/kg over 40 min	2	weekly	12 days	BDI	yes, after 1st infusion	relapse at 18 days
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
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
0.5mg/kg over 3 min	1	once	120 minutes	group mean MADRS	yes; halved at 120min	n/a
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
0.5mg/kg over 40 min	2 - 6	unclear	unclear	MADRS	no	n/a
0.5mg/kg IV push	1	once	6 months	HDRS7, MADRS	yes	through 5 days, unclear afterwards
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 2-5 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

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Supplemental Table 1. Cases with IV administration of ketamine *continued*

	Study	Year	Diagnosis	TRD	N	Gender	Age	Comorbidities	Medication Status	Formulation
Racemic	Srivastava et al.	2015	unclear	yes	1	F	65	none	yes	racemic
	Hassamal et al.	2015	unipolar	yes	1	F	65	none	yes	racemic
	da Frota Ribeiro et al.	2016	psychotic depression	yes	2	2F	54	delusions, auditory hallucinations	continued	racemic
	Gowda et al.	2016	unipolar, grief	no	1	M	28	none	continued	racemic
	Sampath et al.	2016	bipolar, rapid cycling	yes	1	F	19	hypoxic encephalopathy after suicide attempt	continued	racemic
S-ketamine	"Open label crossover Paul et al. [3]"	2009	unipolar	yes	2	1M/1F	51,58	1) nicotine dependence, HTN 2) none	continued	racemic S-ketamine
	Denk et al.	2011	unipolar	yes	1	F	56	none	unclear	S-ketamine
	Segmiller et al. [4]	2013	unipolar	yes	6	?	?	unclear	continued	S-ketamine

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

Dose	Number of Doses	Frequency	Duration of study	Measure	Depression Response within 24 hours	Durability of benefit
0.5mg/kg over 40 min	4	two times a week	1 year	HDRS	yes	1 year
0.5mg/kg over 35 min	12	two times a week, then three times a week	18 months	MADRS	yes	4, 8, and 6 months
0.5mg/kg over 40 min	3 – 5	unclear	unclear	HDRS	yes, 2/2 (100%)	unclear
0.5mg/kg over 40 min	1	once	3 months	clinical assessment	yes	3 months
0.5mg/kg over 40 min	2	5 days later	4 months	MADRS	no, near-response	4 months
0.5mg/kg over 40 min	1	weekly	2 weeks	HDRS	yes; 1/2 (50%)	3 days
0.25mg/kg over 40 min	1	weekly	2 weeks	HDRS	no; 0/2 (0%), though had near-response	n/a
0.25mg/kg over 40 min	1	n/a	100 minutes	MADRS	yes, remission immediately after infusion	n/a
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

Supplemental Table 2. Control trial adverse effects

	Study	Year	Design	Diagnosis	TRD	N	Gender	Age	CADSS ket vs. PBO	BPRS ket vs. PBO	YMRS ket vs. PBO
Unipolar Depression	Berman et al.	2000	double blind crossover	unipolar(8) bipolar(1)	no	9	4M/ 5F	37	not reported	Significantly greater BPRS scores. Non-significant by 80 min. Resolved at 110min	not reported
	Zarate et al.	2006	double blind crossover	unipolar	yes	18	6M/ 12F	47	not reported	Significantly greater BPRS positive symptoms subscale scores compared to placebo, only at +40 min	Higher at 40 min only
	Valentine et al.	2011	single blind crossover	unipolar	no	10	4M/ 6F	42	Significantly greater dissociation at +20 min; non-significant by +60 min	Non-significant greater BPRS positive symptom scores at +20 min to +80 min	not reported
	Sos et al.	2013	double blind crossover	unipolar	no	27	15M/ 15F	43	not reported	Non-significant BPRS increase (p=0.10)	not reported
	Murrough et al.	2013	parallel group	unipolar	yes	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
	Ghasemi et al.	2013	parallel group	unipolar	yes	9/9	8M/ 10F	38	not reported	not reported	not reported

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
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.
"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 +110 min.	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."
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	
"Mild" increases in BP	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); trended toward significance at days 1 and 4 (p=0.06 and =<0.07).
Elevated blood pressure: mean 19 systolic, 9.1 diastolic, resolved at +240 min. Midazolam decreased mean blood pressure, hypotension in N=1.	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 of Infusion: A) Occurring at > 10% incidence: General malaise B) Considered distressing in > 10%: Poor coordination.	N=2 in ketamine condition (Hypertension unresponsive to beta blockers; hypotension, bradycardia)	N=2 SAE, considered unrelated (transient hypotension, bradycardia during venipuncture—vasovagal; Suicide attempt during washout period prior to administration of ketamine or midazolam)
	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) Palpitations and decreased energy. B) Considered distressing in >10%: General malaise and fatigue.		
Non-significant change in both groups. Non-significant and transient elevation in SBP, HR in N=3 ketamine on 2nd and 3rd administrations.	not reported	not reported	not reported	

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Supplemental Table 2. Control trial adverse effects *continued*

	Study	Year	Design	Diagnosis	TRD	N	Gender	Age	CADSS ket vs. PBO	BPRS ket vs. PBO	YMRS ket vs. PBO
Unipolar Depression	Lapidus et al.	2014	double blind crossover	unipolar	yes	20	10M/ 10F	48	"Small increases at 40 minutes" in ketamine group	"Small increases at 40 minutes" in ketamine group	not reported
	Lai et al.	2014	single blind crossover	unipolar	yes	4	2M/ 2F	51	unclear	unclear	unclear
	Murrough et al.	2015b	parallel group	unipolar (13), bipolar (7), PTSD (3), Borderline (1)	no	12/12	8M/ 16F	42	not reported	not reported	not reported
	Singh et al.	2016	parallel group	unipolar	yes	17/18/ 16/17	23M/ 45F	44	Significant only at +40 min, and diminished with repeated dosing (for both ketamine dose groups)	Increased significantly at +40 min only, no delusions or hallucinations reported	not reported
	Loo et al.	2016	parallel group	unipolar	yes	4/5/6	11M/ 4F	49	Dose-response relationship observed for all routes of ketamine, higher peak in IV group	Dose-response relationship observed for all routes of ketamine, higher peak in IV group	"No evidence of mania"
	Li et al.	2016	parallel group	unipolar	yes	16/16/ 16	13M/ 35F	46	not assessed	No significant difference in BPRS	not assessed
Bipolar Depression	Diazgranados et al.	2010	double blind crossover	bipolar I and II	yes	18	6M/ 12F	48	not reported	not reported	not reported
	Zarate et al.	2012	double blind crossover	bipolar I and II	yes	15	7M/ 8F	47	Significantly greater dissociation at +40 min	No significant difference in BPRS or BPRS positive subscale noted.	Non-significantly lower

Total N were reported for crossover studies, while N of each arm were reported for parallel group studies.

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
Mean increase of 7.6 in SBP. 3 pts > 130 SBP. No pts >100 DBP. No pts over 110 BPM	In N>1: 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 min.	Trouble sleeping at +240 min, and +240 min to +24 hrs. Sleep disturbance / nightmares and "overall" adverse effect at +240 min to +24hrs.	None; N=2 withdrew prior to treatment.	in ketamine responders versus nonresponders, higher increase in CADSS score at +40 min: 1.75 +/- 4.17 versus 1.09 +/- 1.76.
unclear	Dose dependent increase in psychotomimetic side effects.	n/a	none	Dose dependent increase in psychotomimetic side effects
N=1 died from cardiorespiratory disease, judged unrelated to study	Headache, poor concentration, poor coordination, restlessness, malaise.	Dizziness on standing, nausea/vomiting, diarrhea, xerostomia, chest pain	not reported	N=5 SAE, considered unrelated (N=4 hospitalization for worsening depression/ suicidality, N=1 death due to cardiorespiratory causes)
None outside of "normal limits"	"3x/wk: headache, nausea, dizziness 2x/wk: anxiety, dissociation, nausea, dizziness"	2x/wk: headache, intervertebral disc degeneration	N=2 in 2x/wk ketamine (anxiety; anxiety, paranoia), N=1 in 2x/wk placebo (disc degeneration), N=1 in 3x/wk ketamine (anxiety, hypoesthesia, dizziness, feeling cold).	N=2 SAE, all in 2x/wk ketamine group, considered unrelated (anxiety from unrelated life events; suicide attempt 4 weeks after last ketamine dose).
Increased MAP / SBP, DBP, HR to > 120% baseline in: N=2 IV and 2 IM / N=1 IV, 1 IM, and 1 SC.	Mild depersonalization, derealization, altered body perception, altered time perception; more so in IV group	not reported	none	All adverse effects resolved by 4 hours; all hemodynamic effects resolved by 30 minutes.
not reported	Cases of "floating sensation" significantly greater in higher dose 0.5mg/kg ketamine arm	none	none	Side effects were "mild and self-limiting and required no additional medical treatment."
Tachycardia and increased blood pressure; resolved in minutes.	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.
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 trial adverse effects

Study	Year	Diagnosis	TRD	N	Gender	Age	CADSS Results	BPRS Results	YMRS Results
Machado-Vieira et al.	2009	unipolar	yes	23	14M/9F	44	not reported	not 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 +40 min compared to family history negative (FHN).	Positive symptoms elevated in FHP and FHN groups at +40 min, back to baseline by +80 min. FHP had significantly fewer dysphoric symptoms at +120 and +230 min.	not reported
Price et.al.	2009	unipolar	yes	26, 0 unique	16M/10F	48	not reported	not reported	not reported
Salvadore et al.	2009	unipolar	yes	11	7M/4F	44	not reported	Significant decrease in psychotic symptoms after +230 min.	not reported
Diazgranados et al.	2010	unipolar	yes	33	20M/13F	46	Inadequate inter-rater reliability	Inadequate inter-rater reliability	not reported
Salvadore et al.	2010	unipolar	yes	15 (8 unique)	?	51	not reported	Significant decrease in positive subscale after +230 min	not reported
Mathew et al.	2010	unipolar	yes	26	16M/10F	48	not reported	Nonsignificant changes in positive symptoms at+240 min	"Significant main effect of time" on item 1. No effect of pretreatment.
aan het Rot et al. [1]	2010	unipolar	yes	10, 0 unique	5M/5F	51	Significantly increased at +40 min, normal by +2 hrs	Nonsignificant mean increase, baseline at +2 hrs	not reported

Hemodynamic, Respiratory, and EKG effects	Subjective adverse effects	Subjective adverse effects	Adverse event leading to ending treatment	Miscellaneous
not reported	not reported	none reported		Changes in BPRS or VAS-high scores did not correlate with percent decreases observed in HDRS scores
not reported	not reported	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."
not reported	not reported	none reported		-
not reported	not reported	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.
not reported	Mild perceptual disturbances observed in most patients only within +1 hr.	none reported	"No serious adverse events occurred during the study."	A) "No serious adverse events occurred during the study." B)No adverse event was significantly different from placebo at 80 min or thereafter.
not reported	not reported	none reported		
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); back to baseline at +40-80 min.	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"	"There were no serious adverse events, and no treatment-emergent mania or suicidality"
"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 desaturation 99% to 94%. No effect noted on respiratory rate after administration period."	No more than N=2 reported any of the following: abnormal sensations, blurred vision, diminished mental capacity, dizzy/faint, drowsy/ sleepy, feeling strange/ unreal, headache, hearing or seeing things, numbness/ tingling, poor coordination/ unsteadiness, poor memory, rapid or pounding heartbeat, weakness/fatigue. [4]	none	N=2 tachycardia and hypertension on repeat infusions; N=1 tachycardia on repeat infusions; N=1 hypertension on repeat infusions. All side effects were manageable. No significant change in peak BPRS+ scores or CADSS scores across the six infusions.	N=2 tachycardia and hypertension on repeat infusions; N=1 tachycardia on repeat infusions; N=1 hypertension on repeat infusions. All side effects were manageable. No significant change in peak BPRS+ scores or CADSS scores across the six infusions.

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Supplemental Table 3. Open label trial adverse effects *continued*

Study	Year	Diagnosis	TRD	N	Gender	Age	CADSS Results	BPRS Results	YMRS Results
Larkin and Beautrais	2011	unipolar	no	14	7M/7F	31	not reported	No significant elevation at +40 min	No significant elevation at first time point of +40 min.
Ibrahim et al.	2011	unipolar	yes	42	24M/18F	47	Significantly increased at +40 min, normal by +80 min	not reported	not reported
Salvadore et al.	2012	unipolar	yes	14, 11 unique	9M/5F	50	not reported	not reported	not reported
Thakurta et al.	2012	unipolar	yes	27	13M/14F	49	not reported	Significant increase in positive subscale at +40 min only	not reported
Cornwell et al.	2012	unipolar	yes	20, 0 unique	15M/5F	46	Significantly increased at +40 min only	Significant decrease in positive subscale at +80 min, +120 min, and +230 min	not reported
Ibrahim et al. [2]	2012	unipolar	yes	42, 2 unique	26M/16F	47	Significantly increased at +230 min	Significantly increased at +230 min	Variably different through time course.
Thakurta et al.	2012	unipolar	yes	22	10M/12F	50	not reported	Significant increase in positive subscale at +40 min only	not reported
Rybakowski et al.	2013	bipolar, unspecified	yes	25	4M/21F	49	not reported	not reported	not reported
Rasmussen et al. [3]	2013	unipolar and bipolar II	yes	10	4M/6F	47	not reported	No significant change in positive subscale or total BPRS noted at +2 hrs or+1 day	Isolated symptoms. No mania.
Murrough et al. [1]	2013	unipolar	yes	24, 14 unique	15M/9F	48	Significant increase from pre-infusion mean of 0.3 ±0.5 to 7.8±12.0 at peak of infusion; baseline by +240 min.	Significant increase in positive symptoms subscale from pre-infusion mean of 4.0±0.1 to 4.5±0.9 at peak of infusion; baseline by +240 min.	Elevated mood measured by the YMRS-1, baseline by +240 min.

Hemodynamic, Respiratory, and EKG effects	Subjective adverse effects	Subjective adverse effects	Adverse event leading to ending treatment	Miscellaneous
not reported	Mild positive psychotomimetic symptoms in N=2, resolving within 40 min; mild unpleasant dissociative symptoms in N=2, resolving within 30 min.	none		
not reported	not reported	none noted		
not reported	not reported	not reported		
Non-specific elevation of blood pressure	Generally reported: elevated blood pressure, euphoria, headache,increased thirst, and dizziness occurring with ketamine administration ceased within 60 min.	none reported	"No serious adverse events occurred during the study."	"No serious adverse events occurred during the study."
not reported	not reported	none reported	Referred to Ibrahim et al. (2012)	Referred to Ibrahim et al. (2012)
Elevations in blood pressure and pulse, resolved within 80 min; 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 80 min.	none reported		
Elevation in blood pressure with administration, resolved within 40 min.	Generally reported: euphoria, headache, increased thirst, and dizziness occurring with administration, resolved within 40 min.	none reported	"No serious adverse events occurred during the study."	"No serious adverse events occurred during the study."
not reported	not reported	none reported		
No clinically significant elevation in blood pressure during the infusions. No arrhythmia. No patients required respiratory support.	N=1 vertigo, N=3 dizziness, N=1 visual hallucinations, N=3 drowsiness, N=1 dysmegalopsia/anxiety and diplopia, N=3 no adverse effects.	none reported		
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.	No serious adverse events occurred during the study; 16.7% reported that any side effect impaired functioning at any time; no trend towards increasing dissociative or psychotomimetic effects over the course of the trial.	No serious adverse events occurred during the study; 16.7% reported that any side effect impaired functioning at any time; no trend towards increasing dissociative or psychotomimetic effects over the course of the trial.

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Supplemental Table 3. Open label trial adverse effects *continued*

Study	Year	Diagnosis	TRD	N	Gender	Age	CADSS Results	BPRS Results	YMRS Results
Shiroma et al. [1]	2014	unipolar	yes	14	14M	54	Significant increase from a pre-infusion mean of 0 to 8.60±6.49 at the end of infusion; returned to baseline by +120 min.	Significant increase in positive subscale from pre-infusion mean of 4.0±0 to 4.6±1.9 at end of infusion, returned to mean by +120 min.	not reported
Chilukuri et al.	2014	unipolar	yes	9/9/9		37	not reported	not reported	not reported
				9 (0.5mg/kg IV)	3M/6F	36	not reported	not reported	not reported
				9 (0.5mg/kg IM)	2M/7F	42	not reported	not reported	not reported
				9 (0.25mg/kg IM)	1M/8F	32	not reported	not reported	not reported
Diamond et al.	2014	unipolar and bipolar	yes	28	16M/12F	47	not reported	not reported	not reported
Vasavada	2015	unipolar	yes	10	8M/2F	48	not reported	not reported	not reported
Cusin et al.	2016	unipolar	yes	14	3M/11F	50	Increased in both 0.5mg/kg and 0.75mg/kg infusions, respectively: amnesia (36%, 31%), depersonalization (64%, 31%); derealization (71%, 62%).	not reported	not reported

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

Hemodynamic, Respiratory, and EKG effects	Subjective adverse effects	Subjective adverse effects	Adverse event leading to ending treatment	Miscellaneous
Elevation from normotensive to hypertensive blood pressure in N=1 (180/92) that rapidly responded to 10mg labetalol; no arrhythmia; no patients required respiratory support.	N=1 with gastroesophageal reflux disease had nausea and vomited after second infusion, responded to ondansetron.	none reported	A) Complete recovery in all patients after 2 hrs. B) Nausea and vomiting in N=1 on one infusion, responded to ondansetron IV 8 mg IV, and used as prophylaxis in subsequent infusions.	A) Complete recovery in all patients after 2 hrs. B) Nausea and vomiting in N=1 on one infusion, responded to ondansetron IV 8 mg IV, and used as prophylaxis in subsequent infusions.
No change in mean SBP or DBP for all pts combined; max SBP was 160, max DBP was 90				
No change in mean SBP or DBP for all pts combined; max SBP was 160, max DBP was 90	Sedation/drowsy 22%, heavy head 11%	none	all well enough to return home at +4 hrs	all well enough to return home at +4 hrs
No change in mean SBP or DBP for all pts combined; max SBP was 160, max DBP was 90	Sedation/drowsy 22%, lightness of body 22%, heavy head 11%	none	all well enough to return home at +4 hrs	all well enough to return home at +4 hrs
No change in mean SBP or DBP for all pts combined; max SBP was 160, max DBP was 90	Sedation/drowsy 33%	none	all well enough to return home at +4 hrs	all well enough to return home at +4 hrs
N=1 withdrew during their first treatment due to a panic attack nine minutes into the infusion, experiencing tachycardia and tachypnea. N=1 was withdrawn due to concurrent upper respiratory tract infection. N=1 had a 10 minute vasovagal episode (BP 77/47, HR 45, reduced level of consciousness) 11 minutes into his first infusion, resolved by +1 hr.	"Most patients" reported some transient effects, including perceptual distortions, detachment, anxiety, nausea, and confusion during infusion. "Most" experienced marked, but well tolerated dissociative symptoms. Specific data includes: anxiety 25%, mood 18% (see notes), nausea with vomiting 7%, Following infusions "the majority of patients experienced an increase in fatigue with a small number of patients also experiencing mild headaches", N=1 hypnagogic hallucination.	N=1, concurrent upper respiratory infection (unrelated); N=1 panic attack; N=1 vasovagal episode; N=4 anxiety; N=1 anxiety, mood, and worsening SI (reported as reaction to lack of effect).	All of the following completed the study: N=1 self-report of rapid cycling, clinically no change in behavior, resolved with increase in antipsychotic. N=3 worsening mood/SI, reported prone to fluctuation in mood/SI prior. N=1 mania, treating psychiatrist reported this as "consonant with pre-existing mood instability". N=1 symptomatic cystitis, self-reportedly secondary to sexual activity, resolved with single dose antibiotics. No other cystitis or abnormal urinary dipsticks reported.	All of the following completed the study: N=1 self-report of rapid cycling, clinically no change in behavior, resolved with increase in antipsychotic. N=3 worsening mood/SI, reported prone to fluctuation in mood/SI prior. N=1 mania, treating psychiatrist reported this as "consonant with pre-existing mood instability". N=1 symptomatic cystitis, self-reportedly secondary to sexual activity, resolved with single dose antibiotics. No other cystitis or abnormal urinary dipsticks reported.
not reported	not reported	none reported	not reported	not reported
Mild transient SBP and DBP increases during infusions; all had at least 10 mmHg SBP increase, and larger increase at the higher ketamine dose. No significant changes in pulse oxymetry or pulse.	Mild visual disturbances, moderate auditory disturbances ("buzzing sound"), headache, nausea, sedation, and "mild dissociative symptoms based on CADSS."	none reported	No serious adverse events reported; the majority of the minor effects dissipated by +120 min.	No serious adverse events reported; the majority of the minor effects dissipated by +120 min.

[4]From week 1 to week 2, prevalence of abnormal sensations increased from one patient to two patients, and additional patient reported weakness/fatigue at week two who had not the week prior.

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