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Serial infusions of low-dose ketamine for major depression

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Keith G Rasmussen[1], Timothy W Lineberry[1], Christine W Galardy[1], Simon Kung[1], Maria I Lapid[1], Brian A Palmer[1], Matthew J Ritter[2], Kathryn M Schak[1], Christopher L Sola[1], Allison J Hanson[1] and Mark A Frye[1]

Abstract

Background: Single infusions of ketamine have been used successfully to achieve improvement in depressed patients. Side effects during the infusions have been common. It is not known whether serial infusions or lower infusion rates result in greater efficacy.

Methods: Ten depressed patients were treated with twice weekly ketamine infusions of ketamine 0.5 mg/kg administered over 100 min until either remission was achieved or four infusions were given. Side effects were assessed with the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale (BPRS). Patients were followed naturalistically at weekly intervals for four weeks after completion of the infusions.

Results: Five of 10 patients achieved remission status. There were no significant increases on the BPRS or YMRS. Two of the remitting patients sustained their improvement throughout the four week follow-up period.

Conclusions: Ketamine infusions at a lower rate than previously reported have demonstrated similar efficacy and excellent tolerability and may be more practically available for routine clinical care. Serial ketamine infusions appear to be more effective than a single infusion. Further research to test relapse prevention strategies with continuation ketamine infusions is indicated.

Keywords

Ketamine, glutamate, NMDA, suicide, major depressive disorder

Introduction

Berman et al. (2000), in a small sample of seven patients, first reported the possible efficacy of ketamine for major depressive episodes. These investigators utilized a randomized, double blind, crossover design in which each patient received one infusion of ketamine 0.5 mg/kg over 40 min and one infusion of saline placebo. The results indicated that there was a rapid, that is, within an hour or so, antidepressant effect of ketamine but no response after placebo infusions. Since that study was published, there have been three other studies utilizing a single infusion, randomized placebo-controlled design with the identical dosing of ketamine (i.e. 0.5 mg/kg over 40 min), one in unipolar depressives (Zarate et al., 2006) and two in bipolar depressives (Diazgranados et al., 2010a; Zarate et al., 2012). With a combined sample size of 56, these four studies show that a single infusion of ketamine results in almost immediate reductions in depression rating scores.

In addition to these randomized placebo-controlled trials, there have been several larger open label case series, with a cumulative sample size over 100, indicating similar rapid reductions in depression severity with single ketamine infusions of 0.5 mg/kg over 40 min (Diazgranados et al., 2010b; Ibrahim et al., 2011, 2012; Mathew et al., 2010; Phelps et al., 2009; Salvadore et al., 2010; Valentine et al., 2007). Kudoh et al. (2002) utilized a creative design to study the possible antidepressant effects of ketamine: a series of patients scheduled for orthopedic surgery, with a previous diagnosis of depression, were split into two groups randomly; one group had anesthesia induction with propofol, fentanyl, and ketamine, while the other group was induced with just propofol and fentanyl. Depression ratings the day after surgery were significantly lower in the group induced with ketamine. There were 25 patients in each group, yielding good statistical power. Of note, the dose of ketamine used was 1.0 mg/kg given as an intravenous bolus at the time of anesthesia induction.

Two other open label case series, with a cumulative sample size of 40, focused on the acute reductions in suicide items of depression ratings with single ketamine infusions (Larkin and Beautrais, 2011; Price et al., 2009). In the Larkin and Beautrais (2011) study, the dose of ketamine was 0.2 mg/kg infused over 1–2 min, while that in the Price et al. (2009) study was 0.5 mg/kg over 40 min. Finally, there are a few case reports of antidepressant effects of ketamine infusions (Correll and Futter, 2006; Ostroff et al., 2005; Paul et al., 2009) and even oral ketamine (Irwin and Iglewicz, 2010; Paslakis et al., 2010).

[1]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, USA
[2]Department of Anesthesiology, Mayo Clinic, Rochester, USA

Corresponding author:
Keith G Rasmussen, Department of Psychiatry, Mayo Clinic, Rochester, MN 55905, USA.
Email: rasmussen.keith@mayo.edu

In all these studies, both the randomized trials and open label series, follow-up periods have been variable, but return of depression within a day to a week has been common, with an occasional patient showing several weeks of remission following the single infusion. An additional point to make is that in the studies assessing side effects of ketamine, acute dissociative and emotionally dysphoric states (psychotomimetic side effects) have been common during the infusions but dissipate shortly after cessation of the infusions (Berman et al., 2000; Diazgranados et al., 2010b; Zarate et al., 2006, 2012).

From the standpoint of the clinical utility of ketamine as an antidepressant treatment, this literature points to at least two immediate questions. First, do serial infusions of ketamine provide better response/remission rates than single infusions while maintaining safety? Second, is 0.5 mg/kg over 40 min the best dosing scheme for ketamine for this indication? Regarding the first question, the issue of serial ketamine dosing has been broached by one open label trial in which preliminary results in the first 10 patients have been reported (aan het Rot et al., 2010) as well as the results in the full sample of 24 including the first 10 (Murrough et al., 2012). In this series of six thrice weekly ketamine infusions (0.5 mg/kg over 40 min), overall response rate (as defined by an at least 50% reduction in depression scores by study end) was 70.8%, which is higher than the response rates reported with the single-infusion studies. Additionally in this study, the dissociative side effects of each infusion dissipated shortly after each infusion and there was no evidence of cumulative or longer-lasting side effects of ketamine. There are also a few case reports of serial ketamine doses for depressed patients (Kollmar et al., 2008; Messer et al., 2010; Murrough et al., 2011; Stefanczyk-Sapieha et al., 2008; Zanicotti et al., 2012). Clearly, more data on the use of serial ketamine infusions in an attempt either to increase acute response rates or perhaps lower post-treatment relapse rates are indicated.

Regarding the second question raised above, pertaining to the issue of what is the best dosing scheme for ketamine, the data thus far are for 0.5 mg/kg over 40 min, which comes out to 0.75 mg/kg per hour. This *rate* of ketamine dosing can be problematic when translating the research to routine clinical practice. For example, at our institution, ketamine dosing at a rate exceeding 0.3 mg/kg per hour requires anesthesia monitoring. The use of anesthesia equipment and personnel would cause the cost of ketamine sessions to be prohibitive for non-grant-funded clinical use. Additionally, even though the side effects of ketamine at 0.5 mg/kg over 40 min are short-lived after the infusion is terminated, the patient can still be emotionally upset during the infusions. Thus, we believed a ketamine study should be conducted utilizing a lower rate of ketamine administration with the goal of not having to utilize anesthesia personnel and to attempt to make the ketamine administration more easily tolerated by patients.

As a first step in addressing the two issues described above, we undertook a small, open label series in 10 depressed patients of serial ketamine infusions, namely, twice weekly for up to two weeks, with each patient treated until remission criteria were met or there were four infusions without remission. Additionally, we utilized an infusion rate of 0.3 mg/kg per hour for 100 min, which comes to a total dose of 0.5 mg/kg but administered over a longer period of time than in previous studies.

Methods and materials

Subjects

Patients were recruited from the adult inpatient units and the outpatient practice in our department. The study was approved by the Mayo Clinic research ethics board. All participants signed written informed consent prior to study enrollment.

Inclusion criteria

1. Presence of a major depressive episode as part of either major depressive disorder (recurrent or single episode) or bipolar II disorder.
2. Age 18 years or above.
3. Refractory to at least two antidepressant medication trials in the current episode of depression.

Exclusion criteria

1. Bipolar I disorder.
2. History of current or past psychotic disorder.
3. Axis II disorder as primary diagnosis.
4. History of illicit substance abuse.
5. History of alcohol abuse within the past 12 months.
6. Pregnancy.
7. History of traumatic brain injury.
8. Dementia.
9. Other significant neurological illness such as multiple sclerosis, epilepsy, or Parkinson disease.
10. Scheduled to receive electroconvulsive therapy.
11. Incompetence to provide consent.
12. Inability to cooperate with the study procedures.
13. Positive drug screen for illicit substances.
14. Baseline ECG revealing an arrhythmia other than sinus arrhythmia.
15. Presence of known coronary artery disease.

General scheme

In this open label study, each patient was treated with up to four ketamine infusions at 0.5 mg/kg over 100 min. Infusions were administered twice weekly. Enrolled patients were administered the depression subset of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996) at baseline to establish the presence of a major depressive episode. Baseline Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) score was assessed on the morning of each infusion, and then the infusion was given with repeat MADRS at 2 h post-infusion and the next morning. If the patient met criteria for remission with the MADRS (a score of 9 or less) on the morning after an infusion or the morning of a next scheduled infusion, then no more infusions were administered. If the patient was given a fourth infusion, then no more infusions were administered regardless of MADRS score the next morning. The sleep and appetite item scores on the MADRS during the afternoon sessions were kept the same as those that same morning as there was no expectation of change in those items in a few hours' time. Other outcome measures, all administered at the same time points as the MADRS,

included the Young Mania Rating Scale (YMRS; Young et al., 1978), the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1988), the Clinical Global Impression Scale (Guy, 1976), the Scale for Suicide Ideations (SSI; Beck et al., 1979), and the Suicide Status Form (SSF; Conrad et al., 2009). Additionally, during the infusions, the patients were regularly questioned about any dysphoric emotions or altered sensory experiences. For the SSF, we scored the first five items, which were self-report questions related to psychological pain, stress, agitation, hopelessness, and self-hate. Each of these items was rated by the patient on a scale of a low of 1 to a high of 5, thus yielding total possible scores from a low of 5 to a high of 25. For the SSI, we scored the sum of the five items on Part 1, which related to wish to live, wish to die, reasons for living outweighing reasons for dying, desire to kill oneself, and degree of desire to save oneself in a life-threatening situation. For each of these items, scores range from a low of 0 to a high of 2, thus yielding total possible scores from 0 to 10.

The infusions were conducted in the recovery room of the ECT suite in our hospital during the mornings when the ECT service was treating patients. Thus, recovery room nurses were in constant attendance, and psychiatry and anesthesiology practitioners were available if needed. ECG and pulse oximetry monitoring were maintained throughout the infusions. Blood pressure was obtained periodically during the infusions. After each 100 minute infusion was completed, the patient stayed in the recovery room 30 more minutes before going back to the hospital room or being discharged to home with a responsible adult. Patients were hospitalized for the first infusion, but subsequent infusions could occur while on outpatient status.

Four weekly follow-up sets of outcome measures were administered after each patient's series of infusions was complete. These were conducted by telephone if the patient was not available for face-to-face interviews. During the course of infusions, patients received treatment-as-usual from their primary psychiatrists, with the exception that we would not enroll patients receiving ECT.

Statistical analysis

For most parameters, descriptive statistics such as means and standard deviations are reported. Comparisons of means before and after treatment are based on *t* tests. Analysis of variance was used to compare serial means of the BPRS scores.

Results

Demographics

The initial plan was to have 10 patients complete the open label trial. "Completion" was defined as receiving infusions until remission criteria were met or four infusions were administered. One patient, a 41 year old male, received two infusions before dropping out not related to any side effects of ketamine but discomfort at having to present to the outpatient ECT area for the infusions. Another patient, a 69 year old male, was initially enrolled on a Friday afternoon and met inclusion criteria; however, on Monday morning, his pre-infusion MADRS score was in the remission range, so no ketamine was administered. For the purposes of this report, he is considered a screen failure. For the patient who dropped out, his scores on the MADRS are generally not reported below except when considering the proportion of patients who responded to the first infusion. Additionally, his side effect scale data are included in that section below.

Of the 10 patients classified as "completers," half were female. Mean (± standard deviation) age was 47.2 ± 15 years with a range of 19–61. The distribution of number of infusions was six with four infusions, three with two infusions, and one with one infusion. Data for each of the 10 completers are presented in Table 1. Concomitant antidepressant medications during the ketamine treatment phase as well as follow-up are presented in Table 2.

Table 1. Demographic and outcome data.

Patient number[a]	Age	Gender	Baseline MADRS	Endpoint MADRS	Number of ketamine infusions	Outcome status[b]	Ketamine side effects
1	44	F	24	6	2	Remit	Vertigo Dizziness
2	61	M	26	2	1	Remit	Visual hallucination
3	19	F	33	25	4	Non-remit	Drowsiness
4	36	F	41	7	2	Remit	Drowsiness
5	39	F	44	18	4	Resp	Dysmegalopsia Anxiety Diplopia
6	47	F	35	19	4	Resp	Dizziness
7	56	M	27	8	2	Remit	None
8	44	M	33	9	4	Remit	Drowsiness Dizziness
9	52	F	32	28	4	Resp	None
10	74	M	38	45	4	Non-remit	None

[a]Patient numbers (i.e. 1–10) correspond to the same patients labeled 1–10 in Figures 1 and 2.
[b]Remit: remission; Non-remit: non-remission and non-response; Resp: response criterion (at least 50% reduction from baseline MADRS score) met at least once during study but not remission criteria.
MADRS: Montgomery–Asberg Depression Rating Scale

Table 2. Concomitant antidepressant medications.

Patient number[a]	Medications during ketamine infusions	Medications during follow-up
1	Bupropion tapered off Duloxetine dose lowered Nortriptyline briefly given for a few days	Duloxetine
2	Venlafaxine dose increase	Venlafaxine
3	Venlafaxine dose held steady	Venlafaxine
4	Citalopram tapered off Venlafaxine started	Venlafaxine
5	Venlafaxine started Lithium started	Venlafaxine Lithium
6	None	None
7	Venlafaxine unchanged	Venlafaxine Electroconvulsive therapy
8	Bupropion lowered Venlafaxine lowered	Venlafaxine
9	Lamotrigine unchanged	Lamotrigine
10	None	Venlafaxine Electroconvulsive therapy

[a]Patient numbers (i.e. 1–10) correspond to the same patients labeled 1–10 in Figures 1 and 2.

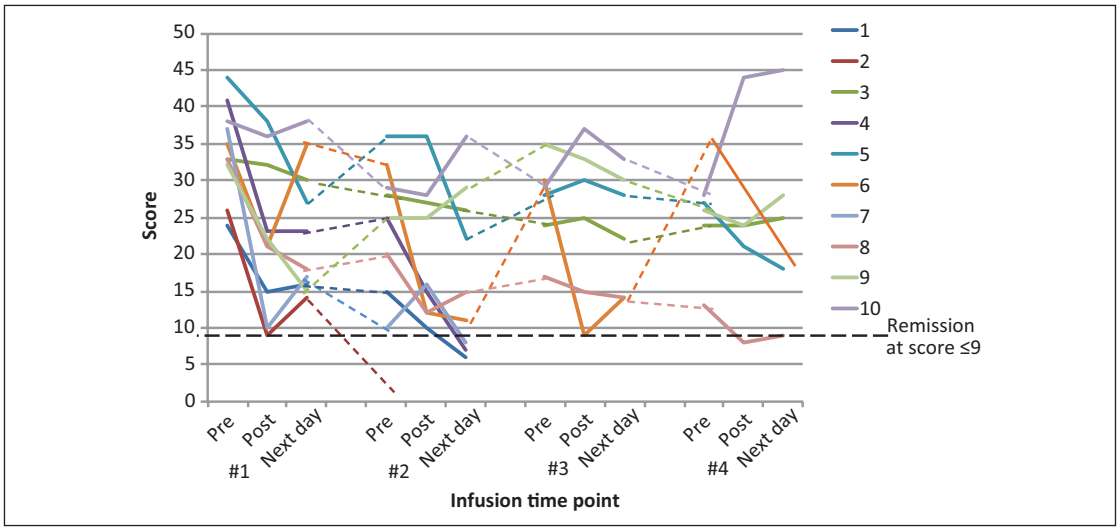

Figure 1. Montgomery–Asberg Depression Rating Scale scores during ketamine treatment.

Depression rating scale scores

Table 1 presents outcome status for each of the 10 completers with baseline and end of treatment MADRS scores. Figure 1 graphically presents all of the MADRS scores during the ketamine treatment phase of the study for these patients. Half of the patients met criteria for remission. Among the remitters, one patient required one infusion, three required two infusions, and one required four infusions. Mean (± standard deviation) MADRS scores at baseline and endpoint of the acute phase, respectively, among all 10 completers were 33.3 (±6.5) and 16.7 (±13.2), a difference that was highly significant ($p = 0.0009$).

Using the outcome criterion of response (defined as an at least 50% reduction in MADRS scores at some point after initial baseline), 80% of the completers responded to ketamine infusions. Three of these eight patients responded after only one infusion, while the other five responders needed two infusions. The one patient who dropped out of the study after two infusions did not meet criteria for response after either infusion.

The data for the follow-up phase are presented in Figure 2. Relapse during this phase was defined as a rise of MADRS score above 9. Of the five patients who remitted in the acute phase, two sustained the remitted state during four weeks of follow-up. During this time, all these patients were receiving antidepressant medications. None of the non-remitting patients for whom at least one follow-up MADRS was available converted to remission status during follow-up. There are missing data, especially in the patients who did not remit with acute phase treatment. All 10

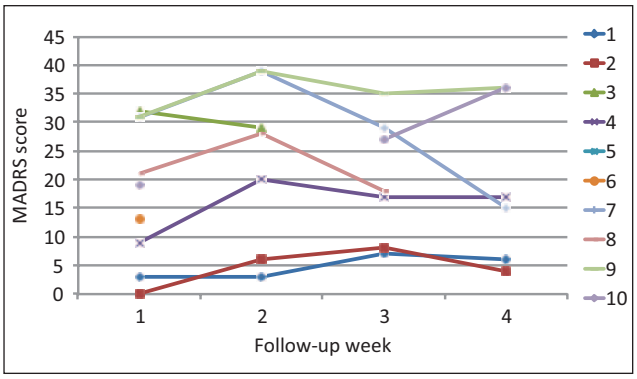

Figure 2. Montgomery–Asberg Depression Rating Scale (MADRS) scores during follow-up. Total MADRS scores of all subjects during the four week follow-up period, which began one week after the final infusion. Some subjects did not complete all four weeks of follow-up.

patients were prescribed various antidepressant medications during follow-up, and two patients received ECT during follow-up (one of the non-remitters, patient #10, and one of the remitters who relapsed quickly, patient #7).

Suicide scale ratings

Mean (±standard deviation) scores for all 10 completers on the SSI at baseline and endpoint, respectively, were 3.7 (±1.95) and 1.6 (±1.65), a difference that was highly statistically significant (t = 3.04, p = 0.007). Analogous scores for the SSF were 18.8 (±3.22) and 14.4 (±5.04), with a resultant t value of 2.25, p = 0.026. Thus, scores for both suicide scales were reduced at the end of the acute phase of the study compared with the baseline scores. Additionally, the scores on these two scales were highly correlated with the MADRS scores. The correlation between SSF and MADRS was r= 0.5944, $p < 0.01$. That between the SSI and the MADRS was r= 0.5056, $p < 0.01$. Thus, the drop in suicidality occurred in concert with overall reductions in depressive symptoms.

Side effect scales

For the BPRS, mean (± standard deviation) scores across all 11 patients who received at least one ketamine infusion for the time points before, 2 h after, and one day after each infusion, respectively, were 39.5 (± 8.7), 36.0 (± 9.1), and 36.5 (± 7.3). These means are not significantly different, and in fact the post-infusion and next day scores are slightly lower (reflecting improvement on BPRS items pertaining to mood). Reviewing items on the BPRS specific to psychosis, there is no signal indicating increases in these items.

Regarding the YMRS, the scores were zero for most patients at most time points, with an occasional item for "racing thoughts," "circumstantial speech," or "sleeplessness" being rated slightly positively. These items in isolation do not represent mania. There was no evidence from history or mental status exam for any patient at any time point in the study that actual mania or hypomania was occurring.

During the infusions, patients were asked about subjective side effects. These are described in Table 1.

Hemodynamic recordings

None of the patients experienced an arrhythmia or clinically significant rise in blood pressure during the infusions. Additionally, none of the patients required respiratory support.

Discussion

In this open label, serial infusion trial of ketamine for treatment-resistant major depression, five of 10 patients who completed the protocol met fairly strict criteria for remission. Of these, only one met this criterion after a single infusion. Thus, a preliminary conclusion is that limiting ketamine trials to only one infusion may result in remission rates less than what might be achieved with serial infusions. Over one month follow-up, while most patients were receiving various psychotropic medication regimens, two of the five remitter patients sustained the remission criteria. Eighty percent of our patients (eight out of 10) met the response criterion. Relapse rates, in some cases quite quickly after response, were high, highlighting the need for effective continuation strategies. As can be appreciated in Table 2, concomitant medication adjustments were common during the ketamine treatment phase and could have impacted the depression ratings in some cases.

A logical next step in clinical ketamine-for-depression research would be to study continuation ketamine infusions after the initial series is completed, which would be analogous to maintenance ECT. The analogy to ECT is instructive: a series of initial, index treatments (infusions, in the case of ketamine) is administered until adequate antidepressant outcome is established, followed by a decreased rate of continuation infusions, perhaps weekly at least to start, to prevent relapse. In such a case, particulars of continuation infusion frequency and safety would need to be worked out. One of the drawbacks of ketamine encountered in various settings is the phenomenon of tolerance, whereby subsequent doses have a lesser and lesser effect over time. Additionally, concerns have been raised about the possible incidence of bladder toxicity with repeated ketamine use (Middela, 2011). Only future clinical research can establish whether maintenance ketamine infusions represent a safe and effective option for initial ketamine responders.

Ketamine has shown promise as a neuropharmacologic probe to be utilized in basic science studies to elucidate glutamatergic function in health and disease, including as a model of psychosis. This line of research, hopefully, over time will lead to new treatments for depression. In the meantime, the accumulated clinical research on ketamine for depression leads to the question as to whether it is appropriate at present to use ketamine in routine clinical care. In translating the current body of clinical ketamine-for-depression research into routine care, there are several issues which require elucidation. First is the question of which depressed patients should be treated with ketamine. It is prudent at present to recommend that only non-psychotically depressed patients be treated with ketamine. Additionally, the current body of research in the depressed population is with relatively younger to middle aged patients who are sufficiently mentally alert and focused that they can easily provide their own consent for ketamine. Whether ketamine would be safe and well-tolerated in highly impaired elderly depressives, for example those who have lost a lot of weight, have poor concentration, are highly ruminative, or who have deep psychomotor abnormalities, remains to be studied.

The second issue regarding routine use of ketamine for depression concerns the details of ketamine delivery. Most of the currently available research involves a strikingly homogeneous scheme: a single dose of 0.5 mg/kg intravenously administered over 40 min. This rather arbitrary dosing scheme was first reported by Berman et al. (2000) and has been used by the vast majority of researchers since that time. As discussed earlier, this rate of dosing comes to 0.75 mg/kg per hour, which at least in our hospital system, and we suspect others as well, requires full anesthesia monitoring. The latter may easily be available at sites with large grants to carry out the research, but if anesthesia monitoring is needed in routine clinical use of ketamine for depression, the resultant cost will be prohibitive in many cases, especially if serial infusions become the norm. In this report, we support the utility of the lower 0.3 mg/kg per hour rate of infusion, keeping it going longer than in previous studies so as to achieve the same total dose. This dose in our institution does not require anesthesia monitoring and was effective and quite well tolerated. Other dosing schemes might be worth studying, such as that of Correll and Futter (2006), who continued their ketamine infusions for several days in two depressed patients to "break" the depressive episode. Although intriguing, such a long period of infusion may not be practical at most hospitals.

Yet another issue concerns the route of administration of ketamine. Some case report literature seems to support oral use of ketamine (Irwin and Iglewicz, 2010; Paslakis et al., 2010). More research should be undertaken for this, as it would obviously be much easier to support an ongoing ketamine program with oral administration. Another issue concerns the frequency of administration of ketamine: if serial infusions are to be used, then how frequently should they be given? If each infusion is well-tolerated and side effects disappear within minutes after infusion termination, then an argument could be made that daily infusions are indicated. Going back to the ECT analogy, the reason ECT is not usually administered this frequently is that accumulation of cognitive side effects occurs, precluding assessment of the antidepressant effect. If no side effect build up occurs with ketamine, though, this issue may be moot.

In summary, our low infusion rate, serial dosing trial with ketamine supports the safety and efficacy of this drug. Ketamine was associated with a transient antidepressant effect in those patients who achieved remission. Future clinical ketamine-for-depression research should focus on optimizing infusion frequency and elaborating the safety and efficacy of continuation ketamine infusions for relapse prevention as well as pursuing optimal dosing parameters.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

aan het Rot M, Collins KA, Murrough JW, et al. (2010) Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry* 67: 139–145.

Beck AT, Kovacs M and Weissman A (1979) Assessment of suicidal ideation: The Scale for Suicide Ideation. *J Consult Clin Psychol* 47: 343–352.

Berman RM, Cappiello A, Anand A, et al. (2000) Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 47: 351–354.

Conrad AK, Jacoby AM, Jobes DA, et al. (2009) A psychometric investigation of the Suicide Status Form II with a psychiatric inpatient sample. *Suicide Life Threat Behav* 39: 307–320.

Correll GE and Futter GE (2006) Two case studies of patients with major depressive disorder given low-dose (subanesthetic) ketamine infusions. *Pain Med* 7: 92–95.

DiazGranados N, Ibrahim L, Brutsche NE, et al. (2010a) A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 67: 793–802.

DiazGranados N, Ibrahim LA, Brutsche NE, et al. (2010b) Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* 71: 1605–1611.

First MB, Spitzer RL, Gibbon M, et al. (1996) *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID – CV)*. Washington, DC: American Psychiatric Press.

Guy W (1976) *ECDEU Assessment manual for psychopharmacology – revised (DHEW Publ No ADM 76–338)*. Rockville, MD: US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, pp. 218–222.

Ibrahim L, Diazgranados N, Franco-Chaves J, et al. (2012) Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs. add-on riluzole: Results from a 4-week, double-blind, placebo controlled study. *Neuropsychopharmacology* 37: 1526–1533.

Ibrahim L, Diazgranados N, Luckenbaugh DA, et al. (2011) Rapid decrease in depressive symptoms with an N-methyl-D-aspartate antagonist in ECT-resistant major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 35: 1155–1159.

Irwin SA and Iglewicz A (2010) Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care. *J Palliat Med* 13: 903–908.

Kollmar R, Markovic K, Thurauf N, et al. (2008) Ketamine followed by memantine for the treatment of major depression. (Letter) *Aus N Z J Psychiatry* 42: 170.

Kudoh A, Takahira Y, Katagai H, et al. (2002) Small-dose ketamine improves the postoperative state of depressed patients. *Anesth Analg* 95: 114–118.

Larkin GL and Beautrais AL (2011) A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int J Neuropsychopharmacol* 14: 1127–1131.

Mathew SJ, Murrough JW, aan het Rot M, et al. (2010) Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: A pilot, randomized, placebo-controlled trial. *Int J Neuropsychopharmacol* 13: 71–82.

Messer M, Haller IV, Larson P, et al. (2010) The use of a series of ketamine infusions in two patients with treatment-resistant major depression. *J Neuropsychiatry Clin Neurosci* 22: 442–444.

Middela SP (2011) Ketamine-induced vesicopathy: A literature review. *Int J Clin Pract* 65: 27–30.

Montgomery SA and Asberg M (1979) A new depression rating scale designed to be sensitive to change. *Br J Psychiatry* 134: 382–389.

Murrough JW, Perez AM, Mathew SJ, et al. (2011) A case of sustained remission following an acute course of ketamine in treatment-resistant depression. (Letter) *J Clin Psychiatry* 72: 414–415.

Murrough JW, Perez AM, Pillemer S, et al. (2012) Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry*. Epub ahead of print 26 July 2012. http://dx.doi.org/10.1016/j.biopsych.2012.06.022

Ostroff R, Gonzales M and Sanacora G (2005) Antidepressant effect of ketamine during ECT. (Letter) *Am J Psychiatry* 162: 1385–1386.

Overall JE and Gorham DR (1988) The Brief Psychiatric Rating Scale (BPRS): Recent developments in ascertainment and scaling. *Psychopharmacol Bull* 24: 97–99.

Paslakis G, Gilles M, Meyer-Lindenberg A, et al. (2010) Oral administration of the NMDA receptor antagonist S-ketamine as add-on therapy of depression: A case series. *Pharmacopsychiatry* 43: 33–35.

Paul R, Schaaff N, Padberg F, et al. (2009) Comparison of racemic ketamine and S-ketamine in treatment-resistant major depression. *World J Biol Psychiatry* 10: 241–244.

Phelps LE, Brutsche N, Moral JR, et al. (2009) Family history of alcohol dependence and initial antidepressant response to an NMDA antagonist. *Biol Psychiatry* 65: 181–184.

Price RP, Nock MK, Charney DS, et al. (2009) Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry* 66: 522–526.

Salvadore G, Cornwell BR, Sambataro F, et al. (2010) Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. *Neuropsychopharmacology* 35: 1415–1422.

Stefanczyk-Sapieha L, Oneschuk K and Demas M (2008) Intravenous ketamine "burst" for refractory depression in a patient with advanced cancer. *J Palliat Med* 11:1268-1271.

Valentine G, Mason GF, Krystal JH, et al. (2007) The acute effects of ketamine on mood and occipital cortex amino acid neurotransmitter content. *Biol Psychiatry* 61: 233S.

Young RC, Biggs JT, Ziegler VE, et al. (1978) A rating scale for mania: Reliability, validity, and sensitivity. *Br J Psychiatry* 133: 429–435.

Zanicotti CG, Perez D and Glue P (2012) Mood and pain responses to repeat dose intramuscular ketamine in a depressed patient with advanced cancer. *J Palliat Med* 15: 400–403.

Zarate CA, Brutsche NE, Ibrahim L, et al. (2012) Replication of ketamine's antidepressant efficacy in bipolar depression: A randomized controlled add-on trial. *Biol Psychiatry* 71: 939–946.

Zarate CA, Singh JB, Carlson PJ, et al. (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 63: 856–864.