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Research report

Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression

Paulo R. Shiroma [a,c,*], Brian Johns [b,c], Michael Kuskowski [a,c], Joseph Wels [d], Paul Thuras [a,c], C. Sophia Albott [a,c], Kelvin O. Lim [a,c]

[a] Mental Health Service Line, Minneapolis VA Medical Center, Minneapolis, MN, USA
[b] Department of Psychiatry, North Memorial Medical Center, Minneapolis, MN, USA
[c] Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA
[d] Department of Anesthesiology, Minneapolis VA Medical Center, Minneapolis, MN, USA

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ABSTRACT

Background: Ketamine has been showing high efficacy and rapid antidepressant effect. However, studies of ketamine infusion wash subjects out from prior antidepressants, which may be impractical in routine practice. In this study, we determined antidepressant response and remission to six consecutive ketamine infusions while maintaining stable doses of antidepressant regimen. We also examined the trajectory of response and remission, and the time to relapse among responders.
Methods: TRD subjects had at least 2-month period of stable dose of antidepressants. Subjects completed six IV infusions of 0.5 mg/kg ketamine over 40 min on a Monday–Wednesday–Friday schedule during a 12-day period participants meeting response criteria were monitored for relapse for 4 weeks.
Results: Fourteen subjects were enrolled. Out of twelve subjects who completed all six infusions, eleven (91.6%) achieved response criterion while eight (66.6%) remitted. After the first infusion, only three and one out of twelve subjects responded and remitted, respectively. Four achieved response and six remitted after 3 or more infusions. Five out of eleven subjects remain in response status throughout the 4 weeks of follow-up. The mean time for six subjects who relapsed was 16 days.
Limitations: Small sample and lack of a placebo group limits the interpretation of efficacy.
Conclusions: Safety and efficacy of repeated ketamine infusions were attained without medication-free state in patients with TRD. Repeated infusions achieved superior antidepressant outcomes as compared to a single infusion with different trajectories of response and remission. Future studies are needed to elucidate neural circuits involved in treatment response to ketamine.

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1. Introduction

The efficacy of current pharmacological agents for depression is disappointing. The largest (4041 patients at 41 clinical sites) and longest (data collected over seven years) study ever done to evaluate depression treatment, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Trivedi et al., 2006), showed that approximately only 30% of patients achieved remission after first-line antidepressant citalopram. A second large-scale study, the Combining Medications to Enhance Depression Outcomes (CO-MED) trial (Rush et al., 2011), compared two antidepressant combinations with serotonin selective reuptake inhibitor monotherapy at 12 weeks and 7 months. Similar to STAR*D, remission rates were modest (37.7–38.9%).

In addition to low response rate, the long delay of traditional antidepressants in the onset of therapeutic action (up to 12 weeks) increases the burden of illness, morbidity, and risk of suicidal behavior (Jick et al., 2004). Current antidepressants exert their primary biochemical effect by targeting monoamine substrates. The delay in the therapeutic actions of existing pharmacologic agents is due to the fact that they initially act on substrates that are considerably upstream of targets that are ultimately responsible for the antidepressant effects. Neurotrophic signaling cascades and the glutamatergic system are expected to be more closely related to adaptive changes in critical neuronal networks responsible for sustainable long-term therapeutic action of antidepressants. More recently, Ketamine, a noncompetitive, high-affinity antagonist of the N-methyl-D-aspartate (NMDA) type glutamate receptor used for induction and maintenance of anesthesia (Green and Li, 2000), has been investigated for its high efficacy and rapid antidepressant effect.

Since Berman and colleagues reported the first finding of a rapid antidepressant response to a single infusion of ketamine as

* Corresponding author at: Mental Health Service Line, Minneapolis VA Medical Center, Minneapolis, MN, USA. Tel.: +1 612 467 2264; fax: +1 612 467 4010.
E-mail addresses: paulo.shiroma@va.gov, seiji.shiroma@gmail.com (P.R. Shiroma).

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compared to saline in nine depressed patients (Berman et al., 2000), multiple case reports, case series, and several clinical trials including placebo-controlled studies (Zarate et al., 2006; Diazgranados et al., 2010; Zarate et al., 2012) have supported the rapid antidepressant effect of a single ketamine infusion in unipolar or bipolar depression. However, follow-up periods have been variable with common return of depression within a day to a week and occasional patient showing several weeks of remission following the single infusion. The strategy of repeated ketamine infusion to maintain antidepressant response has recently been explored.

Murrough et al. (2013b) conducted series of six thrice weekly ketamine infusions (0.5 mg/kg over 40 min) found an overall response rate (as defined by an at least 50% reduction in depression scores by study end) of 70.8%, which was higher than 50–71% reported with single-infusion studies in unipolar depression (Berman et al., 2000; Zarate et al., 2006). Similarly, Rasmussen et al. (2013) had a response rate of 80% using multiple infusions although at a slower rate of administration (0.5 mg/kg over 100 min).

Most studies of ketamine infusion wash subjects out from prior antidepressants, which may be impractical in clinical settings and even unethical especially among patients with TRD. Other studies allow modification of concurrent antidepressant dosages during infusion confounding the effect of ketamine on depression. In this preliminary report, we aim to determine whether antidepressant response and remission can be increased by completing six consecutive infusions as compared to a single infusion. For this purpose, we maintain stable doses of antidepressant regimen including other psychotropic medications used as augmenting agents. By the administration of multiple infusions, the study also examined the trajectory of treatment response, particularly important for those subjects that do not respond after a single infusion. Finally, we also aimed to estimate time to relapse among responders after completion of the six infusions.

2. Methods and material

2.1. Participants

Adult subjects participated in an open-label study of repeat ketamine infusion conducted over 12 days at the Special Diagnostic and Treatment Unit (SDTU) of the Minneapolis VA Medical Center followed by a 4-week follow-up period. Subjects were recruited by direct referral from clinicians in the Mental Health and Primary Care Clinics. Medical records were reviewed prior to a brief phone interview with patients. Those who qualified were invited to a personal interview to determine final eligibility. Baseline assessments were ascertained within 1 week of first ketamine infusion. The Minneapolis VA Medical Center Institutional Review Board approved the study, and written informed consent was obtained from all subjects before participation.

2.1.1. Inclusion criteria

- Men and women aged 18 to 70 years.
- Have recurrent Major Depressive Disorder (MDD) without psychotic features confirmed by depression subset of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996).
- Have 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) score greater than or equal to 14 at screen.
- Current major depressive episode resistant to treatment, defined as failure to achieve remission (elimination of symptoms and restoration of pre-morbid psychosocial functioning) from at least 2 antidepressant trials of different pharmacological classes. Systematic evaluation of previous antidepressant trials was assessed by using the Antidepressant Treatment History Form (Sackeim, 2001).
- If present, current pharmacological antidepressant dosages including augmenting agents must be stable for at least 2 months prior to beginning of the study.

2.1.2. Exclusion criteria

- Inability to speak English.
- Inability or unwillingness to provide written informed consent.
- Mini Mental State Examination (MMSE) (Folstein et al., 1975) scores ≤ 26.
- Current or lifetime diagnosis of post-traumatic stress disorder, acute stress disorder, psychosis-related disorder, bipolar disorder I or II disorder, substance-induced disorder, any mood disorder due to a general medical condition or any Axis I disorder other than MDD that was judged to be the primary presenting problem.
- Diagnosis of Parkinson's disease, dementia of any type, multiple sclerosis, seizures or other CNS related disorders.
- History of traumatic brain injury.
- Comorbid substance use, abuse or dependence within 6 months of assessment plus negative urine toxicology screen test.
- Clinically unstable medical illness including but not limited to history of or current myocardial ischemia or arrhythmias, severe pulmonary secretions, history of or current closed angle glaucoma, congestive heart failure or angina, significant renal or hepatic impairment, scheduled elective surgery or other procedures requiring general anesthesia during the study, uncontrolled hypertension.
- Current use of barbiturates or narcotic medications.
- Non-benzodiazepine hypnotics at doses higher than zolpidem 1 mg qhs or equivalent for insomnia.
- History of antidepressant- or substance-induced hypomania.
- History of first degree relative(s) with an Axis I psychotic disorder.
- For women: pregnancy (confirmed by baseline lab test), the initiation of female hormonal treatments within 3 months of screening, or inability or unwillingness to use a medically accepted contraceptive method for the duration of the study.
- Current active suicidal ideation judged to cause imminent danger.

2.2. Rating scales and procedures

Participants completed six IV infusions of ketamine on a Monday–Wednesday–Friday schedule over a 12-day period. Patients who met response criterion by the last dose of ketamine were followed weekly for 4 consecutive weeks or until relapse was observed. During this follow-up period, patients continued with similar dosages from pre-study antidepressant regimen. Response was defined as $\geq 50\%$ improvement from baseline depression score as measured by the Montgomery–Åsberg Depression Rating Scale (Montgomery and Asberg, 1979) (MADRS). Remission was established by a MADRS score ≤ 9. Relapse was defined as $< 50\%$ of baseline MADRS score at that follow-up visit.

On the day of infusion, subjects arrived in the morning after an overnight fast. An indwelling catheter was placed in the nondominant arm for ketamine administration. Digital pulse oximetry, respiratory rate, heart rate and blood pressure was recorded every 10 min for 1 h beginning 10 min before infusion. Based on the dose, rate of infusion, and endpoint/purpose of the study, the ketamine infusions did not fall into the category of “moderate sedation” and thus no cardiac monitoring was required at our institution. Before each infusion, MADRS score and self-rated

Visual Analog Scales (VAS) for happiness, sadness, energy, tiredness, calmness, worry, worthless and self-esteem were obtained. VAS (Bond, 1974) are easy to rate, can be repeated at short intervals, avoid investigator bias, are not time consuming, and can provide an accurate evaluation of clinical change. Clinical Global Impression (Guy, 1976) (CGI) measure was also ascertained at the time of first infusion.

Subjects then received IV infusion of 0.5 mg/kg of ketamine hydrochloride solution (Myaln Inc.) over 40 min. The dose of ketamine was determined by ideal body weight based on sex, age, height, and body frame in the Metropolitan Life Insurance tables (www.coping.org). MADRS and VAS were ascertained at the end of infusion (t_0+40 min) and again at t_0+100 min and t_0+160 min. The sleep and appetite item scores on the MADRS were kept the same as those obtained before infusion as there was no expectation of change.

Acute dissociative and psychotomimetic effects of ketamine were measured 30 min before the start of each infusion (t_0), immediately upon completion of each infusion (t_0+40 min) and during post-ketamine monitoring period (t_0+100 min and t_0+160 min). Psychotomimetic effects were measured with the four-item positive symptom subscale of the Brief Psychiatric Rating Scale (Overall, 1962) (BPRS) (scale range 4–28) consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization; dissociative effects were measured with the Clinician-Administered Dissociative States Scale (Bremner et al., 1998) (scale range 0–92). Additionally, the patients were regularly questioned during the infusions about any dysphoric emotions or altered sensory experiences.

All subjects were monitored at least for 2 h post-infusion. Before leaving the infusion unit, subjects had to demonstrate that all clinically significant ketamine side effects were resolved by obtaining a score ≥ 9 in the modified Aldrete scoring system (Aldrete, 1995). The mAldrete is a set of criteria commonly used to assess transition from anesthesia to recovery and takes into account activity, respiration, circulation, consciousness, and SpO_2 level to compose a final score. Guidelines established for clinically significant changes in vital signs and mental status during the ketamine infusions were as follows: systolic blood pressure (BP) >161 or <89, diastolic BP >110; heart rate <40 or >130 beats/min; respiratory rate <10 or >30/min; pulse oxymetry $<90\%$; severe hallucinations, confusion, delusions, irrational behavior, or agitation. An anesthesiologist was available during infusions if needed. The infusion was discontinued in the event of significant changes that did not respond to interventions. A psychiatrist was present during the entire procedure until the patient left the unit accompanied by a competent adult. At discharge, subjects received written discharge instructions regarding rare but serious side effects from ketamine and several measures to improve recovery at home.

Procedures for the subsequent infusions at days 3, 5, 8, 10, and 12 were identical to those of the first infusion with the exception of omitting the CGI assessment. Four weekly face-to-face follow-up with sets of outcome measures (MADRS and CGI ratings) were administered after each patient's series of infusions was completed. Subjects continued with same stable dose of antidepressant regimen from their primary psychiatrists during the course of infusions and follow-up visits.

2.3. Statistical analysis

Means and standard deviations were used to describe continuous data and percentages for categorical variables. Comparisons between two time-points for continuous variables were tested with paired *t*-tests. Changes in MADRS score over the course of infusion treatment were examined using a matched-pair *t*-test, with initial baseline MADRS score being compared to the last MADRS recorded after the final infusion. Pearson's product–moment correlation coefficient was used to assess the relationship between two approximately normally distributed continuous variables.

3. Results

3.1. Demographic and clinical characteristics

Fourteen subjects were enrolled in the study; one dropped out after the first infusion due to decreased energy and increased irritability. Another patient dropped out after two infusions due to dissatisfaction of expected therapeutic effect from ketamine. Demographics and baseline characteristics of the study sample are presented in Table 1. Among fourteen patients, all were males, 13 were Caucasians, 10 had at least one first degree relative with mood disorder, 3 had a past history of substance disorder, 4 had prior suicidal attempts, and 2 had received electroconvulsive therapy for depression. The mean age of sample was 54 years, had 15 years of education, and had at least one psychiatric hospitalization. Subjects were chronically depressed with onset of first major depressive episode at age 33, had more than 3 lifetime episodes of major depression, and presented moderate to severe symptoms of depression (17-item HDRS mean score=19.2, S.D: 4.2), with duration of current episode of 17 months.

Table 1
Demographic and clinical characteristics of study sample.

Characteristics	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14
Age	28	55	69	52	32	41	66	67	57	53	64	62	69	43
Gender, male/female	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Education, years	14	14	23	14	14	17	19	14	14	12	13	14	18	14
First degree relative with mood disorder, yes/no	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Psychiatric hospitalizations, Nº	0	1	2	5	0	0	1	3	3	1	1	2	1	0
Past Substance disorder, yes/no	No	No	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes
History of Suicide attempts, yes/no	No	No	No	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes
History of ECT, yes/no	No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No
Lifetime MDD episodes, Nº	2	3	3	5	5	3	3	3	2	3	3	6	2	5
Age at Onset of first MDE, years	22	42	35	31	16	34	30	45	54	43	22	52	18	27
Length of current episode, months	18	24	9	9	7	12	36	15	36	20	9	15	24	9
Baseline HDRS score	19	18	23	16	17	19	18	19	25	14	18	18	28	27
Baseline MADRS score	29	22	23	31	35	26	27	40	39	24	36	24	24	33
MMSE score	29	30	30	29	29	30	29	30	28	28	28	30	30	27
Baseline CGI score	5	5	5	5	5	5	5	6	5	4	6	4	5	5
Failed antidepressants during current episode, Nº	3	3	4	3	3	3	3	3	3	3	3	3	3	4

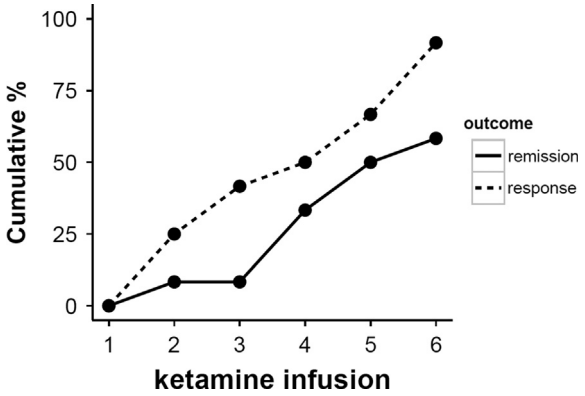

Fig. 1. The cumulative probability of remission and response by repeated ketamine infusions in treatment-resistant major depression. Ketamine IV (0.5 mg/kg) was administered over a 12-day period during on a Monday–Wednesday–Friday schedule, corresponding to study days 1, 3, 5, 8, 10, and 12. Depression severity was measured by Montgomery–Åsberg Depression Rating Scale (MADRS) at baseline, and then 40, 100 and 160 min after infusion was started. Response was defined as $\geq$50% improvement from baseline score in MADRS. Remission was defined as MADRS score $\leq$9.

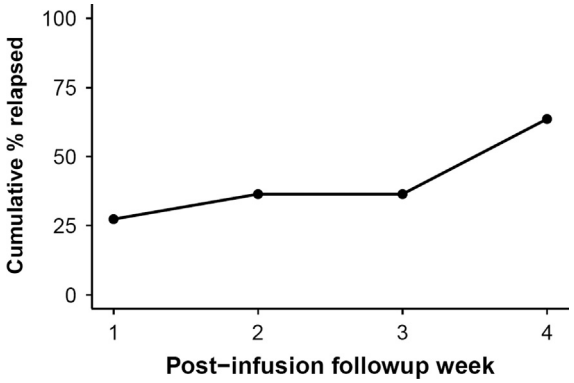

Fig. 2. The cumulative probability of relapse from eleven subjects that achieved response ($\geq$50% improvement from baseline score in MADRS) after completing six infusions. Relapse was ascertained by a weekly visit for 4 consecutive weeks. Relapse was defined as $<$50% improvement in baseline MADRS score at that visit.

3.2. Antidepressant outcomes

Fig. 1 presents cumulative probability of remission and response with each infusion. For the purpose of this report, only scores on the MADRS from those participants who completed six infusions were considered. After the first infusion, only three subjects responded (25%) and one subject remitted (8.3%). Seven subjects reached response and six remitted after receiving 3 or more infusions. Overall, out of twelve subjects who completed all six infusions, eleven (91.6%) achieved response criterion and eight (66.6%) remitted. MADRS scores decreased significantly over the infusion period. The within-subject change in MADRS score from initial baseline MADRS measurement to the final MADRS recorded after the final infusion was statistically significant (average MADRS change = 18.8, 95% CI: 12.3–25.3, $p < 0.001$, matched-pair t-test).

Of the eleven patients who responded in infusion phase, MADRS scores and CGI ratings were obtained weekly for 4 weeks. The MADRS scores for the follow-up phase are presented in Fig. 2. Five out of eleven subjects remain in response status throughout the four weeks of follow-up. The mean time for those six subjects who relapsed after the last ketamine infusion was 16 days (range 7–28 days). Three patients relapsed within 1 week after the last infusion. On the CGI severity measure all 12 patients were considered markedly or severely ill before treatment. By the last follow-up visit, 5 patients were categorized as borderline or mildly mentally ill. The CGI improvement measure was rated much improved in 6 patients by the last follow-up visit.

Fig. 3 presents VAS scores from several emotions measured during ketamine treatment. The mean score of positive emotions such as happiness, calmness, and self-esteem significantly increased from baseline to last infusion. VAS scores of negative emotions such as sadness and tiredness significantly decreased during infusion treatment. Marginally significant changes were found for VAS-energy and VAS-worthlessness from baseline to completion of six infusions ($p = 0.22$ and $p = 0.06$, respectively).

3.3. Acute dissociative and psychotomimetic effects

Ketamine was associated with a small but significant increase in psychotomimetic symptoms as measured by the BPRS (increase from a mean of 4.0 ± 0 before infusion to 4.6 ± 1.9 at the end of the infusion (t_0+40 min); $p = 0.0092$). The BPRS score returned to a mean of 4.0 by 120 min after infusion ends. Ketamine resulted in

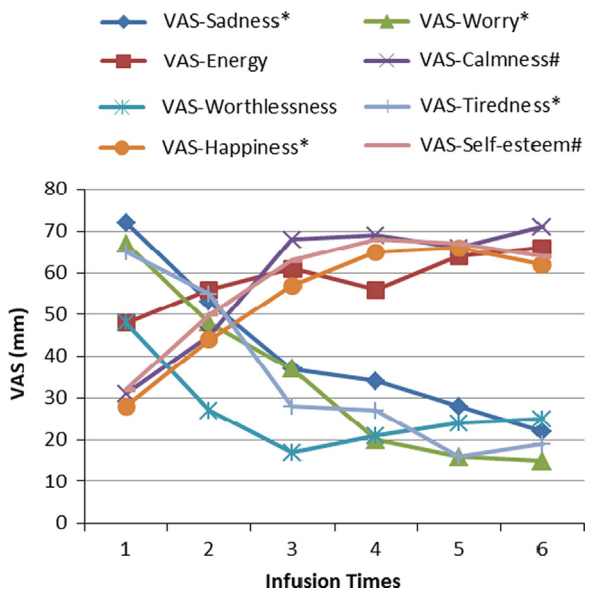

Fig. 3. Visual Analog Scale (VAS) scores from several emotions during ketamine treatment. Patient were asked to indicate on a 100 mm horizontal line where the specific emotion was by making a mark somewhere on the line between two descriptors representing extremes of emotion intensity (not at all and extremely) at each end. VAS was scored by measuring the distance from the "not at all" left end of the line. Measures were obtained before infusion, at the end of infusion (t+40 min) and again at t+100 min and t+160 min. $^{*}p < 0.001$; $^{\#}p < 0.05$.

a mild increase in dissociative symptoms as measured by the Clinician-Administered Dissociative States Scale (increase from a mean of 0 before infusion to 8.60 ± 6.49 at the end of the infusion (t_0+40 min); $p < 0.0001$), which returned to baseline by 120 min after infusion ends.

There was no significant correlation between severity of dissociative side effects and change in MADRS score throughout the infusion stage (Pearson's product–moment correlation coefficient, $r = 0.17$; $p = 0.15$).

3.4. Hemodynamic changes and recover from ketamine

None of the patients experienced arrhythmia or required respiratory support during the infusions. One normotensive 32-year old patient experienced a single episode of rise in blood pressure (180/92) that required 10 mg of IV labetalol. Blood pressure rapidly returned to baseline and remained normal until discharge. Another patient with gastroesophageal reflux disease had nausea and vomited at the end of the second infusion. IV Ondansetron at 8 mg was successfully used

as prophylaxis for the subsequent infusions. The modified Aldrete score for all subjects was 10 (complete recovery from ketamine) after 2 h post-infusion.

4. Discussion

In this open label trial of ketamine for TRD, the major findings are that (1) repeated ketamine infusions increased antidepressant response and remission rates compared to a single infusion, (2) response and remission were achieved without wash out from previous antidepressants, (3) the trajectory of response and remission varied by subjects during ketamine infusions, and (4) durability of antidepressant response after completing six infusions was highly variable.

Using a six infusion protocol, 92% of subjects responded and 67% remitted. This compares favorably with prior reports from single infusion studies in which between 50% and 79% of subjects with unipolar or bipolar depression responded (Berman et al., 2000; Diazgranados et al., 2010) and 29% remitted (Zarate et al., 2006). Within our own sample, adding five infusions increased response from 25% to 92%, and remission from 8% to 67%. Murrough and colleagues (Murrough et al., 2013b) reported a response rate of 62.5% after the first infusion with 70.8% response after a series of six thrice weekly infusions. In the same line, Rasmussen et al. (2013) reported that 3 of 10 subjects (30%) achieved response by the first infusion. After four repeated infusions, the overall response rate was 80%. Our results then support previous findings that suggest higher response rates with more than one infusion.

In this study, there were noticeably different trajectories to achieve response over time. The Murrough et al. study (Murrough et al., 2013b) reported that out of 17 responders to serial ketamine infusions, 15 achieved such status 24 h after the first infusion. The authors pointed out that antidepressant response very early in the course of treatment with ketamine strongly predicted subsequent antidepressant response. In contrast, we found that out of 11 responders, only three did so after the first infusion and six subjects required three of more infusions to reached response status. The cumulative effect of repeated infusions is even more evident in the trajectory of remission where rates are markedly accelerated after three or more infusions where 6 out of 7 remitters achieved such status.

Both early and delayed improvements have been described in large clinical trials. For instance, the Genome-Based Therapeutic Drugs for Depression (GENDEP) study showed that more than half of the subjects who eventually reached remission showed a pattern of delayed improvement, and their eventual outcome could not be predicted from early time points. In the same vein, the first step of the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study, 56% of participants who responded at some point during a 12-week trial of citalopram did so only at or after 8 weeks of treatment. The high response rate observed very early in the course of treatment by Murrough et al. (2013b) might be related to the fact that an initial cohort of nine subjects, who achieved response by the first infusion, were allowed to continue with additional infusions.

In this study no wash out was required but subjects remained on stable doses of previous antidepressant regimens throughout the study. Augmentation strategies add an agent that is not conventionally used as first-line monotherapy (e.g., atypical antipsychotic, lithium, T3) to an antidepressant and is frequently practiced in routine clinical care. In that sense, ketamine could be seen as an augmenting agent. The exact mechanism of the clinical effects of augmentation is not known but is thought to occur via a synergistic effect or via different neurotransmitter and second messenger systems (Schweitzer and Tuckwell, 1998).

Chronic, but not acute, administration of traditional antidepressants in rodent studies slowly increase expression of cAMP response element binding protein (CREB) (Nibuya et al., 1996) and brain-derived neurotrophic factor (BDNF) (Nibuya et al., 1995), enhance synaptic plasticity (Guirado et al., 2012), and neurogenesis (Malberg et al., 2000). However, these agents target only monoamines, which are modulatory transmitters, and may not exert a profound effect over synaptic transmission, activity-dependent release of BDNF, and synaptogenesis as ketamine does (Duman et al., 2012; Kavalali and Monteggia, 2012; Li et al., 2010). It is conceivable that a more robust antidepressant response and remission rates, such as those reported in this study, may the result of a synergistic effect between the modulatory effects from monoamine neurotransmitter in conjunction with agents such as ketamine that directly exert action on fast excitatory glutamate transmission and increase BDNF release and synaptogenesis. The effects of ketamine when used in patients who are taking other psychotropic agents deserve further study with larger sample.

Time to relapse after single ketamine infusion ranges between several days to 1 week (Zarate et al., 2006). In line with previous reports (Murrough et al., 2013b; Rasmussen et al., 2013), our study suggests that serial infusions prolong durability of antidepressant response compared with a single infusion with highly variable inter-individual relapse rates. While three out of 11 responders relapsed within the first week after the last infusion (27%), five remained in response status at least 4 weeks after the last infusion (45%). Continuation of ketamine infusions as a bridge to relapse prevention after initial response to serial infusions have not been reported yet. Two trials of riluzole (Ibrahim et al., 2012; Mathew et al., 2010), a glutamatergic modulator with antidepressant and synaptic plasticity-enhancing effects, did not significantly alter the course of antidepressant response to ketamine alone. In general, failure to maintain remission remains a major limitation in antidepressant treatment.

Recent investigations in continuation/maintenance of response after acute course of electroconvulsive therapy (ECT) may provide a model of dosing schedule of ketamine infusions and prevent relapse. For instance, flexible dosing of ECT focus on “catching” symptom recurrence before the patient fully relapses may guide individualized care in contrast to a rigid continuation schedule. Tolerance (Wolff and Winstock, 2006; Leccese et al., 1986) and potential deleterious effects such as neurotoxicity (Liao et al., 2011; Olney et al., 1991), bladder toxicity (Middela and Pearce, 2011), and addiction raise concerns about feasibility of repeated ketamine infusions in routine clinical practice.

Consistent with previous reports (Berman et al., 2000; Zarate et al., 2006; Diazgranados et al., 2010; Murrough et al., 2013b; Rasmussen et al., 2013), repeated ketamine infusions induced transient and tolerable psychoactive and hemodynamic changes. Severe psychotogenic changes such as hallucinations, delusions, or paranoia were not observed in any participant. Dissociative side effects were well-tolerated and dissipated shortly after cessation of the infusions. Cumulative increase in severity of side effects was not observed with additional infusions. The absence of a correlation between peak perceptual changes and changes in MADRS scores in this study suggests that ketamine's antidepressant effect is not dependent on the induction of a dissociative state.

Mild increase in blood pressure and heart rate were not uncommon but no subject was discontinued from infusion due to hemodynamic changes. While continuous cardiorespiratory monitoring and an anesthesiologist accessible at all times are strongly advisable to minimize risk of adverse events, full anesthesia monitoring was not required in our hospital system for the rate of dosing used in this study. The resultant decreased in personnel cost and demands for specialized infrastructure makes feasible the use of ketamine for depression in routine clinical practice. Larger studies should confirm

whether safety and tolerability of ketamine infusions are deemed practical enough to be implemented at most hospitals.

There are several limitations to consider in the interpretation of the study. The number of subjects is small and the results should be confirmed by larger samples. All subjects were male and excluded if they were older than 70 years of age. To our knowledge, no gender difference has been reported on the antidepressant effect of ketamine. The efficacy and tolerability of ketamine among elderly patients need further study given greater medical comorbidity and possibly etiology of late-life depression based on brain vascular pathology. The lack of a placebo group in the design limits the interpretation of efficacy; however, our primary aim to examine whether serial ketamine infusions improved response as compared to a single infusion was achieved.

Previous reports from studies using saline as a placebo have demonstrated greater ketamine antidepressant response in TRD unipolar or bipolar depression. The use of saline as placebo appears to be suboptimal as the experience of perceptual disturbances induced by ketamine biased masking intention. Recently, the use of IV benzodiazepine midazolam as an active placebo to mimic dissociative effects of ketamine resulted in incomplete masking as higher transient side effects were found among those who received ketamine (Murrough et al., 2013a). Intravenous amphetamine (a dopamine agonist) has also been proposed as an active placebo as it would produce positive symptoms of psychosis, thought disorganization, and euphoria similar to ketamine. However, despite some overlap, ketamine and amphetamine would have distinct side effect profiles. Euphoria by amphetamines has been associated with psychomotor activation and hostility; whereas that of ketamine was associated with sedation (Krystal et al., 2005). Amphetamine also would not mimic perceptual changes commonly experienced with ketamine.

In conclusion, six serial ketamine infusions produce high response and remission rates among individuals with treatment-resistant depression. Seventy-two percent of TRD subjects in our sample that would have been declared as non-responders to single infusion achieved antidepressant response (92%) and even remission (66%) through subsequent infusions. Moreover, the durability of antidepressant response was maintained at least for 4 weeks in 45% of responders after the last infusion. A randomized clinical trial with an appropriate placebo control would be the next step to substantiate these findings. The therapeutic effect of ketamine in this study was achieved in patients who were taking other psychotropic agents. These results provide initial evidence about the safety and efficacy of repeated ketamine infusions without the acquisition of a 7-day medication-free state in patients with treatment-resistant depression. Finally, patients appear to show different trajectories of response during repeat ketamine infusions. While some patients reached antidepressant response very early in the course of treatment (fast-responders), others required multiple infusions to achieve response (slow-responders). Future studies are needed to elucidate the influence of baseline states in neural circuits and subsequent changes that accompany treatment response to ketamine.

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Conflict of interest

I can affirm that all the authors do not have any conflict of interest whether it is actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, their work.

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