Pilot Randomized Controlled Trial of Titrated Subcutaneous Ketamine in Older Patients with Treatment-Resistant Depression

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Objective: *To assess the efficacy and safety of subcutaneous ketamine for geriatric treatment-resistant depression. Secondary aims were to examine if repeated treatments were safe and more effective in inducing or prolonging remission than a single treatment.* **Methods:** *In this double-blind, controlled, multiple-crossover study with a 6-month follow-up (randomized controlled trial [RCT] phase), 16 participants (≥60 years) with treatment-resistant depression who relapsed after remission or did not remit in the RCT were administered an open-label phase. Up to five subcutaneous doses of ketamine (0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg) were administered in separate sessions (≥1 week apart), with one active control (midazolam) randomly inserted (RCT phase). Twelve ketamine treatments were given in the open-label phase. Mood, hemodynamic, and psychotomimetic outcomes were assessed by blinded raters. Remitters in each phase were followed for 6 months.* **Results:** *Seven of 14 RCT-phase completers remitted with ketamine treatment. Five remitted at doses below 0.5 mg/kg. Doses ≥ 0.2 mg/kg were significantly more effective than midazolam. Ketamine was well tolerated. Repeated treatments resulted in higher likelihood of remission or longer time to relapse.* **Conclusion:** *Results provide preliminary evidence for the efficacy and safety of ketamine in treating elderly depressed. Dose titration is recommended for optimizing antidepressant and safety outcomes on an individual basis. Subcutaneous injection is a practical method for giving ketamine. Repeated treatments may improve remission rates (clinicaltrials.gov; NCT01441505).* (Am J Geriatr Psychiatry 2017; 25:1199–1209)

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Highlights

- This first small RCT of ketamine treatment in older treatment-resistant depressed patients found significant efficacy.
- Individualized dosing using a dose-titration method and the subcutaneous route was well tolerated and is recommended for further investigation.
- Preliminary results suggest repeated treatments may improve remission rates and lead to longer lasting remission in some participants.

INTRODUCTION

Depression is the second most disabling condition globally.[1] In older patients antidepressant medications may have lower efficacy.[2] Electroconvulsive therapy has greater risks,[3] and the efficacy of novel brain stimulation treatments is less certain,[4] highlighting the need for new effective and safe antidepressant treatments.

Numerous placebo-controlled studies in adult patients have reported rapid, large reductions in depression scores after a single treatment of ketamine, but none has been undertaken specifically in older depressed patients.[5] Current knowledge on ketamine in older depressed patients (aged ≥ 65 years) is limited to five case reports. Among four treatment-resistant participants given up to six treatments of 0.5 mg/kg ketamine by 40-minute intravenous infusion, only one participant benefitted, with a partial early response that was not sustained despite repeated treatments.[6] Further, the three nonresponders all reported severe dissociative adverse effects. Another report of a less-treatment-resistant 65-year-old patient reported remission lasting a year after four intravenous ketamine infusions, with only transient psychotomimetic and cognitive side effects.[7]

Although antidepressant effects appear to be dose related, side effects of ketamine are also dose related, including psychotomimetic and dissociative effects, transient elevation of blood pressure and heart rate, cognitive impairment, hepatotoxicity, and inflammation of the bladder endothelium[8,9] (i.e., the pharmacokinetics of drug administration is an important factor). Potential useful strategies to minimize side effects are dose optimization and alternative routes of administration. In studies in an adult population, doses were individually titrated (such that each individual received the lowest dose required for efficacy), resulting in good tolerance and meaningful efficacy at doses below the commonly used 0.5 mg/kg.[10–12] This suggests that individualizing mg/kg dosage on an individual patient basis may be a better approach than using set mg/kg doses (e.g., 0.5 mg/kg) in all patients. Further, the subcutaneous route of administration was used and found to be simple and well tolerated and to have similar efficacy to intravenous ketamine.[11,12]

To date, most controlled studies have examined the effects of a single dose of ketamine, which does not lead to lasting remission for most participants. A few open-label studies have examined whether the duration of antidepressant effect can be increased by repeated treatments. For example, Murrough et al.[13] found that repeated treatments may prolong antidepressant effects, extending the time to relapse to a few weeks. They also reported that initial response to the first treatment strongly predicted remission after six treatments. A meta-analysis found a larger effect size at 14 days for repeated infusions compared with single infusions.[14] To date, however, there has been limited systematic evaluation of the safety of repeated treatments of ketamine, although there are reports of safe use in the short term in adult patients with various neuropsychiatric disorders.[13,15–18]

This double-blind, placebo-controlled pilot study examined the safety and efficacy of ketamine as an antidepressant for geriatric treatment-resistant depression. The study further assessed the utility of subcutaneous ketamine and an individualized dose-titration treatment approach. The within-subjects design facilitates examination of dose–response relationships (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E4/Step4/E4_Guideline.pdf). Finally, the study aimed to explore

in an open-label phase if repeated dosing was more effective than single dosing in inducing remission (for nonremitters to a single dose) or more lasting remission (for remitters to a single dose who relapsed within 6 months).

METHODS

The study was approved by the University of New South Wales Human Research Ethics Committee. All participants gave written informed consent. Treatments were conducted at Wesley Hospital, Sydney, Australia.

Participants

Sixteen participants, aged ≥ 60 years, with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of Major Depressive Disorder or Bipolar Disorder and a depressive episode of duration ≥ 4 weeks (confirmed with the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [research version] and clinician-conducted interview) were included in the study. Participants were required to have a Montgomery-Asberg Depression Rating Scale (MADRS)[19] score ≥ 20 and insufficient therapeutic response to ≥1 adequate trials of an antidepressant medication during the current depressive episode (as defined by Antidepressant Treatment Response Questionnaire).[20] Exclusion criteria were high suicide risk requiring urgent management, pregnancy, schizophrenia, current psychotic symptoms, drug abuse or dependence in the last 6 months, known hypersensitivity or medical contraindication to ketamine, and a history of ketamine abuse. Medical fitness to receive ketamine was evaluated by a physician, based on history, examination, blood screen (complete blood count, renal and hepatic function), and any additional investigations judged necessary by the physician. Physical comorbidities were rated using the Cumulative Illness Rating Scale.[21] Participants were allowed to remain on psychotropic medications, with no changes in medications permitted in the 4 weeks before and during the trial.

Randomized Controlled Trial Phase

Study Design

Subcutaneous doses of ketamine HCl (Ketalar; Hospira, Melbourne, VIC, Australia) were given in an ascending dose design (0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg) in separate treatment sessions at least a week apart. A single dose of an active control treatment, midazolam 0.01 mg/kg (Hypnovel; Roche Products, Dee Why, NSW, Australia), was randomly inserted within the first 3 treatment sessions. Midazolam was used as an active control to optimize study blinding because similar side effect profiles have been reported for midazolam and ketamine in a prior randomized controlled trial (RCT).[22] Given the increased rate of physical comorbidities and polypharmacy in this age group and because multiple adverse effects are dose related as noted above, the dose-titration approach previously used successfully in a general adult population[11] was seen as particularly suitable, allowing the use of the smallest dose required to attain remission, thus minimizing side effects. The subcutaneous route of administration was selected based on prior reports of ease of use and tolerability.[11]

A randomization list was created, with the position of the control treatment randomly assigned by a computer-generated random number sequence. An anesthetist investigator sequentially assigned participants to the randomization list, drew up the medications for each treatment, and blinded the injection volume by taping over the barrel of the syringe. This anesthetist was not involved in any treatment sessions, contact with participants, or study assessments. This ensured treaters, participants, and raters were blinded to treatment assignment until the entire study was completed. The randomization list was kept in a locked cupboard only accessible to the anesthetist drawing up the study drug. Participants, treaters, and raters were aware that the RCT included one session with a control treatment but did not know the control treatment was inserted within the first three sessions. Participants were not aware of the ascending dose design.

Subcutaneous injections were given into the abdomen (Day 1), and participants were followed up for 1 week. Participants were assessed on Day 7 after treatment, and a MADRS score ≥ 20 was required to continue onto the next treatment. Participants

completed and exited the RCT phase of the study if they were in remission (defined as MADRS < 10) at day 7 after any treatment. Remitters were followed up with MADRS ratings weekly for 4 weeks and then monthly for another 5 months or until relapse (defined as MADRS ≥ 20).

All participants received at least two treatments to ensure they received ketamine at least once (i.e., not potentially exiting the study after only receiving midazolam control). The exception was one participant, who remained in remission for the duration of the follow-up period (6 months) after the first injection.

Assessment of Mood and Side Effects

The primary outcome measure was the MADRS, rated pretreatment, 4 hours after treatment (Day 1), and then on Days 2, 4, and 7 by a trained blinded rater. The MADRS rater was not present when treatment was given or during assessments of side effects and safety outcomes (described below), which were rated by a separate blinded rater. Inter-rater reliability on the MADRS was established between study raters (intraclass correlation ≥ 0.8). Response was defined as a decrease in MADRS score ≥ 50% from the pretreatment score.

Participants were monitored for 4 hours after each treatment. Participants' heart rate and blood pressure were assessed 5, 15, 30, 60, and 240 minutes after injection. Psychiatric side effects were assessed using five items (hallucinations, grandiosity, suspiciousness, unusual thought content, conceptual disorganization) from the Brief Reactive Rating Scale[23] and item 1 (mood elevation) from the Young Mania Rating Scale.[24] Psychotomimetic and dissociative side effects were assessed using the Clinician Administered Dissociative Symptoms Scale (CADSS)[25] at study baseline, after 40 minutes (based on symptoms experienced from 0 to 40 minutes), and at 4 hours after each treatment. A modified version of Systematic Assessment of Treatment Emergent Effects scale[26] was administered 4 hours after each treatment, assessing for physical side effects experienced over the treatment session. Orientation (nine items) and simple and complex reaction times were assessed at study baseline and 4 hours after each treatment. Participants were only discharged from treatment sessions if there was no decline in the orientation score from study baseline and reaction times were within 1 standard deviation of the baseline score. Liver function tests were done before the first treatment and at RCT exit.

Analysis

An intention-to-treat analysis of MADRS scores for all participants enrolled in the RCT was performed. A mixed-effects model was used to analyze MADRS scores using the PROC MIXED in SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Times of measurement were entered as coefficients of linear and quadratic orthogonal polynomials with adjustment for the unequal time intervals. Post hoc tests were conducted where main effects were statistically significant. Statistical significance was set at $p < 0.05$.

Open-Label, Repeated-Treatments Phase

Assessment of Mood and Side Effects

The RCT phase was followed by an open-label, repeated-treatments phase that examined whether (1) participants who remitted and then relapsed after a single treatment would remain well for longer after repeated treatments given at that same dose, and (2) participants who did not respond to a single treatment would remit with multiple treatments (given at the same dose as the single treatment). All participants who completed the RCT phase, either remitters who relapsed during follow-up or nonremitters at the maximum dose and who had a MADRS score ≥ 20, were eligible to enter the open-label, repeated-treatments phase. Twelve subcutaneous injections of ketamine were given twice weekly for 4 weeks and then weekly for 4 weeks. Ketamine was administered at the highest dose received in the RCT phase, that is, either the dose at which remission occurred (leading to RCT exit) or the highest dose received without remission. Mood was rated (MADRS) before each treatment and after the treatment course. Participants in remission at the end of the treatment course had further follow-up (MADRS ratings) for 6 months, using the same schedule as follow-up after the RCT phase.

Safety outcomes measured at each treatment session were heart rate, blood pressure, and a side effects checklist (numbness, dizziness, headache, nausea) assessed pretreatment and 1 hour after each treatment; CADSS; and orientation (nine items) 1 hour after treatment. A checklist assessing for urinary problems was administered at each session before treatment (pain,

burning, difficulty with initiation, decrease in force/stream, frequency, change in color), assessing for changes since the last treatment session. Liver function tests and a battery of neuropsychological tests were done before the treatment course and 3–5 days after the last treatment to assess for any cumulative hepatic or cognitive adverse effects over the course. Neuropsychological tests used were Rey Auditory Verbal Learning Test; Medical College of Georgia Complex Figure Test; Cross Out Test; Controlled Oral Word Association Test, letter and category; Digit Span forward and backwards; and Symbol Digit Modalities test, with alternate versions used where available.

RESULTS

Participants

Three participants had onset of depression after age 60. Participants were highly treatment resistant and had multiple medical comorbidities, including Parkinson disease, polymyalgia rheumatica, chronic pain, recent major bowel surgery, and multiple sclerosis. Nonremitters tended to be more treatment resistant than remitters (Table 1).

Seven participants exited the RCT after meeting the criterion for remission 1 week after treatment (ketamine doses 0.1 mg/kg: N = 1; 0.3 mg/kg: N = 1; 0.4 mg/kg: N = 3; and 0.5 mg/kg: N = 2). Seven participants received up to 0.5 mg/kg but did not experience remission lasting at least 1 week after treatment. A positive finding was that dose titration up to 0.5 mg/kg did not have to be aborted for any participants because of unacceptable side effects (Figure 1).

RCT Phase

Mood Outcomes

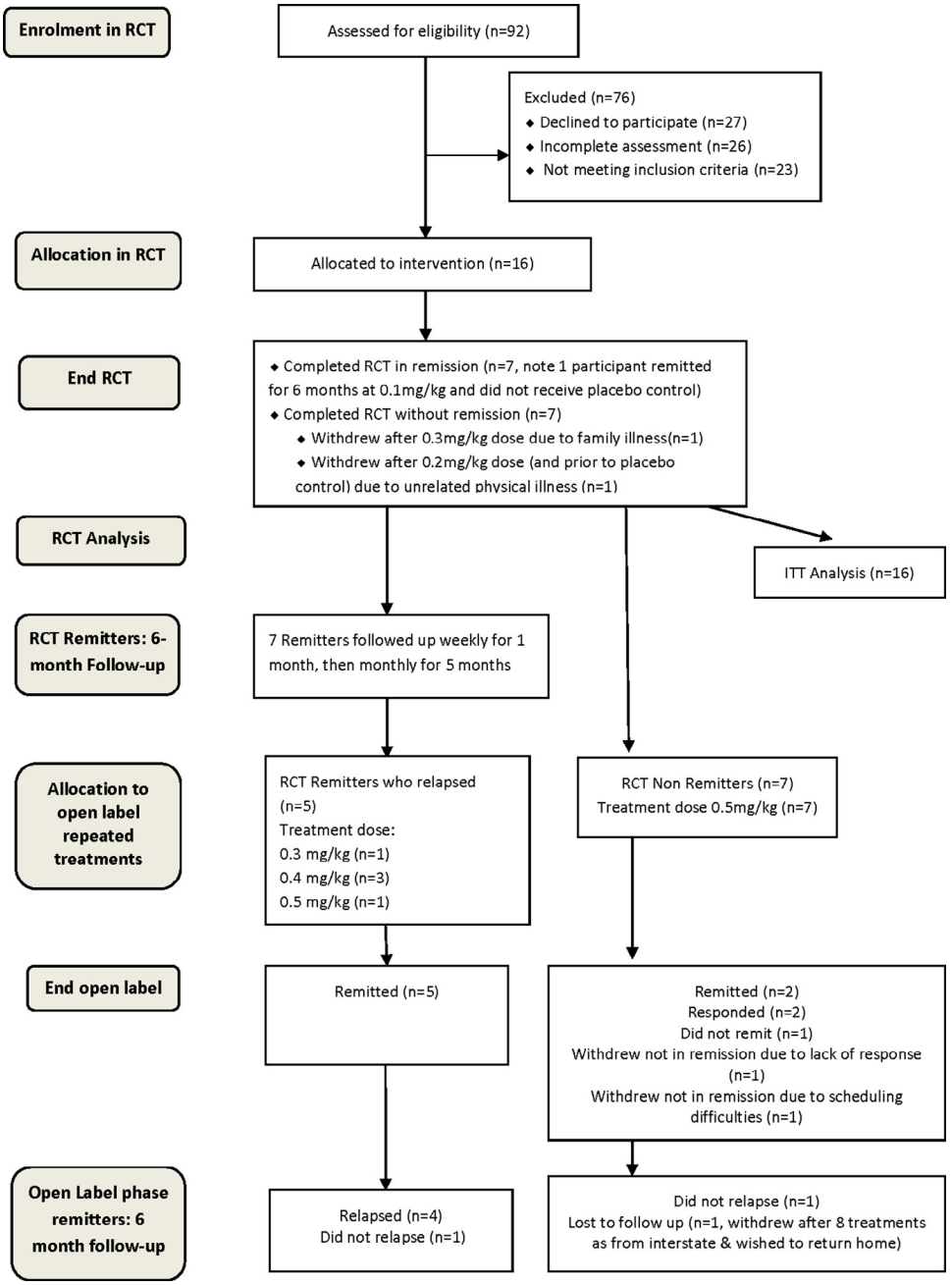
The mean changes in MADRS scores and the number of participants treated with midazolam and at each ketamine dose level are shown in Figure 2A. Eleven of 16 participants met the criteria for both response and remission after treatment with ketamine at least at one point during the trial (across all dose levels and time points), corresponding to overall acute response and

TABLE 1. Clinical and Demographic Data for the Whole Sample and for Remitters and Nonremitters

Variable	Total (N = 16)	Remitters End RCT (N = 7)	Nonremitters End RCT (N = 7)
Demographic variables			
Mean age, yr (SD)	65.6 (5.7)	67.4 (7.6)	64.6 (4.2)
Gender, male	10 (62.5)	4 (57.1%)	5 (71.4)
Clinical variables			
Mean BMI, kg/m^2 (SD)	26.6 (4.7)	27.9 (5.3)	34.9 (4.4)
Mean age at onset, yr (SD)	37.5 (17.5)	35.9 (17.8)	34.4 (19.1)
Melancholic features (yes)	12 (75)	6 (85.7)	4 (57.1)
Atypical features (yes)	1 (6.3)	0	0
Bipolar diagnosis (yes)	1 (6.3)	1 (14.3)	0
Mean baseline MADRS score (SD)	34.8 (3.5)	34.4 (4.7)	35.4 (2.3)
Mean current episode duration, mo (SD)	115.9 (174.2)	92.3 (217.5)	116.55 (96.8)
Mean lifetime duration of illness, yr (SD)	16.9 (16.1)	18.0 (20.3)	16.2 (10.1)
Concurrent physical illness	13 (81.3)	6 (85.7)	6 (85.7)
Mean cumulative illness rating scale score	9.5 (3.0)	11.1 (3.0)	7.9 (2.2)
DSM-IV anxiety disorder	10 (62.5)	4 (57.1)	5 (71.4)
Treatment-related variables			
Mean antidepressants failed current episode (SD)	4.3 (4.7)	1.9 (0.7)	6.6 (6.2)
Mean antidepressants failed lifetime (SD)	7.8 (4.3)	7.6 (3.6)	8.9 (5.4)
Failed ECT current episode, yes	2 (12.5)	1 (14.3)	1 (14.3)
Concurrent psychotropic medications	14 (87.5)	7 (100)	5 (71.4)
Antidepressant	11 (68.8)	6 (85.7)	3 (42.9)
Anticonvulsant (mood stabilizer)	3 (12.5)	1 (14.3)	2 (28.6)
Antipsychotic	3 (18.8)	2 (28.6)	1 (14.3)
Benzodiazepine	6 (37.5)	2 (28.6)	2 (28.6)

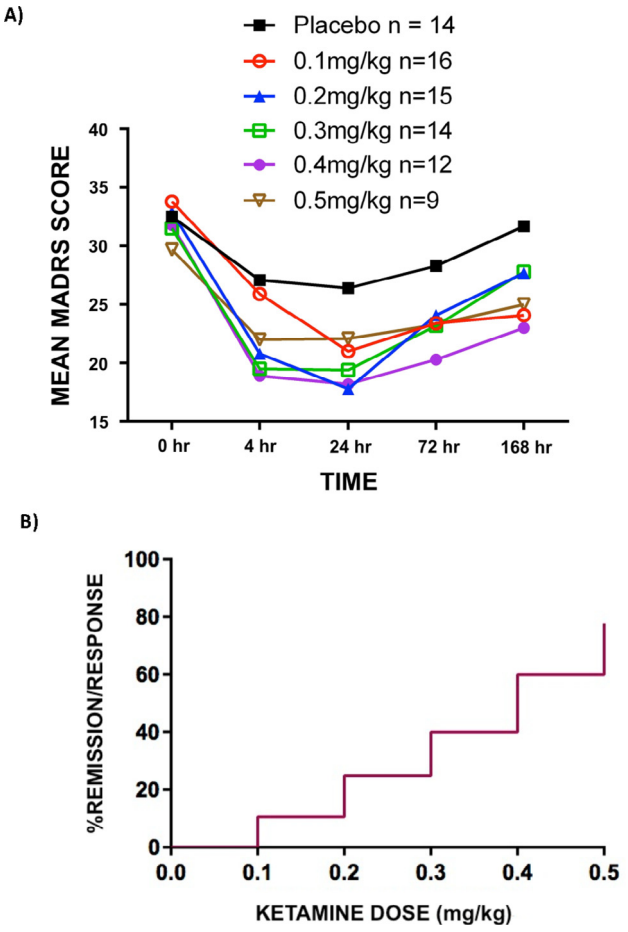
Notes: Values are number of cases with percents in parentheses unless otherwise denoted. BMI: body mass index; DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; ECT: electroconvulsive therapy; SD: standard deviation.

FIGURE 1. Study flowchart and CONSORT (Consolidated Standards of Reporting Trials) diagram. ITT: intention to treat analysis.



remission rates of 68.8%. Four of 14 participants (29%) who received midazolam treatment met response and 2 of 14 (14%) attained remission at one time point. However, no participant sustained response or remission to midazolam treatment at Day 7. The proportion of the whole sample who met response and remission criteria increased as the ketamine dose was increased from 0.1 mg/kg to 0.5 mg/kg (Figure 2B). The seven participants who exited the RCT in remission were followed up until relapse.

FIGURE 2. **[A] MADRS scores for midazolam and all ketamine dose levels in the RCT phase. [B] Percentage of remitters and responders at any time point across ketamine dose levels in the RCT phase. Note data are identical for remission and response rates because all responders were also remitters.**

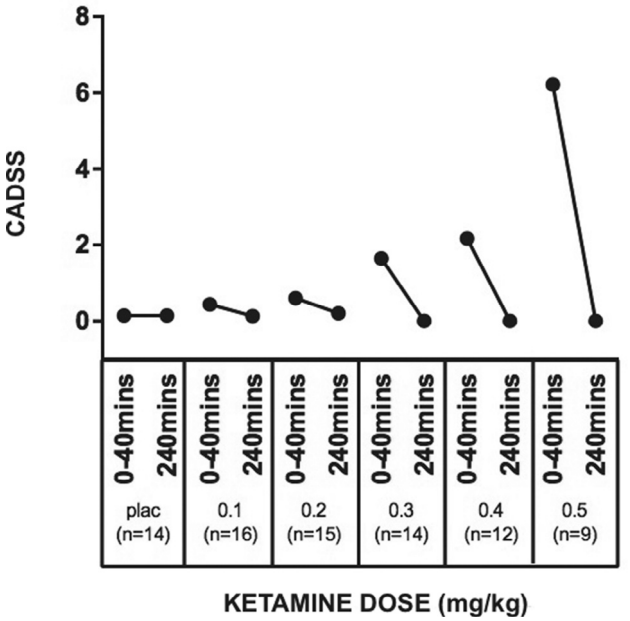


Eighty treatment sessions (including midazolam and ketamine at a range of doses) were completed in 16 participants. A set of preliminary mixed-effects model analyses of MADRS scores examined for any effects of order or carryover and found no evidence for either of these. Because only 9 participants received ketamine at 0.5 mg/kg, further analyses were restricted to ketamine treatments given at 0.1–0.4 mg/kg and midazolam. In terms of significant effects of time, across the five time points (0, 4, 24, 72, and 144 hours for each treatment session) there was no linear trend (reflecting the return to essentially Time 0 levels by Day 7; $F(1, 262) = 0.00$, $p = 0.963$), but the quadratic trend was significant (reflecting improvement followed by attenuation of improvement; $F(1, 303) = 22.0$, $p < 0.001$). There was an overall main effect of dose ($F(4,216) = 6.12$, $p < 0.001$). Post hoc tests showed that MADRS scores were significantly lower for 0.2 mg/kg ($p < 0.01$), 0.3 mg/kg ($p < 0.001$), and 0.4 mg/kg ($p < 0.001$) and nonsignificantly lower after treatment at 0.1 mg/kg ($p = 0.06$) compared with midazolam. The dose by time interaction was not significant ($F(4, 300) = 0.19$, $p = 0.943$). Plots of the residuals showed them to be highly normal.

Adverse Effects and Safety Outcomes

A dose–response relationship was observed between dissociative psychotomimetic effects and ketamine dosage (Figure 3). Adverse effects typically reported included mild perceptual disturbance (colors or sounds seemed different), derealization, altered body perception, and altered time perception. Peak effects occurred 10–15 minutes after injection, resolving without intervention by 40 minutes postinjection at all sessions. Brief

FIGURE 3. **Mean increases in the CADSS (maximum score: 108) across dose levels in the RCT phase. plac: placebo.**



Reactive Rating Scale and Young Mania Rating Scale items showed no evidence of treatment-emergent psychiatric symptoms at any time point. No clinically significant changes in Brief Reactive Rating Scale or CADSS scores were observed in the midazolam condition.

Transient increases in systolic and diastolic blood pressure were occasionally observed with peak incidence 4 hours after ketamine. The maximum changes in mean arterial pressure were recorded at 4 hours after treatment (baseline: 94.9 mm Hg [standard deviation: 12.7]; 4 hours: 96.2 mm Hg [standard deviation: 12.1]). Across all treatments, increases in heart rate only exceeded 120% of baseline in four instances and never exceeded 131.5%. Overall, across all ketamine doses, mean heart rate did not change from baseline 73.0 beats per minute (standard deviation: 9.6) to after treatment at 4 hours 72.3 beats per minute (standard deviation: 10.5).

A range of adverse effects were reported on the Systematic Assessment of Treatment Emergent Effects scale with ketamine and midazolam (Table 2). Hemodynamic and other effects resolved spontaneously, within 30 minutes and 1 hour, respectively, without the need for medical intervention. All participants were oriented at 4 hours post-treatment. Likewise, for simple and complex reaction times, performance was within 1 standard deviation of baseline means for each participant.

Liver function tests were within normal limits in all participants pretreatment and were obtained at RCT end for the 14 completers. All results were within normal limits except for slight elevations in aspartate aminotransferase of (from 30 U/L to 42 U/L) in one participant and alanine aminotransferase (from 36 U/L to 51 U/L) and gamma-glutamyl transferase (from 73 U/L to 99 U/L) in another at RCT end.

TABLE 2. Acute Side Effects After Treatment with Ketamine at Different Dose Levels and Midazolam in the RCT Phase Assessed Using the Modified SAFTEE Scale

	Side Effects									
Treatment	Palpitations	Flushing	Light-Headedness/ Dizziness	Fatigue/Sleepiness/Poor Concentration/Feeling Vague (Spaced Out)	Paresthesia	Nausea	Dry Mouth	Blurred Vision/Diplopia	Restlessness	Headache
Ketamine 0.1 mg/kg	0/16	1/16	1/16	3/16	0/16	0/16	2/16	1/16	2/16	2/16
Ketamine 0.2 mg/kg	1/15	0/15	4/15	3/15	1/15	0/15	1/15	2/15	1/15	0/15
Ketamine 0.3 mg/kg	0/14	0/14	5/14	2/14	1/14	0/14	0/14	3/14	0/14	1/14
Ketamine 0.4 mg/kg	0/12	1/12	5/12	3/12	3/12	1/12	0/12	4/12	1/12	1/12
Ketamine 0.5 mg/kg	0/9	0/9	4/9	6/9	1/9	1/9	0/9	4/9	0/9	0/9
Midazolam 0.01 mg/kg	0/14	0/14	2/14	5/14	0/14	1/14	1/14	1/14	0/14	2/14

Notes: Values are number of participants who experienced the side effect, at that treatment dose/total number of participants who received treatment at that dose. SAFTEE: Systematic Assessment of Treatment Emergent Effects.

Open-Label, Repeated-Treatments Phase and Further Follow-Up

Mood Outcomes

Twelve participants from the RCT phase received repeated treatments (given at the highest mg/kg dose received during the RCT phase) in the open-label phase (5 RCT remitters who relapsed and 7 RCT nonremitters). See Supplementary Figure S1 for MADRS scores. The five RCT remitters (who had

relapsed during follow-up) also remitted after repeated treatments and entered further follow-up. For these five participants time to relapse after repeated treatments was relatively longer (63, >183, 10, 10, and 14 days, respectively) than with a single treatment (RCT phase) (19, 12, 20, 12, and 19 days respectively). For the seven RCT nonremitters, two attained remission with repeated treatments (Figure 1).

Adverse Effects and Safety Outcomes

Ketamine was generally well tolerated, with no serious adverse events occurring. There were minimal increases in heart rate, blood pressure, and CADSS scores and no evidence of cumulative increases in these measures over the treatment course (see Supplementary Figures S2–S4). Five patients occasionally reported mild neurologic symptoms (dizziness: N = 5; numbness: N = 2; headache: N = 1) after treatment, with full resolution within 2 hours. One patient reported occasional urologic symptoms, such as the urge to urinate slightly more often. All participants were oriented 1 hour after treatment. No decline in neuropsychological test scores was observed (see Supplementary Table S1). Liver function tests were obtained before and after the treatment course in eight participants. All results were within normal limits, except for elevation in transaminases (aspartate aminotransferase: 42–60; alanine aminotransferase: 25–44) in one participant after 12 treatments at 0.5 mg/kg.

DISCUSSION

This study is the first RCT to test the efficacy and safety of ketamine in older depressed treatment-resistant patients aged over 60. Single doses of subcutaneously administered ketamine in older patients were effective, safe, and well tolerated. The participants included in this study were highly treatment resistant and had an average current episode duration of 8.9 years. Of note, participants included in the study reflected a "real-world" cohort, with most participants having a comorbid anxiety disorder or concurrent physical illness.

In contrast to an earlier report of poor efficacy in older depressed adults (all of whom had a history of failed response to electroconvulsive therapy),[6] 68.8% of completers in our RCT remitted at some time point and 50% had a remission lasting 7 days after treatment. A possible explanation for this difference may be the level of treatment resistance: Only two in our cohort had failed to respond to electroconvulsive therapy during the current episode. The reported rates of response to ketamine are lower in patients who have failed to respond to electroconvulsive therapy.[27] Supporting this interpretation, nonremitters in the RCT phase mainly differed from remitters in having failed more antidepressant courses. The efficacy results in this study are broadly comparable with results reported in the general adult population[13,28,29] but are lower than our prior results in a general adult age cohort treated using the same dose-titration study design (overall 80% remission).[11]

Most studies to date have used a set mg/kg dose for ketamine. Our study results suggest that the dose-titration method may be useful, particularly in older participants, in terms of maximizing efficacy outcomes while minimizing adverse effects. Two participants remitted at a dose of only 0.1 mg/kg, and a further four participants remitted at doses < 0.5 mg/kg. Starting at a dose of 0.5 mg/kg (as used in many other studies) may therefore have exposed some participants to unnecessarily high doses and increased risk of side effects. Compared with the results from a similar study conducted in a general adult population,[10,11] older participants appeared to require higher doses of ketamine to attain remission from depression.

Of the seven participants who did not remit after a single treatment (in the RCT phase) and who went on to receive multiple treatments in the open-label phase (given at the highest dose reached in the RCT), two attained remission, with one of these remaining in remission for at least 6 months. This suggests that some who do not remit after one treatment may yet attain a meaningful remission after repeated treatments given at the same dose level at this treatment frequency. These results are promising but preliminary, noting the small numbers involved and that repeated treatments were given on an open-label basis compared with the single treatment given under double-blind conditions.

Another aim of the open-label phase was to examine if repeated treatments would result in a longer duration of remission compared with a single treatment given at the same dose. For two of five participants, this strategy was effective, prolonging remission to 9 weeks and more than 6 months, respectively. Results,

however, were no different for the other three who remitted after both single and multiple treatments.

Ketamine was well tolerated, with no participants experiencing severe or problematic side effects. The most common side effects were transient dizziness, fatigue, and blurred vision, consistent with findings in the general adult population.[11] Dose titration in the RCT phase showed that dissociative symptoms were greater with higher ketamine doses, although none of these was severe or persistent. This study did not find tolerance developing to dissociative side effects with repeated treatments (open-label phase), unlike the study of Singh et al.[15] Repeated treatments did not lead to cumulative urologic, neurologic, or neuropsychological symptoms. However, 3 of 16 participants developed slightly elevated liver transaminases. Until this risk is better understood, liver function should be monitored when giving repeated ketamine treatments. Overall, this study found that the safety of ketamine in older patients was similar to that observed in a general adult age group. Overall, there is a need for further formal assessment of the safety of repeated treatments of ketamine.

Limitations include the small sample size, although because of the detailed assessment of dosing in a multiple crossover design, data were available from 80 treatment sessions (i.e., more than in prior crossover studies). The study lacked participants in the "old-old" cohort, as none of the participants was aged 80 and over; thus, findings may not be generalizable to older patients. Also, findings may not be generalizable to patients with other characteristics, such as those who are acutely suicidal or more treatment resistant. Finally, there was no formal assessment of blinding.

There were several strengths of the study. First, it was the first controlled study of ketamine in an older depressed cohort. Second, it provided detailed information on antidepressant response to ketamine at five different doses. Third, detailed structured assessments of efficacy and safety were used. Finally, we used an innovative approach to dose titration and a subcutaneous method of drug administration.

The current results support the further investigation of ketamine as a potentially effective and safe treatment for treatment-resistant older depressed patients. Outcomes provide preliminary evidence for subcutaneous injection as a practical and safe method for giving ketamine. Further investigations of ketamine as a treatment should test a dose-titration approach, which our results suggest may be useful for optimizing both efficacy and safety.

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Professor Brodaty has no direct conflicts of interest with this study but has received honoraria for participation on the advisory board for Nutricia for an Alzheimer nutraceutical. Over the last 3 years his department has conducted trials on patients with Alzheimer disease sponsored by Tau Therapeutics, Servier, and Sanofi. Professor Glue has a contract with Douglas Pharmaceuticals to develop novel ketamine formulations. Within the last 3 years Professor Glue has received research funding from DemeRx Inc. and had participated in an advisory board for Janssen Pharma. The statistical analyses were performed by Dr. Hadzi-Pavlovic at the University of New South Wales. The protocol can be obtained from colleen.loo@unsw.edu.au.

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APPENDIX: SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at doi:10.1016/j.jagp.2017.06.007.

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