Original Paper

Safety and efficacy of maintenance ketamine treatment in patients with treatment-refractory generalised anxiety and social anxiety disorders

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Paul Glue[1], Shona M Neehoff[1], Natalie J Medlicott[2], Andrew Gray[3], Guy Kibby[4] and Neil McNaughton[5]

Abstract

Objective: In this maintenance treatment study, we sought to evaluate the effect on anxiety ratings, safety and tolerability of 3 months of weekly ketamine in 20 patients with treatment-refractory DSM IV generalised anxiety disorder (GAD) and/or social anxiety disorder (SAD), and subsequent assessment of remission post-treatment.

Methods: This was an uncontrolled open-label study in 20 patients who had been responders in an ascending dose ketamine study. The study was undertaken in a university clinic. Patients received one or two weekly ketamine doses of 1 mg/kg injected subcutaneously for 3 months. Data were collected from December 2015–June 2017.

Results: There were 10 women (50%) and 10 men (50%); 15 patients (75%) met criteria for GAD and 18 (90%) for SAD. One hour after dosing, Fear Questionnaire ratings decreased by ~50%, as did Hamilton Anxiety ratings. Clinician Administered Dissociative States Scale mean scores declined over time, from 20 points at week 1 to 8.8 points at week 14. Compared with pre-dose values, mean systolic and diastolic blood pressure increased by ~10 mm Hg at 30 min. The most common adverse events were nausea, dizziness and blurred vision. Of the 20 patients, 18 reported improved social functioning and/or work functioning during maintenance treatment.

Conclusions: Weekly ketamine dosing was safe and well tolerated, and post-dose dissociative symptoms tended to reduce after repeated dosing. Patients reported marked improvements in functionality and in their personal lives. Maintenance ketamine may be a therapeutic alternative for patients with treatment refractory GAD/SAD.

Trial Registration: http://www.anzctr.org.au/ACTRN12615000617561

Keywords

Ketamine, generalised anxiety disorder, social anxiety disorder, maintenance treatment

Introduction

The initial report that low-dose ketamine had rapidly acting antidepressant effects in treatment-resistant depression (TRD) (Berman et al., 2000) has now been replicated in numerous randomised clinical trials and case series (Katalinic et al., 2013; Xu et al., 2016). Subsequent studies have reported similar rapid improvement in symptom severity in obsessive compulsive disorder (OCD) (Rodriguez et al., 2013) and post-traumatic stress disorder (PTSD) (Feder et al., 2014) and, most recently, in treatment-refractory anxiety (TRA) (Glue et al., 2017). Most patients report recurrence of depressive or anxiety symptoms within a week after dosing. A major, and as yet unresolved, question is how to maintain symptomatic improvement. A course of four to six ketamine treatments over 2 weeks did not prevent early relapse in most patients with TRD (Aan Het Rot et al., 2010; Shiroma et al., 2014; Szymkowicz, 2014). We have previously reported that a patient with TRD remitted after 10 months of weekly ketamine treatment (Zanicotti et al., 2012), and hypothesised that maintenance treatment for longer than 2 weeks might increase likelihood of remission. The objective of this maintenance treatment study was to evaluate the effect of 3 months of weekly ketamine dosing on anxiety ratings, safety and tolerability in 20 patients with treatment refractory generalised anxiety disorder (GAD) or social anxiety disorder (SAD), and subsequent assessment of remission post-treatment.

Materials and methods

The protocol and consent forms for this study were approved by the Southern Health and Disability Ethics Committee (15/

[1]Department of Psychological Medicine, University of Otago, Dunedin, New Zealand
[2]School of Pharmacy, University of Otago, Dunedin, New Zealand
[3]Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand
[4]Southern District Health Board, Dunedin, Otago, New Zealand
[5]Department of Psychology, University of Otago, Dunedin, New Zealand

Corresponding author:
Paul Glue, School of Medical Sciences, University of Otago, PO Box 913, Dunedin, New Zealand.
Email: paul.glue@otago.ac.nz

STH/86). The study was registered with the Australian New Zealand Clinical Trials Registry: http://www.anzctr.org.au/ACTRN12615000617561. This was an uncontrolled, open-label study in 20 patients with treatment refractory DSM-IV GAD and/or SAD, who had been responders to an earlier ascending dose ketamine study (Glue et al., 2017). Inclusion and exclusion criteria were as previously described (Glue et al., 2017). Patients were permitted to remain on current medication regimens and to continue with ongoing psychotherapy. However, no new treatments were to be started or doses/visit schedules changed.

Ketamine was administered as a subcutaneous injection in the upper arm, using each individual patient's highest tolerated dose. Dosing frequency was based on duration of response to ketamine: those who remained free of anxiety for 5 days or longer were dosed once weekly, whereas those with shorter duration of response could be dosed twice weekly. Patients were monitored in the clinic for 2 h post-dose, with vital signs obtained pre-dose, and 30, 60, and 120 min post-dosing. Anxiety assessments included the Fear Questionnaire (FQ) (Marks and Matthews, 1979) and the Hamilton Anxiety Scale-A (HAMA) (Hamilton, 1959) pre-dose and at 1 and 2 h post-dose. Dissociation was assessed using the Clinician Administered Dissociative States Scale (CADSS) scale (Bremner et al., 1998) pre-dose, and 30 and 60 min post-dose. Tolerability assessments included reported adverse events throughout the study. Functionality assessment included the Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002).

Summary statistics were calculated and reported for demographic, vital signs and rating scale data. Categorical variables were reported using counts and percentages. To evaluate changes in pre-dose mood ratings (as pre-dose HAMA and FQ scores decreased over time), an exponential decay was fitted using non-linear regression (GraphPad Prism version 7.0). The first derivative of this was used to determine when the curves reached a plateau ($dy/dx < -0.5$). For the first derivative calculations, the Savitzky Golay algorithm was used with second-order smoothing (four points either side).

Results

The patient flow diagram is shown in Figure 1. Of the 25 patients who entered the ascending dose phases of this research, 21 patients were treatment responders and were eligible to receive maintenance treatment. One patient declined maintenance treatment, and, subsequently, two dropped out (at weeks 4 and 9, respectively). The remaining 18 patients received 14 weeks of maintenance treatment. Clinical, demographic and treatment details of the 20 patients who entered maintenance treatment are listed in Supplementary Table 1. There were 10 females (50%) and 10 males (50%). Mean age was 32 years (range 18–65), and mean duration of their anxiety disorders was 13.9 years (range 5–37). Fifteen patients (75%) met criteria for GAD, and 18 (90%) for SAD. There was significant comorbidity, with four subjects (20%) also having panic disorder. Eighteen patients were currently taking antidepressants (see Supplementary Table 1). Mean HAMA at entry to maintenance treatment was 12.6 (it had been 25 prior to entering the initial ascending dose phase of the study). All patients elected to remain on doses of 1 mg/kg, as they felt this dose gave the greatest magnitude and most durable improvement in anxiety symptoms. Four patients requested twice weekly dosing due to early recurrence of anxiety (usually within 4 days of dosing), and 16 received once weekly.

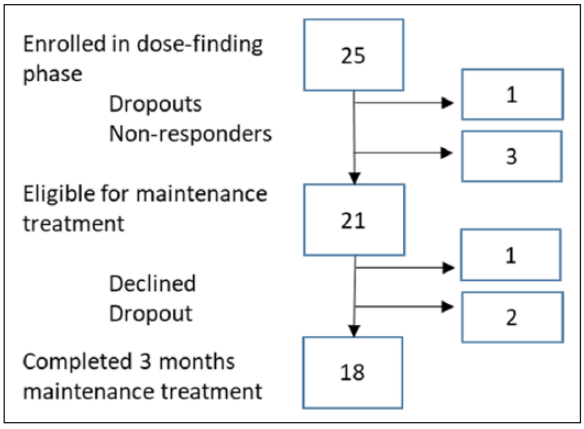

Figure 1. Patient flow diagram.

Changes in anxiety rating scales

FQ. The mean FQ rating-time profile is shown in Figure 2(a). There was a progressive decline in pre-dose FQ ratings, reaching asymptote by 7.5 weeks. At 1 h post-dosing, all ratings decreased by ~50%, with no further decrease noted at 2 h post-dose.

HAMA. The mean HAMA rating-time profile is shown in Figure 2(b). Pre-dose HAMA ratings reached asymptote by 3.5 weeks. At 1 h post-dosing, all ratings decreased by ~50%, with no further decrease noted at 2 h post-dose.

Safety and tolerability

CADSS. CADSS scores at 30 min post-dose during maintenance treatment were available for only 10 patients. Mean and individual patient 30-min CADSS scores are shown in Figure 3. Mean CADSS scores showed a decline over time, from 20 points at week 1 to 8.8 at week 14. However, there was significant population heterogeneity. The scores of six patients decreased over time. Three patients reported consistently high CADSS scores throughout maintenance treatment, and the CADSS score of one patient increased gradually towards the end of maintenance treatment.

Blood pressure and heart rate

Changes from pre-dose to 30 min post-dose in systolic and diastolic blood pressure and heart rate are shown in Figure 4. Compared with pre-dose values, mean systolic and diastolic blood pressure increased by ~10 mm Hg at 30 min, with no evidence of change over 14 weeks. Mean heart rate fell consistently by around 5 beats/min.

Adverse events

The most common non-dissociative adverse events were nausea, dizziness and blurred vision. Nausea was reported by 25% of

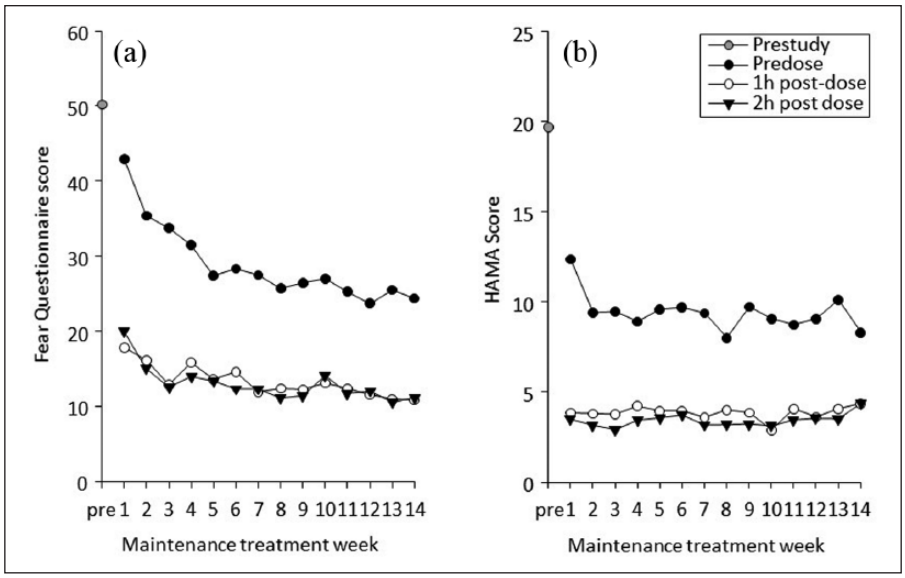

Figure 2. Effects of maintenance ketamine treatment on mean FQ ratings over 14 weeks, pre-dose and 1 and 2 h post-dose (a), and mean HAMA ratings (b). FQ and HAMA scores prior to receiving any ketamine are also shown (grey symbols).
FQ: Fear Questionnaire; HAMA: Hamilton Anxiety Scale.

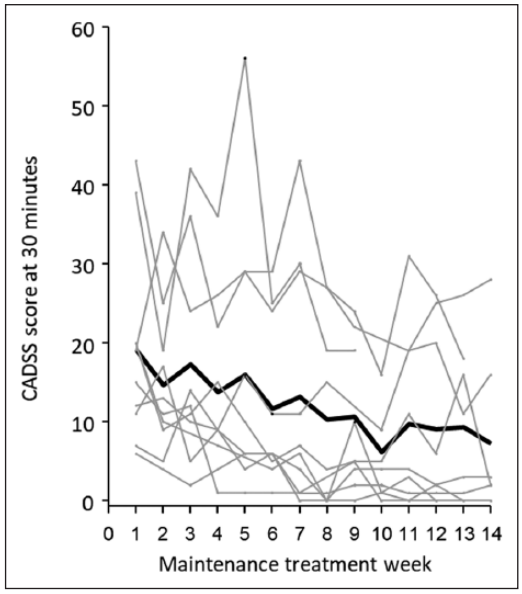

Figure 3. Effects of maintenance ketamine treatment on mean (black line) and individual (grey line) CADSS scores at 30 min post-dose.
CADSS: Clinician Administered Dissociative States Scale.

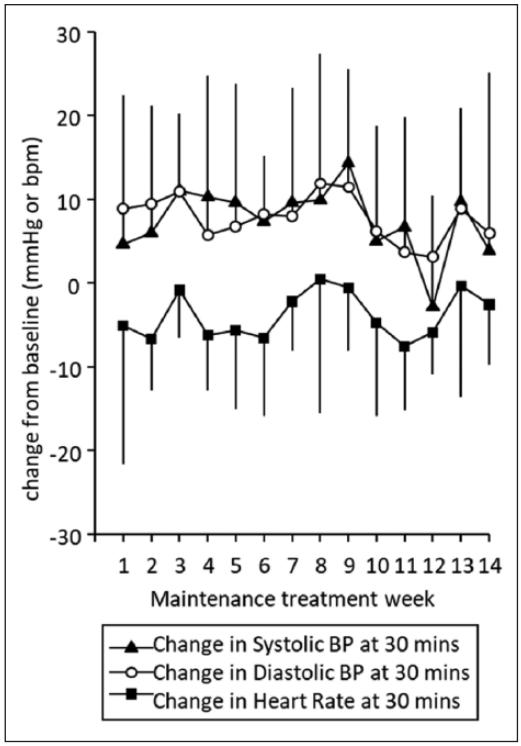

Figure 4. Effects of maintenance ketamine treatment on mean (SD) change in systolic and diastolic blood pressure and heart rate at 30 min post-dose.
SD: Standard deviation.

patients at week 1 of maintenance, declining to 0% by week 14. Dizziness was reported by 40% of patients at week 1, down to 28% at week 14. Blurred vision was reported by 10% of patients at week 1, and by 22% at week 14. Two significant adverse events included a pulmonary embolus in a female patient who had just started on an oral contraceptive. A male patient was noted to have markedly elevated blood pressure (141/78 to 207/103) and delirium within 5 min of dosing, which resolved within 15 min and returned to baseline by 60 min. The speed of onset of these symptoms presumably reflected inadvertent intravenous injection. No patients reported symptoms of cystitis or memory problems at any time during maintenance treatment.

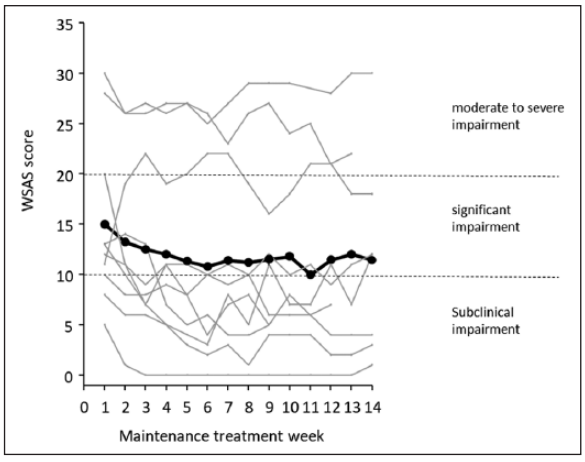

Figure 5. Effects of maintenance ketamine treatment on mean (black line) and individual (grey lines) WSAS scores prior to ketamine dosing. WSAS: Work and Social Adjustment Scale.

Social and work functioning

Pre-dose WSAS scores during maintenance treatment were available for only 10 patients. Mean and individual patient pre-dose WSAS scores are shown in Figure 5. Mean WSAS scores showed a decline over time, from 15 points at week 1 to 11.4 at the end of maintenance treatment. However, there was significant population heterogeneity. The scores of seven patients decreased over time, while the scores of three patients remained consistently above 20 (representing moderate to severe impairment) throughout maintenance treatment. Of the 20 patients, 18 reported improved social functioning (16/20) and/or work functioning (11/20) during maintenance treatment. Five patients who were previously unemployed returned to paid employment, and three patients enrolled in tertiary education. Socially, patients reported reduced or minimal social avoidance (i.e. were able to attend parties, go on dates, speak up at meetings/presentations).

Post-maintenance

Once maintenance treatment finished, five patients (25%) remained well over at least 3 months of follow up. Eight patients reported partial re-emergence of anxiety symptoms, and five patients reported full re-emergence, within 2 weeks of their last ketamine dose. One patient elected to continue weekly ketamine treatment from his family doctor, and one patient dropped out early.

Discussion

The main findings of this study are that most patients with TRA disorders who respond to ketamine can remain in remission with maintenance treatment over 3 months. Ketamine treatment was safe and well tolerated, and most patients reported marked improvement in work and social functioning. Most patients reported partial or complete recurrence of symptoms within 2 weeks of stopping maintenance treatment.

Almost all published maintenance ketamine data have been in patients with chronic pain (Blonk et al., 2010; Sigtermans et al., 2009); however, there are several case reports/series of repeated dosing in patients with TRD (Aan Het Rot et al., 2010; Shiroma et al., 2014; Szymkowicz, 2014). This study is the first describing maintenance ketamine treatment in TRA. Of note, anxiety ratings, as measured by the HAMA, showed maximal improvement within 3.5 weeks, whereas FQ ratings took longer (7.5 weeks) to achieve maximal improvement (Figure 2(a) and (b)). It is possible that the anxiolytic effect of ketamine is rapid, whereas changes in phobic severity are slower, presumably reflecting additional cognitive or exposure elements to achieve improvement.

Of the 20 patients, 5 (25%) remained well for at least 3 months after completing maintenance treatment; most (13/20) reported symptom recurrence relatively quickly, within 2 weeks of stopping treatment. In contrast, we found that most patients with TRD do not relapse after 3 months of maintenance treatment (unpublished data). This could reflect different temporal patterns of these disorders (i.e. depression tends to be episodic and anxiety chronic). Because of the limited published data on maintenance ketamine treatment for TRA or TRD, further studies are needed to identify optimal duration of treatment, and durability of response.

Maintenance treatment was safe and well tolerated. Dissociative symptom intensity tended to diminish over time in most patients. Other main side effects noted were nausea, dizziness and blurred vision, which have been noted previously (Katalinic et al., 2013; Xu et al., 2016). There were no reports of cystitis or memory problems. The magnitude of blood pressure and heart rate changes at 30 min post-dose did not change over time. Overall, we believe the benefits of treatment (reduced anxiety and improved functionality) outweigh any safety issues in this 3 month study. Close attention to patient safety will be important if maintenance treatment is given for longer durations.

Perhaps the most striking benefit of maintenance treatment was the improvement in work and social functioning. Most patients reported being markedly impaired by anxiety since adolescence. Their experience of ketamine treatment enabled them to make substantial changes to their lives (e.g. employment, study, making friends, engaging socially and travelling). Reduced anxiety meant everyday tasks were less onerous. Most patients reported an increase in their ability to concentrate, leading to improvement in their functionality. Those patients who were in employment reported they were more effective at work. For many, ketamine treatment reduced their social anxiety to a level where they were able to conceptualise that they could effect changes in their lives, and this experience was empowering for them. Patients gained greater perspective on life after having ketamine treatment, and many reported that even after treatment stopped they had a better understanding of their experience of anxiety. They came to recognise that it was ‘just anxiety’ and that anxiety did not define who they were as people. This treatment response meant that, for some of the patients, relapse was only partial and they were able to take what they had learned about themselves during ketamine treatment and continue to apply it in their everyday lives.

A number of limitations with the current study should be acknowledged. This was a small (n = 20) open-label study with 20 patients with TRA. Dosing (1 mg/kg) and dose frequency (once or twice weekly) were based on individual patient’s responses to ketamine in an ascending dose phase prior to maintenance treatment, and treatment duration (3 months) was chosen pragmatically. It will be important to explore alternative dosing regimens and treatment durations in future studies; however, at this time there are limited published maintenance treatment data in either TRA or TRD. It is possible that some aspects of improved

mood and functionality were due to non-specific factors, for example the 2 h spent weekly talking with a psychiatrist or registered nurse after dosing.

Treatment-responsive generalised anxiety, social anxiety, unipolar depression, atypical depression, panic and OCD have overlapping response profiles to a range of classes of anxiolytic and/or antidepressant medications, but with a pattern across treatments that suggests each can involve a distinct neural system (McNaughton and Corr, 2016). How is it that ketamine can be effective in all these disorders, particularly in cases when they (and the amalgam that is PTSD) are treatment resistant? A clue comes from the fact that all these disorders share a common risk factor in high levels of the personality trait of neuroticism, to the extent that it is reasonable to class them as neurotic disorders (Andrews et al., 1990; Kendler et al., 1992a, 1992b). Neuroticism can interact with life events (McFarlane, 1989) or prior disposition (Dantendorfer et al., 1995; Holt, 1990) to generate disorder. Thus, disease- or symptom-specific substrates (affected by specific conventional treatments) appear to interact with a common neuroticism-related sensitivity through which ketamine could affect treatment resistance in all cases.

In conclusion, maintenance treatment is an approach that may allow sustained mood improvement from ketamine. There are too few data to yet identify optimal duration of maintenance treatment; however, we have demonstrated that 3 months treatment was safe and well tolerated, and that 25% of patients remained free of anxiety post-treatment. It is possible that this effect could be augmented with use of other treatments, such as concurrent cognitive behaviour therapy (Wilkinson et al., 2017) or medication (e.g. D-cycloserine) (Heresco-Levy et al., 2006, 2013).

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Drs Glue and Medlicott have a contract with Douglas Pharmaceuticals to develop novel ketamine formulations. Within the last 3 years Dr Glue has participated in an advisory board for Janssen Pharma. Within the last 3 years Dr McNaughton has a confidential disclosure and consulting agreement with Janssen Research & Development, LLC. No other authors have disclosures.

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