



Safety and efficacy of extended release ketamine tablets in patients with treatment-resistant depression and anxiety: open label pilot study

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Abstract

Background: Ketamine's defining side effects are dissociation and increased blood pressure/heart rate. An oral formulation with delayed absorption could minimize these effects. We recently reported safety and tolerability data for an extended release ketamine tablet in healthy volunteers.

Methods: To assess safety, tolerability, efficacy, and pharmacokinetics of an extended release oral ketamine tablet in patients with treatment-resistant depression/anxiety. This was a multiple dose open-label flexible dose uncontrolled study in seven patients with treatment-resistant depression/anxiety, who had all previously demonstrated mood improvement to subcutaneous ketamine. Assessments included ratings of anxiety, depression and dissociation, safety and tolerability, and blood samples for ketamine pharmacokinetics and brain-derived neurotrophic factor (BDNF) concentrations.

Results: Improvements in anxiety and depression ratings occurred gradually over 96 h; all patients had >50% improvements in mood ratings. Ketamine was safe and well tolerated, with no changes in vital signs, and a single brief report of dissociation. Ketamine may induce its own metabolism, as the ratio of norketamine to ketamine increased out to 96 h. Serum BDNF concentrations did not change during the study.

Conclusion: Ketamine's safety/tolerability may be improved with an extended release oral formulation. Onset of mood improvement is slightly delayed compared with parenteral dosing. These data support the further development of extended release ketamine tablets for treatment of resistant depression and anxiety disorders.

Keywords: anxiety, depression, dissociation, extended-release ketamine tablet, first-in-patient, pharmacodynamics, pharmacokinetics, safety

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Introduction

Ketamine, an *N*-methyl-*D*-aspartate (NMDA) antagonist, has fast-onset activity in patients with treatment-resistant depression and anxiety disorders.^{1,2} Although most published data have been in studies where ketamine is administered as an intravenous infusion, activity has also been reported after alternative routes of administration, including oral, sublingual, intranasal, intramuscular, and

subcutaneous routes.³ Evaluation of comparative efficacy is limited by differences in dosing and lack of head-to-head comparative data. A pilot study comparing changes in depressed mood after intravenous (IV), intramuscular (IM), and subcutaneous (SC) dosing reported comparable antidepressant effects, independent of route of administration.⁴ The most common side effects reported after parenteral administration include

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dissociation and increases in systolic and diastolic blood pressure, which are associated with peak plasma concentrations of ketamine.^{4,5} One strategy to improve tolerability might be to administer ketamine orally using an extended release formulation, to delay absorption and thus minimize side effects associated with peak ketamine concentrations. This strategy should not interfere with ketamine's antidepressant/anxiolytic effects, because norketamine and its hydroxy-metabolites appear to have important roles in ketamine's antidepressant actions.⁶⁻⁸ We recently reported data from an ascending dose study of a ketamine tablet designed to release drug over 10 h, and found it did not alter blood pressure or heart rate, and had very minor dissociative effects at 240 mg doses.⁹ This paper reports on the efficacy and safety of this formulation in patients with treatment-resistant depression and/or anxiety, who had previously responded to parenteral ketamine.

Materials and methods

The objectives of this pilot study were to evaluate the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of an extended release ketamine tablet formulation in patients with treatment-resistant depression and/or anxiety. The protocol for this study was approved by the Southern Health and Disability Ethics Committee (16/STH/121) and SCOTT (16/SCOTT/67), and the study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12616001351404).

This was a multiple dose, open-label, uncontrolled study in up to 12 patients with treatment-resistant DSM-5 major depressive episode (MDE) and/or social anxiety disorder (SAD) and/or generalized anxiety disorder (GAD), performed at the Zenith Technology Clinical Trials Unit. Patient inclusion criteria included having a Hamilton anxiety scale (HAMA¹⁰) score of >20, and/or a Liebowitz social anxiety scale (LSAS¹¹) score of >60, and/or a Montgomery-Asberg depression rating scale (MADRS¹²) score of >20 at screening. All patients had to have previously received subcutaneous ketamine in clinical trials or in clinical settings,^{5,13} with positive mood responses. All patients provided signed informed consent prior to enrolment, and were assessed as suitable to participate based on review of medical history, physical examination, safety laboratory tests, vital signs, and electrocardiography (ECG). Patients could remain on established treatments,

but could not change these for 4 weeks prior to dosing.

Details of the 60 mg tablet formulation are provided elsewhere.¹⁴ On Day 1, after an overnight fast, patients received a 60 mg dose at 8 a.m., and 60–120 mg at 8 p.m. On Days 2–4, patients could receive 60–240 mg doses 12-hourly, with the final dose being given at 72 h. The actual dose administered to each participant was based on whether or not their symptoms had improved, along with assessments of safety and tolerability. The selected dose range was based on safety and tolerability data from an earlier healthy volunteer study.⁹

Safety assessments included vital signs, ECGs, safety laboratory tests pre-dose through to 96 h post-dose. Tolerability assessments included reported adverse events throughout the study. Suicidality was assessed using the Columbia Suicide Rating Scale (CSSRS) and dissociation monitored using the Clinician Administered Dissociative States Scale (CADSS) pre-dose and throughout the study.^{15,16} Anxiety symptoms were evaluated using the HAMA and Fear Questionnaire (FQ) scales and depression using the MADRS.¹⁷

Blood samples to determine plasma ketamine and norketamine concentrations were taken pre-dose and then at 2, 12, 14, 24, 26, 36, 38, 48, 50, 60, 62, 72, 74, and 96 h post-dose (i.e. pre-dose and 2 h post-dose). Blood samples for serum brain-derived neurotrophic factor (BDNF) concentrations were taken pre-dose and then at 2, 12, 14, 24, 72, 74, 84, 86, and 96 h post-dose. Samples were centrifuged and serum stored at –80°C until analyzed. Details of the ketamine, norketamine, and BDNF assays are reported elsewhere.⁹

Summary statistics (means, standard deviations, and coefficients of variation) were determined for safety laboratory test data, ECG, and ketamine, norketamine, and BDNF concentration data. Categorical variables were analyzed using counts and percentages. The relationship between norketamine:ketamine ratios and time was evaluated by regression analysis.

Results

Nine patients were screened, and a single cohort of seven patients enrolled in and completed this study. All patients had failed to respond

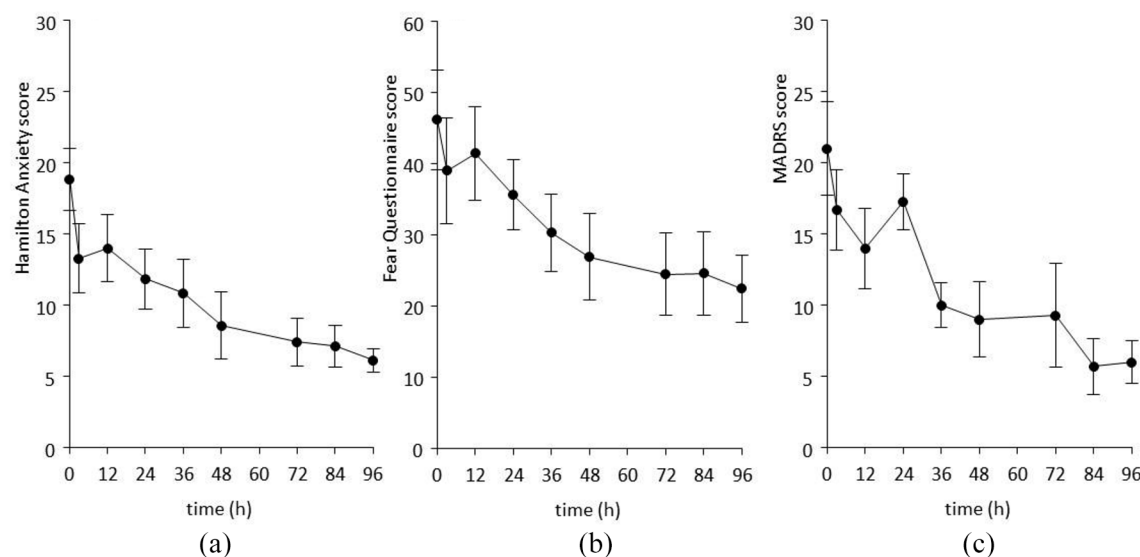


Figure 1. Effect of extended release ketamine tablets on mean (SEM) HAMA (A), FQ (B), and MADRS (C) scores.

HAMA, Hamilton anxiety scale; FQ, fear questionnaire; MADRS, Montgomery-Asberg depression rating scale; SEM, standard error of the mean.

to multiple prior medication and psychotherapy trials, and had extensive comorbidity (see Supplementary table for details). There were three females and four males. Mean age was 27.0 years (range 22–33). All seven met criteria for SAD, and 6/7 had current MDE of moderate or greater severity (MADRS scores >20). Mean HAMA at screening was 22.9 (indicative of severe anxiety). All patients were currently taking antidepressants and had not responded to prior trials of antidepressants and group or individual psychotherapy, including cognitive behavioral therapy (CBT). All patients titrated up to 240 mg by 60 h. Mean doses were 60 mg at 0 h; 120 mg at 12 h; 180 mg at 24 h; 223 mg at 36 h; 231 mg at 48 h; 240 mg at 60 h and 240 mg at 72 h.

Changes in anxiety rating scales

Mean HAMA rating-time profiles are shown in Figure 1A. There was an initial rapid decrease in scores at 12 h, with a more gradual reduction out to 96 h (final mean score = 6.1). All seven patients had 50% or greater reductions in HAMA compared with baseline. Mean FQ rating-time profiles are shown in Figure 1B. There was gradual reduction in scores out to 96 h (final mean score = 22.4). Six of seven patients had 50% or greater reductions in FQ compared with baseline. Mean MADRS rating-time profiles are shown in Figure 1C. There was a gradual reduction in

scores out to 96 h (final mean score = 5.7). All seven patients had 50% or greater reductions in MADRS compared with baseline.

Safety and tolerability

A total of five adverse events, rated as mild in intensity, were reported: dizziness ($n=1$), dissociation ($n=1$), and headache ($n=3$). Dissociation, with onset 30 min after dosing and which lasted 2 h, was reported by one patient whose dose increased from 120 mg to 180 mg. No dissociation was reported at 240 mg. There were no changes in CADSS scores. There were no changes in safety laboratory tests or vital signs during the study. There were no ECG changes of note: no patients had QTcF values >500 ms or increases from baseline >60 ms. CSSRS assessments showed no evidence of increased suicidal ideation at any time during the study by any patient.

Pharmacokinetic data

Mean ketamine and norketamine concentration-time profiles are shown in Figure 2A. Norketamine concentrations were substantially higher than ketamine at all timepoints. The increasing concentrations of both analytes over time reflects increasing doses (all patients were receiving 240 mg 12 hourly by 60 h). Norketamine:ketamine ratios increased over time, from 10.8 at 2 h to

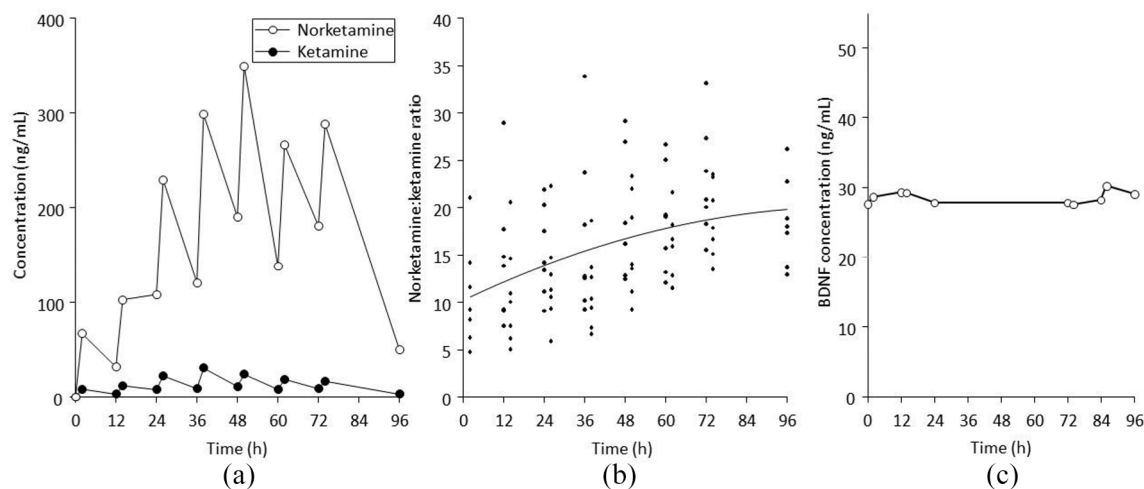


Figure 2. (A) Mean concentration-time profiles for ketamine and norketamine after 12 hourly dosing of extended release ketamine tablets out to 72 h. (B) Individual norketamine:ketamine ratios over time, with a fitted regression line. (C) Mean serum BDNF concentration-time profiles after 12 hourly dosing of extended release ketamine tablets out to 72 h. BDNF, brain-derived neurotrophic factor.

Table 1. Mean and post-dose FQ, HAMA and CADSS scores after oral and SC dosing in six patients with both sets of data (subcutaneous data are from references).^{5,13} The time at which CADSS data were obtained postdose corresponds to time of peak ketamine concentration.^{5,9}

Formulation	SC/injectable		Oral/ext-release tablet	
Time	pre	24 h	pre	48 h
HAMA	21.7	6.8	18.3	7.7
FQ	47.8	28	43.7	22.7
Time	pre	0.5 h	pre	3 h
CADSS	2.4	22.3	5.6	3.3

CADSS, clinician administered dissociative states scale; HAMA, Hamilton anxiety scale; FQ, fear questionnaire; SC, subcutaneous.

18.6 at 96 h (Figure 2B). Data variability also decreased over time, from 51.7% at 2 h to 25.2% at 96 h. Serum BDNF concentrations remained unchanged over 96 h (Figure 2C).

Discussion

The main findings of this pilot study are that ketamine had broad anxiolytic and antidepressant effects in patients with severe treatment-resistant SAD/GAD/MDE. Ketamine was safe and well tolerated in this population, with only one report of

dissociation, and no evidence of sympathomimetic changes in blood pressure or heart rate. Most drug present after oral dosing was norketamine. Changes in norketamine:ketamine ratios over 96 h may indicate autoinduction. Serum BDNF concentrations were not changed by ketamine.

We observed anxiolytic and antidepressant effects in all patients; however, the speed of onset with the extended release tablet formulation appeared to be modestly slower than after subcutaneous dosing. Six of the seven patients had participated in subcutaneous dosing in earlier studies for resistant anxiety.^{5,13} The reductions in HAMA and FQ scores at 48 h after oral dosing in this study were comparable to changes 24 h after subcutaneous dosing (Table 1).

Oral ketamine was well tolerated by all participants. There were no changes in blood pressure or heart rate at any dose. There was one report of dissociation of mild intensity at a dose of 180 mg, but not at higher doses. In contrast, in our earlier ascending dose study in healthy volunteers, there were 11 reports of dissociation at 240 mg but not at lower doses.⁹ It is possible that the lower rates of dissociation in this study are due to tolerance development, and that dissociation might be minimized in future studies by dose titration. CADSS data were available for six of the seven patients who had prior subcutaneous dosing in earlier studies for treatment-resistant anxiety.^{5,13} At the time when ketamine concentrations were maximal,

CADSS scores increased by 20 points after subcutaneous dosing, whereas scores fell by three points after oral dosing (Table 1). We previously reported that dissociation scores correlated with peak ketamine concentrations after subcutaneous dosing,^{4,13} and the decline in dissociation ratings after oral dosing may reflect relatively lower peak concentrations, which occur some hours after dosing.⁹

Although the modestly slower (~24h) onset of anxiolytic/antidepressant activity after oral dosing compared with subcutaneous dosing could be one reason to favour parenteral over oral dosing, the improved tolerability (no changes in blood pressure or heart rate, and minimal dissociation) are important advantages for oral dosing. Presumably, these changes would shorten the time patients would need to be observed after initial dosing, could allow patients to dose themselves at home, and might improve compliance.

Formal pharmacokinetic analysis was not possible in this study due to the limited number of pharmacokinetic samples collected (pre-dose and 2h post-dose), and a study design that permitted flexible dosing. As we reported previously, after five doses of oral ketamine given 12-hourly, AUC₀₋₁₂ values were smaller than the corresponding single dose mean area under the curve (AUC_{0-∞}) values for higher (120 and 240mg) dose groups.⁹ Lin *et al.* reported that daily oral dosing of ketamine to rats for 2 weeks increased activity of CYP1A2, -3A, and -2B6, based on metabolism of probe substrates.¹⁸ CYP3A and -2B6 are involved in the metabolism of ketamine to norketamine, and CYP2B6 in the metabolism of norketamine to hydroxy-metabolites. Our finding of increasing norketamine:ketamine ratios over 96h would be consistent with autoinduction. From a drug interaction perspective, if ketamine dosing in depression occurs twice weekly, induction may be minimal. This should be evaluated in future studies.

Changes in central BDNF levels have been identified as one component of ketamine's antidepressant mechanism of action.⁷ Haile *et al.* reported a negative association between plasma BDNF concentrations and decrease in depression rating scores 4h after ketamine dosing in depressed patients.¹⁹ We did not identify any changes in this study, and we have previously reported negative findings for BDNF changes after subcutaneous dosing of ketamine in patients with resistant anxiety and in healthy

volunteers after oral ketamine.^{5,9} Additionally, we have reported on acute changes in plasma and serum BDNF in rodents given ketamine that are unrelated to brain BDNF concentrations.²⁰ In summary, peripheral BDNF does not appear to be a useful biomarker for brain BDNF changes.

The limitations of this study should be acknowledged. This was a brief (96h) phase Ib study in a small number of anxious/depressed patients, who had extensive comorbidities, and who had previously shown positive mood responses to ketamine. Based on the small number of subjects, and their selection based on prior positive mood responses to ketamine, it is not possible to compare efficacy data with unselected populations. Definitive safety and tolerability information and establishing appropriate dose ranges for patients with resistant depression and anxiety disorders will require further testing in larger clinical populations. The extended release oral formulation used in this study has slow dissolution across the physiological pH range and in ethanolic solution.¹⁴ Taken together with the fact that the tablet is very hard, and potentially difficult to crush, this could limit abuse potential. Additional studies are needed to further examine the impact of formulation on abuse liability.

In conclusion, multiple doses of extended release ketamine tablets up to 240mg 12-hourly were safe and well tolerated in patients with treatment-resistant depression and anxiety. There was only one report of dissociation, and no evidence of sympathomimetic changes in blood pressure or heart rate. Oral ketamine had broad anxiolytic and antidepressant effects, with onset delayed (~24h) compared with parenteral ketamine dosing. The results of this study support the further development of extended release ketamine tablets for treatment resistant depression and anxiety disorders.

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Conflict of interest statement

Paul Glue and Natalie Medlicott have a contract with Douglas Pharmaceuticals Ltd to develop novel

ketamine formulations. Within the last 3 years, Paul Glue has attended an advisory board for Janssen Pharmaceuticals. Peter Surman is an employee of Douglas Pharmaceuticals Ltd. No other authors have disclosures.

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Supplemental material

Supplemental material for this article is available online.

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