Psychopharmacology (2018) 235:393–398
https://doi.org/10.1007/s00213-017-4786-3

ORIGINAL INVESTIGATION

# Impact of oral ketamine augmentation on hospital admissions in treatment-resistant depression and PTSD: a retrospective study

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Received: 10 May 2017 / Accepted: 7 November 2017 / Published online: 18 November 2017


**Abstract**
*Rationale* Depressive episodes are the leading cause of mental health-related hospital admissions in Australia, and 44% of those admitted have a previous history of hospitalisations for depression (Admitted patient mental health-related care: (Australian Institute of Health and Welfare Aust Hospital Stat 2011–12, 2013). Despite numerous available antidepressant treatments, many patients do not respond to conventional therapy, having what is called 'treatment resistance' (Fava Biol Psychiatry 53:649–659, 2003). In recent years, ketamine has risen to prominence as an effective, rapidly acting antidepressant (Ketamine: a light in the darkness: Paleos and Ross 28–33, 2013). However, customary intravenous (IV) and intramuscular (IM) routes of administration and relapse rates after cessation remain barriers to more widely adopted usage.
*Objectives* This study represents the largest retrospective review of patients receiving long-term oral ketamine for treatment-resistant depression and post-traumatic stress disorder (PTSD). Our purpose was to examine the safety and efficacy of oral ketamine therapy in an outpatient setting as measured by changes in hospitalisation for psychiatric episodes.
*Methods* Hospital records of 37 patients who received oral ketamine treatment were reviewed to compare the number and duration of psychiatric hospital admissions before and after treatment. Records were also screened for adverse medical events and changes in ketamine dosage over time.
*Results* Following treatment, inpatient hospital days were reduced by 70%, and hospital admissions were reduced by 65%. The dose of ketamine patients required was stable over time with no evidence of tolerance building. There were no serious adverse events and no long-term negative effects associated with ketamine.
*Conclusions* Oral ketamine offers a promising pharmacologic adjunct to depression treatment. It may offer a more approachable alternative to IV or IM ketamine. The results warrant further investigation into the safety and efficacy of oral ketamine for psychiatric treatment.

**Keywords** Treatment resistant depression · PTSD · Oral ketamine

Ketamine was first developed in 1962 as a rapidly acting general anaesthetic (Jansen 2000). Unlike other anaesthetic agents, it does not cause significant respiratory depression and has a comparatively large therapeutic window (Kurdi et al., 2014. It is, therefore, useful in settings where respiratory assistance is impractical or where specialists prefer a single-drug choice for anaesthesia. It continues to be safely used for this purpose around the world and is listed as an essential medicine for basic healthcare by the World Health Organization (World Health Organization 2015). Its accepted primary mechanism of action is as an NMDA receptor antagonist (Kurdi et al., 2014), blocking the effects of excitatory glutamate signalling in the CNS.

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## Ketamine in psychiatric therapy

Spurred by decades of anecdotal reports and off-label use of its beneficial effects, the first placebo-controlled study investigating ketamine as an antidepressant was published in 2000 (Berman et al. 2000). Since that time, ketamine's reputation for treating major depressive disorder (MDD) and bipolar disorders has prompted numerous investigations, in large part because of its rapid action—taking less than 48 h to have beneficial effects similar to those seen after 2 weeks using current antidepressant medications (Berman et al. 2000; Murrough et al. 2012; Price et al. 2009; aan het Rot et al. 2009).

Despite its rapid effect after a single administration, one hindrance to ketamine's adoption as a therapeutic adjunct is the rate of relapse in the weeks following treatment. In one study, 24 patients with treatment-resistant depression were given six serial IV infusions of ketamine. Ketamine proved effective with an antidepressant effect measured in 17 of 24 patients, a response rate of 70.8%. In the weeks following treatment, however, all patients eventually relapsed around 18 days after the final infusion (Murrough et al. 2012). In a similar study, 26 patients responded positively to ketamine infusions, and the average time to relapse was 12 days (Price et al. 2009). In another, the reduction in depressive symptoms was measured at 85% following the last infusion using the Montgomery-Asberg Depression Rating Scale (MADRS), and 8 of 9 patients relapsed an average of 19 days post-therapy (aan het Rot et al. 2009). These data suggest that, although initially effective, therapeutic benefits of ketamine alone last only a few weeks. To be effective as a long-term therapeutic adjunct, it should be administered at regular intervals (Rasmussen et al. 2013).

Adherence to this method can be difficult because patients must return to the clinic for IV infusions. Additionally, IV and IM routes of administration carry inherent risks unrelated to the pharmacologic safety profile of the drug being administered including infection, hematoma, extravasation and pain (Canterbury District Health Board 2015; Columbia University n.d.). It is not surprising, then, that patients prefer oral therapy to parenteral routes of administration (Borner et al. 2001; Liu et al. 1997) leading to better patient compliance. Ketamine's beneficial use in therapy could be assisted by safer, more convenient routes of administration. Both oral and sublingual methods have been used for this reason (Schoevers et al. 2016).

## Methods

### Setting

The clinical setting was a private, suburban psychiatric practice specialising in the management of depression, anxiety and suicide risk. Clinicians had utilised oral ketamine as augmentation therapy for the previous 3 years.

### Participants

All participants enrolled in therapy were over 18 years of age and referred from psychiatrists or general practitioners for oral ketamine augmentation. Patients had been diagnosed with a presenting complaint of treatment-resistant major depressive disorder. A significant proportion also had a diagnosis of either post-traumatic stress disorder or severe anxiety symptoms. Many of them also presented with significant suicide risk due to current ideation or history of suicide attempts. Treatment resistance was defined as having previously failed at least two separate, evidence-based pharmacological treatments for depression. This is a more selective definition than the common usage of one failed therapy (Fava 2003). All participants were involved in an intensive community-based psychiatric follow-up or were still inpatients in a psychiatric facility at the time of referral. Patients were psychologically evaluated during an interview with a psychiatrist and general practitioner. These patients were screened using the Kessler-10, a validated clinical measure of current affective disorders (Hides et al. 2007). Eligible participants scored higher than 20 out of 50 on the K-10. Informed consent was obtained from the patient and included permission to gather de-identified data from their medical records. A physical examination was performed by a general practitioner. Patients were screened for thyroid, liver and renal function disorders at presentation and six monthly during treatment. ECG and urine test were also obtained at regular intervals.

Exclusion criteria included acute medical problems, abnormalities on the screening tests that required clinical intervention to address, a diagnoses of psychosis or a substance use disorder. As a precaution, pregnant patients were also excluded from treatment. Patients agreed to receive ketamine in conjunction with psychiatric consultations, psychological intervention and GP follow-up as clinically indicated. Patient selection is summarised by Fig. 1 flowchart. A total of 37 patients with MDD were included in the analysis, 15 of whom

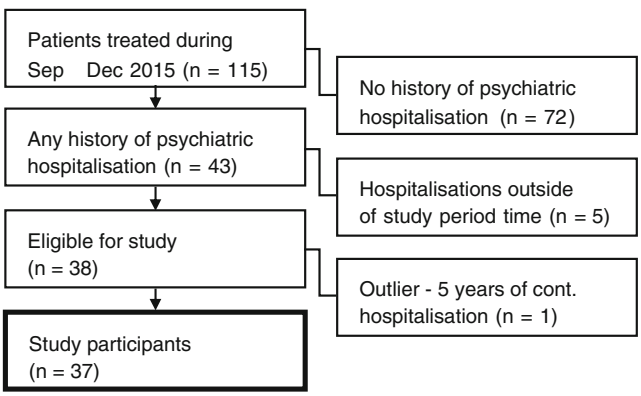


**Fig. 1** Patient selection process. Records of patients who received ketamine treatment between September and December 2015 were examined for inclusion in the study

had been referred with post-traumatic stress disorder as their primary diagnosis.

### Therapy design

At the beginning of a therapy session, patients' vitals were taken to rule out hypertension and tachycardia, each contraindicated with ketamine. During their first session, participants were administered an individually titrated, sub-anaesthetic, sublingual dose of ketamine to assess for adverse reactions. This initial sublingual dose of 0.5 mg/kg was held under the tongue for 2–3 min to ensure the patient could discard it if an adverse reaction was observed. After the clinician was satisfied that there was no adverse reaction, all subsequent doses were mixed with a flavoured drink and swallowed. Blood pressure was recorded before the dose and 30 min after. At that time, if the participant was alert and stable, they were allowed to leave the clinic. Participants were not permitted to drive or operate machinery for 12 h following treatment.

Dosage began at 0.5 mg/kg and was titrated up by 20–50% at each subsequent treatment. During the titration period, participants were given ketamine twice daily, 3 h apart. This was conducted at most twice per week. After titration was complete, they received treatment between twice weekly and fortnightly. Titration was deemed complete when the patient exhibited transient signs of psychotropic effects—often described as a 'glass of wine' feeling. Additionally, any other systemic effects, such as a change in blood pressure, would mark titration as complete. Final doses ranged from 0.5 to 7.0 mg/kg. Doses were adjusted throughout the course of therapy to target minimum threshold psychoactive effects. All participants continued to use their usual medication initially, but many required adjustments to their regime depending on their response to ketamine augmentation. During the maintenance phase of treatment, participants attended the clinic between weekly and fortnightly.

### Outcome measures

Primary outcome measures were the number of days spent as an inpatient in a hospital, along with the number of hospital admissions, before and after treatment. These measures were chosen because we believe they reflect a patient's general functionality and the severity of illness. Secondary measures included medical chart data to evaluate treatment safety and the patient's dosage of ketamine over the course of treatment. Data were acquired directly from patients' discharge summaries and hospital records. Previous physicians and hospitals were contacted to fill in gaps as necessary.

Using December 1, 2015 as an endpoint, we counted the number of days each patient had been receiving ketamine therapy. Patient charts were then examined for that same number of days prior to initiating therapy. Thereby, we obtained an individualised but consistent number of days before and after treatment for each patient. This method was chosen because the study was retrospective, with each patient having a different starting date, and obtaining a consistent interval across individuals was not practical. Of 115 patients receiving ketamine therapy at the clinic, 37 patients were found to have met selection criteria of hospitalisations during the study timeframe. Records of these patients were analysed for the purposes of this study. The length of time each patient had been receiving therapy varied among the group as summarised in Fig. 2.

Ketamine's safety profile has been established over decades of use in anaesthesia at doses much higher than those used during psychiatric therapy (Kurdi et al., 2014). Still, there remain questions surrounding safety of administration on a regular basis, questions which have slowed adoption of the therapy by a larger number of clinicians. Concerns largely centred on addiction, bladder toxicity and hypertensive crises (Schak et al. 2016; Shahani et al. 2007; Chu et al. 2007; Broughton and Waldron 1983). In order to mitigate these and other medical issues, patients were monitored for medical problems before, during and after their treatment course, as described in the aforementioned inclusion criteria.

The measure of dosage over time was chosen to evaluate for signs of tolerance to ketamine. Reports of bladder damage associated with ketamine abuse show a dose-dependent relationship with the severity of injury (García-Larrosa et al. 2012; Grégoire et al., 2008). If tolerance were to build over time, the therapeutic dose of ketamine may enter potentially damaging levels. We compared the dose administered at the end of titration with the endpoint of December 2015.

### Data analysis

Pairwise *t* tests were performed to compare total inpatient hospital days and hospital admissions for each patient before and after therapy. For primary analyses, comparisons were calculated for the overall study population as well as subcategorical diagnoses of MDD with and without PTSD. Pairwise analyses used nonparametric Wilcoxon signed rank test and significance of $p < 0.05$. Similar analysis was used to compare ketamine dosages at two time points. Analysis was conducted in GraphPad Prism (GraphPad Software, n.d.) and

| | Min. | Max | Median |
|---|---|---|---|
| Age | 21 | 84 | 46 |
| Number of Admissions | 1 | 30 | 3 |
| Inpatient Days in Hospital | 8 | 899 | 77 |
| Months of Ketamine Treatment | 6 | 36 | 31 |
| Gender | Female = 28<br>Male = 9 | | |

**Fig. 2** Patient data. Demographics and hospitalisation history

Microsoft Excel (Microsoft Corporation, n.d.). Figures were created in GraphPad Prism.

## Results

Patients were found to have reduced numbers of both hospital admissions and inpatient hospital days in the period following oral ketamine therapy compared with the period before therapy.

A total of 171 admissions to psychiatric facilities were recorded before treatment. During a matching period following oral ketamine treatment, 65 admissions were recorded ($p < 0.001$). Seventy-six of those admissions were recorded for the PTSD population pre-treatment. Following treatment, patients were admitted 23 times admissions to hospital. Overall, this represents a reduction in hospital admissions by an average 70% per patient. Figure 3 illustrates the reduction of inpatient hospital days in the total study population. Similarly, Fig. 4 illustrates the overall reduction in number of hospital admissions before and after therapy ($p = 0.001$).

The average dose recorded in December 2015 was 2 mg/kg compared to 3 mg/kg at the end of titration. Patients either stayed at the same dose or experienced a reduction in the amount of ketamine needed to be effective (Fig. 5). None of the patients required an increase in dose over time following the end of the titration phase.

### Adverse events

During the period encompassed by this study, no serious adverse events were recorded among patients. There were no medical emergencies and no psychotic or psychiatric crises attributable to ketamine administration. There were no hypertensive or hypotensive crises. There were also no reported cases of bladder toxicity. Orally administered ketamine was, overall, well tolerated. The most common side effects were lightheadedness, sedation and mild dissociative effects felt during the few minutes following administration. These effects were transient and subsided within an hour after administration. Less frequently reported event included blood pressure changes, nausea and headache (5–10%). Also in those instances, side effects were short-lived and did not require active intervention.

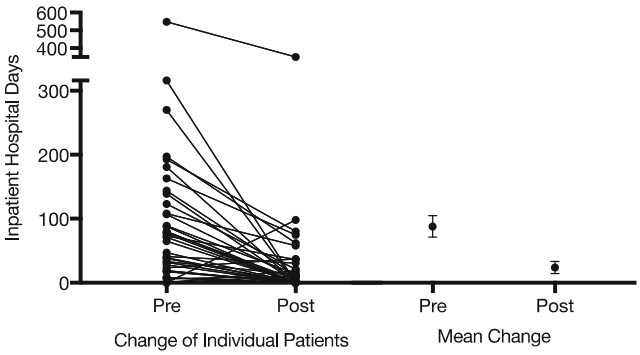


**Fig. 3** Change in total days spent as an inpatient in hospital, pre- and post-ketamine therapy. Significant decreases in the days spent as a hospital inpatient were supported by pairwise *t* test using nonparametric Wilcoxon signed rank test among individuals and mean with s.e.m. ($p < 0.001$, $n = 37$)

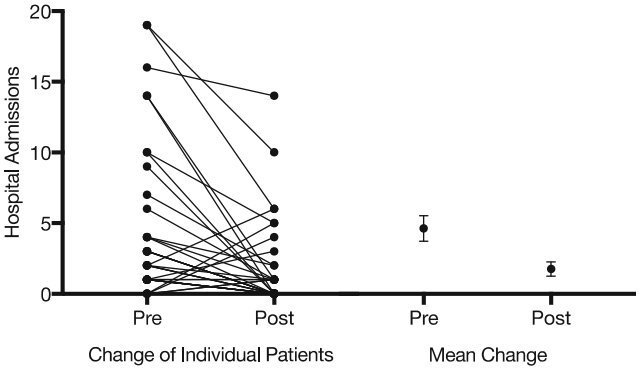


**Fig. 4** Change in hospital admissions, pre- and post-ketamine therapy. Significant decreases in admissions were evident following ketamine therapy among most individuals (left) and mean (right) with s.e.m. ($p < 0.001$, $n = 37$)

## Discussion

In this retrospective analysis, we have shown that oral ketamine augmentation in an outpatient setting is a promising therapy for treatment-resistant depression and PTSD. Over the past several years, several hundred patients have been treated with oral ketamine at this clinic, a subset of whom have been examined in this study. During that time, there was a significant reduction in both the number of admissions and days spent in inpatient psychiatric

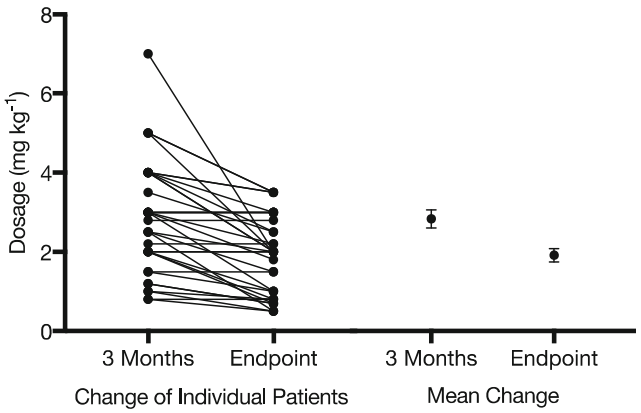


**Fig. 5** Comparison of dosage between 3 months into treatment (end of titration), and the endpoint of December 2015. Change is significant among individuals and calculated mean with s.e.m. ($p < 0.001$, $n = 37$)

facilities. The dosage and frequency of administration and the parameters used to monitor patients ensured their safety during treatment.

Close monitoring of dosage over time revealed that patients did not develop tolerance to ketamine despite the lengthy treatment period. Rather, there was typically a decrease in the amount of drug needed over time to be therapeutically effective. This effect may ease clinicians' concerns of tolerance leading to physical damage or drug dependence.

One of the strengths of the report is the long follow-up period of up to 3 years for some of the patients which reduces the impact of fluctuations in severity of mental illness over time. We also recognise the limitations of a retrospective study, having no controls to account for confounding factors such as modifications in drug treatments or changes in the treating team. Instead, this is a *real-world* implementation of a treatment modality to determine whether a positive outcome could be achieved in an outpatient setting. Accordingly, we were able to demonstrate that a nonintensive community program is effective in a population with severe mental illness.

As stated in the introduction, one of the difficulties of ketamine for depression and other psychiatric illnesses is the relapse rate. In studies with IV ketamine, researchers have found serial infusions more effective at meeting antidepressant response criteria and lengthening the time to relapse (Rasmussen et al. 2013). Recent protocols, including this one, have focused on administering ketamine in a care facility, either a hospital or clinical setting. However, for ketamine to maintain its efficacy long term, many patients require additional doses of the drug. For these patients, weekly and biweekly visits to a clinical setting are an inconvenience and represent additional cost burdens to patients. As observed by Schoevers et al., once safety has been established, ketamine will likely 'be prescribed to depressed patients outside of the hospital environment for maintenance purposes' (Schoevers et al. 2016). Home use of oral ketamine offers a possible method for patients to regularly administer the drug in a way that parenteral routes of administration do not allow.

It is our hope oral ketamine will be considered by practitioners as an alternative to IV or IM routes of administration. The results of this study and others warrant further investigation of the safety and efficacy of ketamine for psychiatric treatment, and the authors wholly encourage further research in this regard.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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