



Journal of Psychopharmacology
1–9

© The Author(s) 2014
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0269881114527361
jop.sagepub.com



Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic

Peter R Diamond¹, Andrew D Farmery², Stephanie Atkinson¹, Jag Haldar³, Nicola Williams⁴, Phil J Cowen⁵, John R Geddes⁵ and Rupert McShane^{1,5}

Abstract

Background: Ketamine has a rapid antidepressant effect in treatment-resistant depression (TRD). The effects on cognitive function of multiple ketamine infusions and of concurrent antidepressant medication on response rate and duration are not known.

Method: Twenty-eight patients with uni- or bipolar TRD were treated over three weeks with either three or six ketamine infusions (0.5 mg/kg over 40 minutes) in the recovery room of a routine ECT clinic. Post-treatment memory assessments were conducted on day 21 (4–7 days after the final infusion). Patients were followed up for six months where possible, with severity of depression and side effects monitored throughout.

Results: Eight (29%) patients responded of whom four remitted. Only three (11%) patients had responded within six hours after a single infusion, but in all responders, the response had developed before the third infusion. The duration of response from the final infusion was variable (median 70, range 25–168 days). Discontinuations included two (7%) because of acute adverse reactions during the infusion and five (18%) because of failure to benefit and increasing anxiety. Ketamine was not associated with memory impairment. The ECT clinic was rated suitable by patients and offered appropriate levels of monitoring.

Conclusion: This small, open label naturalistic study shows that up to six low dose ketamine infusions can safely be given within an existing NHS clinical structure to patients who continue their antidepressants. The response rate was comparable to that found in RCTs of single doses of ketamine in antidepressant-free patients but took slightly longer to develop.

Keywords

Antidepressant, ketamine, memory, treatment resistant depression

Introduction

Since Berman et al. (2000) demonstrated the rapid antidepressant effect of ketamine in patients with major depression, there have been five further randomised controlled trials (RCTs) confirming that a single ketamine infusion (0.5 mg/kg administered over 40 minutes) can have rapid antidepressant effects in both bipolar and unipolar refractory depression (Zarate et al., 2006, 2012; DiazGranados et al., 2010; Valentine et al., 2011; Murrrough et al., 2013). The overall response rate at 72 hours is 29% compared to 7% with saline placebo (Aan het Rot et al., 2012). In a recent trial against the active comparator midazolam, Murrrough et al. (2013) established response rates to a single dose of ketamine at 3 and 7 days of 60% and 46% compared to 21.5% and 17.5% with midazolam. The duration of the antidepressant response in these RCTs has been highly variable, ranging from a matter of hours to several weeks, with most patients eventually relapsing. Due to this rapid but transient antidepressant effect, the safety and efficacy of administering repeated infusions to sustain this effect was explored in patients who had initially responded to a single ketamine infusion (Aan het Rot et al., 2010). Six infusions were administered over two weeks to a group of nine medication free patients with TRD resulting in a mean time to relapse of 19 days for eight of the patients, with one patient exhibiting a

response for three months. This was longer than in the studies using single infusions. Murrrough et al. (2013a) used this treatment regime in a larger series of 24 patients with TRD, again finding an extended period of response lasting a median of 18 days. Neither study found this number of infusions to be associated with any cognitive deficits, however no formal assessments of memory were reported. Memory performance is known to be impaired in volunteers when ketamine is given acutely (Morgan and Curran, 2006). Furthermore, those who regularly abuse high doses of ketamine recreationally demonstrate long term semantic and episodic memory deficits which continue after cessation of

¹Oxford Health NHS Foundation Trust, Oxford, UK.

²Nuffield Department of Anaesthetics, University of Oxford, Oxford, UK.

³Oxford University Hospitals NHS Trust, Oxford, UK.

⁴Centre for Statistics in Medicine, University of Oxford, Oxford, UK.

⁵Department of Psychiatry, University of Oxford, Oxford, UK.

Corresponding author:

Rupert McShane, Oxford Health NHS Foundation Trust, Warneford Hospital, Warneford Lane, Oxford, OX3 7JX, UK.
Email: Rupert.mcshane@oxfordhealth.nhs.uk

the drug (Morgan and Curran, 2006). These are potentially relevant when considering repeated administration of ketamine to treat patients suffering from chronic depression.

The main aim of the present open label study was to explore the safety and efficacy of repeated infusions in patients who continued other psychotropic medication, with particular emphasis on memory functioning. We reasoned that if the benefit of ketamine was shown to share mechanisms of action with that of ECT, for which it may potentially be an alternative, then it would be important to know that ketamine does not share ECT's impact on episodic and autobiographical memory. For many years, the subjective complaints of patients receiving ECT of permanent autobiographical memory impairment were attributed to residual depression. It has now been confirmed however, that ECT does contribute to this problem (Lisanby et al., 2000). We were also interested to make preliminary observations about whether, like ECT, the response develops over time in those who do not respond to the first infusion. Finally, we aimed to explore whether the background noise and activity of a busy ECT clinic would be a barrier to patients receiving ketamine infusions alongside other patients receiving ECT.

Methods and materials

Participants

Participants with treatment resistant bipolar or unipolar depression were recruited via secondary care referrals and self-referrals through advertisements in the media and a study website. The diagnosis was confirmed by clinical interview, Structured Clinical Interview of DSM-IV (First et al., 1997) and Hamilton Rating Scale for Depression (HRSD) (1960). Treatment resistance was defined as a current or past history of lack of response to two adequate antidepressant trials using the Antidepressant Treatment History Form (Sackeim, 2001). Patients were excluded if they met any of the following criteria: schizophrenia or schizoaffective disorder, dementia or mild cognitive impairment, closed angle glaucoma, female participants who were pregnant, lactating or planning pregnancy during the course of the study, significant renal or hepatic impairment, scheduled elective surgery or other procedures requiring general anaesthesia, terminal illness, known hypersensitivity to ketamine, poor spoken English, uncontrolled hypertension. Initially, suicide risk was an exclusion but this was lifted after evidence emerged indicating ketamine could reduce suicide ideation (Price et al., 2009). Written informed consent was obtained prior to any study procedures. The study was approved by the Oxfordshire Research Ethics Committee.

Intervention

This was an open label study with increasing frequency of ketamine administration. In the first stage patients were recruited to receive ketamine (Ketalar®) infusions once a week for three weeks. In the second stage a separate group was recruited to receive ketamine infusions twice a week for three weeks. The dose of ketamine administered was 0.5 mg/kg (ideal body weight) administered intravenously over 40 minutes. In both stages, if a participant responded to ketamine and then relapsed after the final infusion they entered the maintenance phase of the trial, the

results of which are reported separately. Participants were followed up for 6 months where possible.

Measures

The primary measure of mood was the Beck Depression Inventory (BDI) (Beck and Beamesderfer, 1974). HRSD (1960) was also used to monitor mood. Side effects during the infusion were monitored using the Brief Psychiatric Rating Scale (Overall and Gorham, 1962) and visual analogue scales (VAS). Two measures of autobiographical memory were used, the Autobiographical Memory Interview – Short Form (AMI-SF) (McElhiney et al., 1997) and the Autobiographical Fluency Task (AFT) (Dritschel et al., 1992). Using the AMI-SF patients were asked about the details of six different events. Questions were then asked about these same events at follow up and the percentage of information recalled correctly was recorded. Using the AFT, participants were asked to recall information in three separate categories ('personal semantic', 'personal episodic' and 'impersonal semantic') within 90 seconds. The Story Recall test (Powell et al., 1993) was used to assess episodic memory. Patients are required to listen to a story comprising 24 items and then to recall as many of these items as possible immediately after and following a 20 minute delay. Subjective memory was assessed using a new ECT Memory Questionnaire (ECT-MQ) (Kershaw, 2010), comprising of 22 statements relating to memory problems associated with ECT treatment. A five-point Likert scale ranging from 'Strongly Agree' to 'Strongly Disagree' was used to assess the suitability of the ECT suite to receive infusions.

Procedure

After giving informed consent participants were screened using the Structured Clinical Interview of DSM-IV to confirm diagnosis, a history, an AMI-SF, a HRSD, a physical examination, and blood and urine analysis. The day before the first infusion a baseline assessment was completed including HRSD, BDI, VAS, ECT-MQ, AFT and Story Recall.

All infusions took place in the recovery room of the ECT suite at the Warneford Hospital, Oxford, UK during the twice weekly morning ECT sessions. Patients were allowed a light breakfast before treatment. 0.5 mg/kg of ketamine hydrochloride was diluted in 40 mL of saline and administered over 40 minutes using a Graseby 3200 infusion pump. Vital signs were recorded for approximately 50 minutes from the beginning of the infusions. Twenty minutes before the start of the infusion ($t_{(-20m)}$) a HRSD, BDI and VAS were completed. VAS scales were then completed at twenty minute intervals for two hours. At $t_{(40m, 120m)}$ a BPRS was conducted. At $t_{(120m)}$ participants were then discharged from the unit if they were deemed to be fully recovered. They were then seen at $t_{(360m)}$ at home or in the hospital to complete a further HRSD, BDI and VAS.

Infusions were administered on days 0, 7 and 14 in stage one and days 0, 3, 7, 10, 14 and 17 in stage 2. Participants were seen on day 6 and 13 to complete a HAMD, BDI and VAS. Following the three weeks of treatment participants completed a further VAS and all mood (HRSD, BDI) and memory (AMI-SF, Story Recall, AFT, SMQ) assessments on day 21. All participants were then followed up at 2 weeks, 4 weeks, 8 weeks, 12 weeks and 26 weeks. Further memory assessments were carried out at 12 and

Table 1. Patient demographics. BDI = Beck Depression Inventory.

Patients, <i>n</i>	28
Age (mean)	47 (SD 15)
Gender (male:female)	16:12
Diagnosis (bipolar:unipolar)	6:22
Baseline BDI (mean)	34.91 (SD 9.67) (severe)
Current no. of psychotropic medications taken (mean)	3.2 (SD 2.1)

26 weeks. Antidepressant response was defined at a $\geq 50\%$ reduction in BDI score from baseline to the end of the three week treatment on day 21, and remission as a score falling within the normal range (0–10) on the BDI. Length of response was calculated from the final infusion until the patient no longer showed $\geq 25\%$ decrease in score. At this point the patient was deemed to have relapsed. The study was exploratory and was not powered for comparisons. Statistics are therefore descriptive.

Results

Forty-four patients were screened, of whom 28 are included in the analysis (see Table 1); 15 patients were recruited to receive three infusions over three weeks and a separate 13 patients were recruited to receive six infusions over three weeks.

Safety and tolerability

In total, 8/28 (29%) patients failed to complete all the planned infusions, 2 because of acute adverse reactions during the infusion, 5 because of failure to benefit and increasing anxiety and 1 for unrelated reasons. In stage one, 12/15 (80%) patients completed all three infusions. One patient withdrew during their first treatment due to a panic attack nine minutes into the infusion, experiencing tachycardia and tachypnoea. Two patients withdrew after their second treatment, one due to lack of perceived benefit and increased anxiety and one was withdrawn due to concurrent upper respiratory tract infection. Two of the three withdrawals were followed up to day 21. In stage two 8/13 (62%) completed all 6 infusions. Two withdrew after the first infusion: one participant had a 10 minute vasovagal episode (bp 77/47, pulse 45 bpm, reduced level of consciousness) 11 minutes into his first infusion, becoming symptom free over the next hour. One experienced increased anxiety, worsening mood and increased suicide ideation in the afternoon following treatment. This increase in suicide ideation was related to the acute loss of hope following the ineffectiveness of the patient's treatment. Two patients withdrew after four infusions and one after the fifth due to lack of perceived benefit from the ketamine and increasing anxiety over the course of treatment. Two of the five withdrawals agreed to be followed up to day 21.

Side effects which did not result in dropout included the following. One bipolar patient experienced a rapid cycling of mood following three infusions. This included a hypomanic episode which was mild and self-reported, characterised by racing thoughts and reduced sleep, did not result in clinically noticeable changes in behaviour, resolved with an increased dose of antipsychotic medication and did not prevent the patient from going on to

receive maintenance ketamine after the end of the study. Three other patients experienced mood instability over the course of infusions with worsening mood and increased suicide ideation. All three patients were prone to fluctuating levels of suicide ideation prior to being treated with ketamine. One patient in stage one was recorded as having developed a manic episode four days after her final ketamine infusion resulting in prolongation of admission. The psychiatrist treating her judged this to be consonant with pre-existing mood instability and probably unrelated to treatment. One patient experienced a panic attack during his second infusion. Two patients vomited during treatment. In the afternoon following the infusions the majority of patients experienced an increase in fatigue with a small number of patients also experiencing mild headaches. One patient experienced an episode of symptomatic cystitis after four infusions. Although she was not a responder at 21 days, she had an acute improvement of mood and attributed the cystitis to sexual activity. It resolved after a single dose of antibiotics. No other patient experienced symptomatic cystitis or developed significant abnormalities on urinary dipstick testing. One patient experienced a hypnagogic hallucination thought to be related to treatment 150 minutes after her fourth infusion.

Transient side effects were experienced by most patients including perceptual distortions, detachment, anxiety, nausea and confusion during the infusion. Most, but not all, patients experienced marked, but well tolerated dissociative symptoms. There was no relation between this acute experience and response at day 21 (data not shown).

Memory

Autobiographical memory. This study was exploratory and was not powered to detect differences in memory. On the AMI-SF similar levels of forgetting of autobiographical material was observed in both stage one and stage two, with the median percentage of baseline information recalled at 21 days in stage 1 being 92 % (range: 76.8–100) and in stage 2 being 94.1% (range: 71.4–98) (see Figure 1(a)). Two of 22 participants were able to recall less than 78% of baseline items. On the AFT personal semantic, personal episodic and impersonal semantic fluency were generally improved in both stages 1 and 2 (see Figure 1(b)). In stage 1 there were mean increases of 5.1 (SD 9.1), 2.7 (SD 7.91) and 0.9 (SD 8.93) and in stage 2 there were increases of 10 (SD 7.45), 5.7 (SD 4.15) and 7.8 (SD 5.63), respectively, for personal semantic, personal episodic and impersonal semantic indices of fluency. The single participant (no. 14) in whom all three indices had deteriorated had withdrawn from the study and received ECT on the morning of her day 21 assessment.

Episodic memory. In general, both immediate and delayed recall was improved following ketamine infusions, with no obvious differences between those receiving 3 or 6 infusions (see Figure 1(c)). Mean increases were + 2.5 (SD 5.2) for immediate recall and + 3.4 (SD 3.82) for delayed recall in stage 1 and + 3.7 (SD 3.16) and + 3.2 (SD 3.87) in stage 2. One participant (no. 9), whose initial scores were high (22/24 and 18/24 compared to a group mean of 11.7 and 10.3) had a marked reduction in both immediate and delayed recall. Despite this change, his final scores at D21 were the same as the group mean for both immediate and delayed recall (14/24).

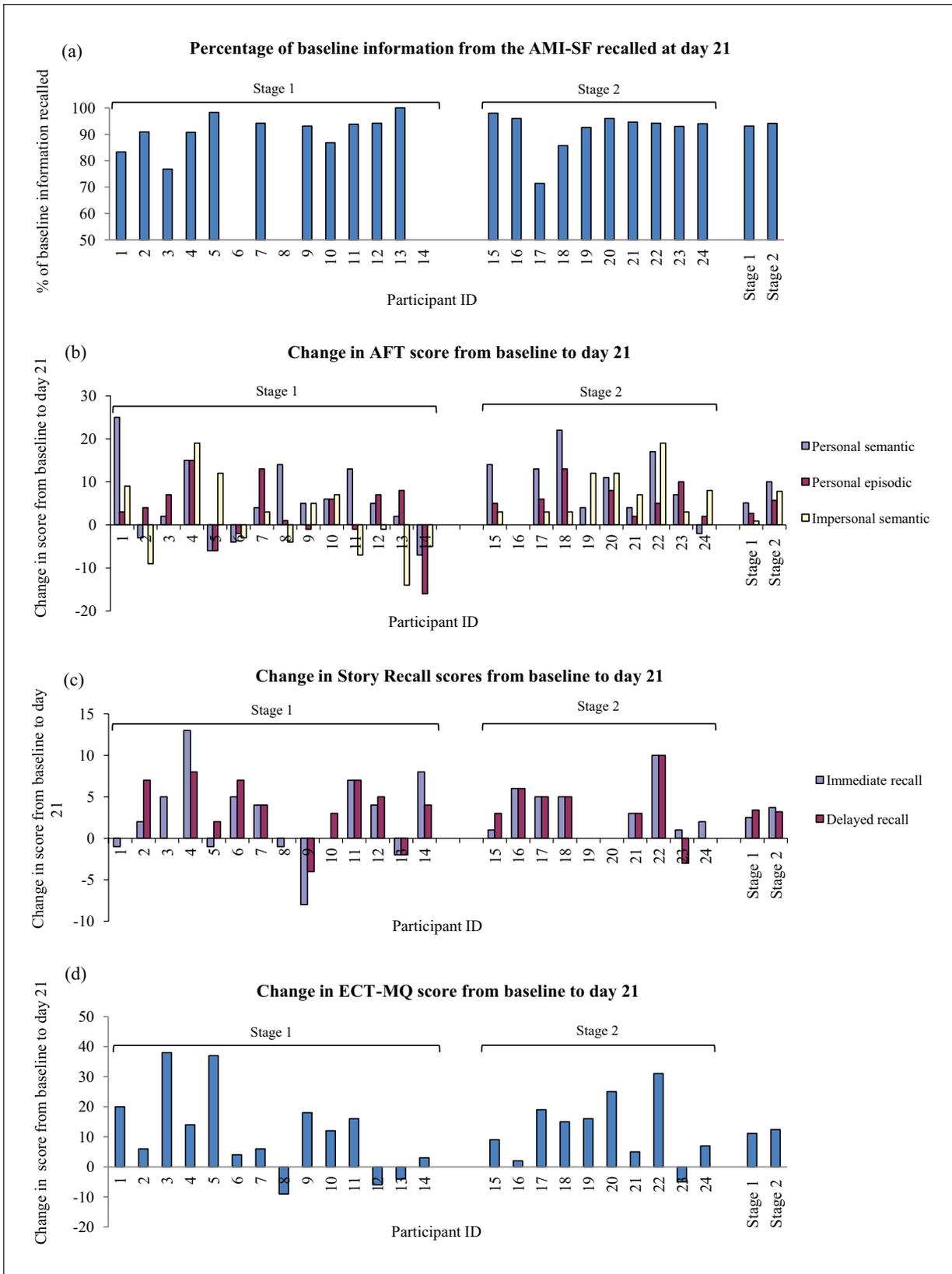


Figure 1. Individual and group changes in memory performance from baseline to day 21. (a) Percentage of baseline information recalled in Autobiographical Memory Interview – Short Form at day 21 for individual participants and group medians. (b) Individual changes and mean group changes in Autobiographical Fluency Task scores from baseline to day 21. (c) Individual changes and mean group changes in Story Recall performance from baseline to day 21. (d) Individual changes and mean group changes in ECT-Memory Questionnaire scores from baseline to day 21.

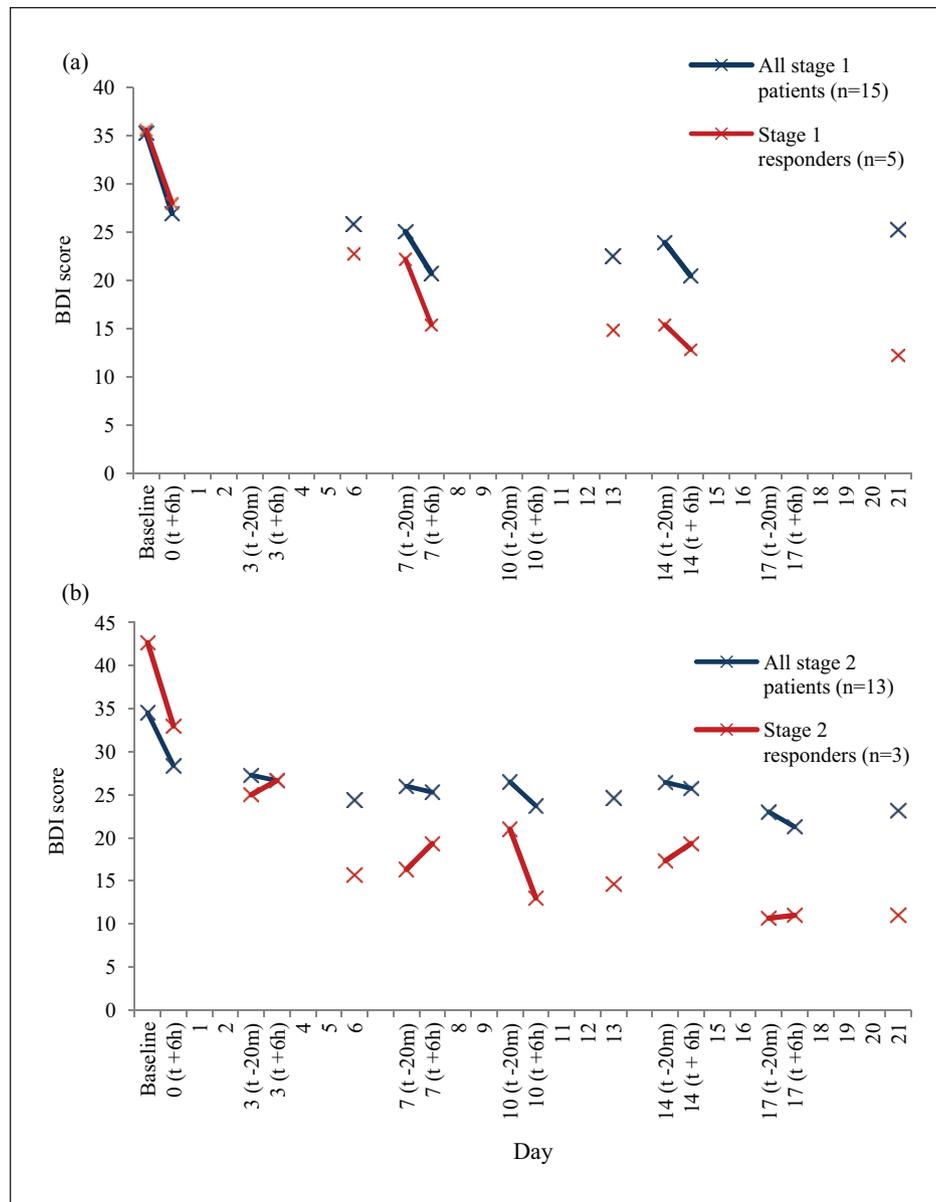


Figure 2. Mean severity of depression in (a) stage 1 (infusions on days 0, 7, 14) and (b) stage 2 (infusions on days 0, 3, 7, 10, 14, 17). -20m denotes 20 minutes before start of infusion; +6h denotes 6 hours after infusion.

Subjective memory performance. Participants reported subjective improvements, or little change, in memory after ketamine: mean change scores in stage one was + 11.1 (SD 14.27). In stage two it was + 12.4 (SD 10.92) (see Figure 1(d)).

Mood

The mean reduction in BDI scores 6 hours after the first ketamine infusion was 7.3 (SD 7.9). Of those starting treatment, the response criteria of $\geq 50\%$ reduction in BDI was met by 3/28 (10.7%) at the 6 hour time point. This represents 12.5% of the 24 completers. At day 21 8/28 (29%, or 33% of completers) had reached response criteria, 5/15 (33.3%) from stage 1 and 3/13 (23%) from stage 2. In all patients that met response criteria at day 21 a response had developed before the third infusion. The mean

BDI score at day 21 in stage 1 and stage 2 for responders was 12.2 (SD 7.5) and 11 (SD 4.4), respectively, with an average reduction of 23.4 (SD 10.5) and 31.7 (SD 7.6) from baseline (see Figure 2). At day 21, half of all responders (14% of all patients) had reached remission criteria, 3/5 in stage 1 and 1/3 in stage 2. Amongst the 8 patients who were responders at 21 days the length of response was variable (median 70, range 25–168 days); stage 1: 84 days; stage 2: 25 days. Table 2 details the medication taken by responders.

We observed a reduction in suicide ideation in 61% of patients within 6 hours of receiving a single infusion, as measured by the five-point scale of item 3 on the HRSD. Following a single infusion the mean score for all patients had dropped from 2.0 (SD 0.9) to 0.7 (SD 1.1). This persisted to day 21 in responders (mean reduction 2.13 (SD 0.64)) but was not apparent in non-responders

Table 2. Demographics of patients classed as responders at day 21, including details of medication taken for the duration of the trial and both mood and suicidality scores as measured on the Beck Depression Inventory (BDI) and item three on Hamilton Rating Scale of Depression (HRSD) respectively at baseline and day 21. Length of response preceded with > if still exhibiting response at final follow up assessment.

Patient	Stage	Diagnosis	Age	Sex	Medication	Baseline BDI score	Baseline suicidality score	Day 21 BDI score	Day 21 suicidality score	Length of response
1	1	Bipolar depression	28	F	Quetiapine 600 mg, modafinil 400 mg, temazepam 40 mg, bisoprolol 5 mg, aripiprazole 20 mg, olanzapine 10 mg prn Baseline: Sertraline 100 mg, olanzapine 5 mg, clonazepam 0.5 mg prn Day 17: Reduced sertraline 50 mg, olanzapine 0.25 mg Day 52: Fluoxetine 20 mg added Day 54: Pregabalin 50 mg added, increased olanzapine 5 mg Day 74: Fluoxetine stopped, pregabalin stopped. Increased sertraline 100 mg, duloxetine 60 mg added. Day 98: Duloxetine stopped. Aripiprazole 5 mg added Baseline: Venlafaxine 300 mg, olanzapine 15 mg, lithium 800 mg	40	3	2	0	28
2	1	Unipolar depression	59	M	Baseline: Sertraline 100 mg, olanzapine 5 mg, clonazepam 0.5 mg prn Day 17: Reduced sertraline 50 mg, olanzapine 0.25 mg Day 52: Fluoxetine 20 mg added Day 54: Pregabalin 50 mg added, increased olanzapine 5 mg Day 74: Fluoxetine stopped, pregabalin stopped. Increased sertraline 100 mg, duloxetine 60 mg added. Day 98: Duloxetine stopped. Aripiprazole 5 mg added Baseline: Venlafaxine 300 mg, olanzapine 15 mg, lithium 800 mg	22	3	9	1	>84
5	1	Unipolar psychotic depression	34	F	Day 70: Reduced olanzapine 5 mg Baseline: Tranylcypromine 50 mg, propranolol 80 mg, clonazepam 4 mg, quetiapine 150 mg, agomelatine 25 mg, haloperidol 4.5 mg Day 21: Reduced haloperidol 2mg. Stopped clonazepam & propranolol. Increased quetiapine 300mg. Day 28: Discontinued agomelatine & tranylcypromine. Haloperidol increased to 10 mg following manic episode Day 42: Reduced quetiapine 150 mg Day 70: Reduced haloperidol 5 mg Day 182: Reduced haloperidol 3 mg Baseline: Lamotrigine 250 mg, lithium 600 mg Gabapentin 1.4 g, lorazepam 2 mg, zolpidem 5 mg	48	2	18	0	>84
9	1	Bipolar depression	34	M	Day 70: Reduced olanzapine 5 mg Baseline: Tranylcypromine 50 mg, propranolol 80 mg, clonazepam 4 mg, quetiapine 150 mg, agomelatine 25 mg, haloperidol 4.5 mg Day 21: Reduced haloperidol 2mg. Stopped clonazepam & propranolol. Increased quetiapine 300mg. Day 28: Discontinued agomelatine & tranylcypromine. Haloperidol increased to 10 mg following manic episode Day 42: Reduced quetiapine 150 mg Day 70: Reduced haloperidol 5 mg Day 182: Reduced haloperidol 3 mg Baseline: Lamotrigine 250 mg, lithium 600 mg Gabapentin 1.4 g, lorazepam 2 mg, zolpidem 5 mg	42	2	21	0	>168
10	1	Unipolar depression	38	F	Baseline: Lamotrigine 250 mg, lithium 600 mg Gabapentin 1.4 g, lorazepam 2 mg, zolpidem 5 mg	26	2	11	0	56
15	2	Mixed anxiety, unipolar depression, unstable personality disorder	43	M	Baseline: Lamotrigine 250 mg, lithium 600 mg Gabapentin 1.4 g, lorazepam 2 mg, zolpidem 5 mg	37	2	14	1	>165
18	2	Bipolar depression	44	F	Venlafaxine 187.5 mg, clonazepam 2 mg, diazepam 15 mg	43	2	6	0	25

Table 2. (Continued)

Patient	Stage	Diagnosis	Age	Sex	Medication	Baseline BDI score	Baseline suicidality score	Day 21 BDI score	Day 21 suicidality score	Length of response
20	2	Unipolar depression with anxiety	37	M	Baseline: Aripiprazole 30 mg, venlafaxine 600 mg, diazepam 15 mg, lorazepam 1 mg, lansoprazole 60 mg, quetiapine 600 mg, modafinil 400 mg, gabapentin 1800 mg Day 28: Reduced aripiprazole 10 mg, gabapentin 1200 mg, lansoprazole 30 mg. Stopped diazepam, gabapentin, lorazepam, loperzolam and zopiclone Day 70: Started diazepam 15 mg, lorazepam 1 mg	48	2	13	0	25

(-0.25 (SD 0.58)). Correlations between change in mood (BDI total) and change in HRSD suicidality score, were modest and non-significant at 6 hours after the first infusion ($r = 0.331$, $df = 26$, $p = 0.085$) and at day 21 ($r = 0.368$, $df = 26$, $p = 0.054$).

The ECT suite as a suitable location for receiving ketamine

Of the 23 patients who rated the ECT suite as a place to have ketamine infusions, 17 agreed or strongly agreed that it was suitable. Those who felt the ECT suite was not suitable ($n = 4$) commented that it was too noisy, there was too much movement around them, and that hearing other distressed patients in the recovery room could be upsetting. Anecdotally, our impression was that response to treatment was not related to the actual or perceived level of noise or to the quality of interactions with staff during the infusion.

Discussion

We report a descriptive study with wide inclusion criteria in which participants were not withdrawn from medication prior to commencing ketamine, and in which they were treated within a routine clinical setting.

The results suggest that ketamine does not cause memory deficits when given on up to six occasions. Confidence in this conclusion is enhanced by the fact that the two measures of autobiographical memory function and a measure of episodic memory function concur, as does an assessment of subjective memory. Although there is a possibility of practice effects influencing the AFT and story recall tasks, both assessments have previously been shown not to result in learning bias in similar study designs (Cunje et al., 2007). Comparison with the memory deficits associated with ECT is instructive. Objective deficits in autobiographical memory on the AMI-SF are described following ECT and can be permanent, typically reducing recall to a mean of 78.4% of baseline (Kershaw, 2010). This level of deficit was seen in only 2/22 in the current study of ketamine (median 92–94%). Whilst this lack of memory deficit is reassuring, higher frequency, higher doses or longer duration of ketamine infusions could potentially cause cognitive problems. However, the doses known to be associated with cognitive impairment are typically daily administration of grams of street ketamine (Morgan and Curran, 2006). Sensitive subjective measures of memory impairment are likely to be adequate for screening for this possibility in future studies.

We found that the ketamine infusions could safely be given in this setting but were not always well tolerated. Amongst the acute side effects, the most important included a single patient who experienced a marked vasovagal episode lasting 10 minutes. Of unknown significance was that this patient was the only patient treated who was ethnically Chinese. Two patients experienced marked anxiety and two vomited during the infusions. Three of these four elected to continue the course but none were responders. Patients commonly, but not invariably, experienced dissociative side-effects. These were generally well tolerated. The lack of relation between these acute effects and the response on mood measures suggests that it is unlikely that patients will continue to be motivated to receive ketamine because of a euphoriant effect.

Our study included patients with bipolar as well as unipolar depression. The observation that short term ketamine treatment may be associated with subsequent mood instability, whilst possibly just due to the natural history in difficult-to-treat patients, is a reminder that these patients require continued contact after the course has finished. Both up- and down-swings in mood were observed. Similar to others (Price et al., 2009), we also observed a rapid reduction in suicidal ideation. Whilst the potential utility of ketamine in situations where rapid reduction in suicidality is of high importance (Larkin and Beautrais, 2011) merits exploration, we would caution that in three patients there was an increase in suicidal ideation during the three weeks of treatment. These patients were prone to fluctuations in suicide ideation prior to beginning treatment. One of these increases in suicidal intent was directly linked to the acute loss of hope and disappointment resulting from the lack of antidepressant response to the ketamine treatment. Although not reported in this series, our subsequent experience (in preparation) has highlighted the importance of the known risk of a window of increased risk of suicidal behaviour that can occur as patients with severe depression recover.

The study adds to the growing literature showing the dramatic antidepressant effect ketamine can have on patients with TRD. In this small sample, at the end of the treatment course on day 21 (4–7 days after the final infusion) 14% of this severely depressed, treatment resistant sample remitted, with 29% reaching response criteria. This is exactly the same as the 29% response rate found three days after a single ketamine infusion in a review of five RCTs (Aan het Rot et al., 2012) but lower than that seen at 3 and 7 days (60% and 46%, respectively) after a single infusion in a recent trial of 72 TRD patients (Murrough et al., 2013). Indeed, the rate we observed was closer to that of the active comparator in the latter (e.g. 21.5% at 3 days) (Murrough et al., 2013). Although direct comparison with the randomised STAR*D trial is not possible, it is worth noting the lower and slower response rate in STAR*D for comparable patients who had failed two previous trials of antidepressants (16.8% response after 6.4 weeks on a third antidepressant) (Rush et al., 2006). Following the first ketamine infusion we found a lower rate of response (11%) than that found in the current literature, comparable to that of a saline placebo (7%) (Aan het Rot et al., 2012). However, in the 29% classed as eventual responders, a response had developed in all cases before the third infusion. If replicated in other samples taking antidepressants, the finding would imply that a trial of at least two infusions would be required to establish responsiveness in those who are continuing their antidepressants.

The main issue facing clinicians who are considering using ketamine for TRD is the limited duration of response usually observed following infusions, and the lack of available maintenance strategies (Aan het Rot et al., 2012). We observed a longer response time amongst responders (median 70, range 25–168 days) than previous studies administering both single and multiple infusions, possibly because patients in our study remained on their antidepressants. Two recent studies into the antidepressant effect of multiple ketamine infusions observed a median time to relapse of 19 days following six infusions, with one patient remaining well for over 3 months (Aan het Rot et al., 2010), and a median time to relapse of 18 days following five infusions over 2 weeks (Murrough et al., 2013a). In both these studies patients

were medication free before entering the trial and the majority remained so until relapse.

The limitations of this study are the lack of a control group and the open label nature of the trial. The design of our study means that the possibility that our results could be explained by a placebo effect was not addressed. There is no substitute for well controlled, randomised studies with careful attention to longer term outcomes and the timing of acute and sub-acute relapse rates. The heterogeneity of patients and of concurrent medication enhances generalisability, but reduces confidence in any of the conclusions. This preliminary observational study was not powered to detect differences between 3 and 6 infusions.

In summary, this case series suggests that ketamine infusions in treatment resistant depression can be given safely to patients who remain on antidepressants, but that they can occasionally cause marked acute anxiety, vomiting and vasovagal episodes. Potential problems regarding cognitive function were not realised. The ECT clinic appeared to offer an appropriate level of acute monitoring and supervision for initial infusions. Ketamine has complex effects on suicidality, and may cause mood instability which requires careful monitoring. Our experience raises the possibilities that its dramatic and useful antidepressant effect may require at least two infusions to become apparent and last longer if taken with other antidepressants, but clearly more work is needed to confirm this.

Acknowledgements

We thank all the staff of the ECT suite where this research was conducted, the R & D team, Professor Paul Harrison and Professor Guy Goodwin for their support and advice throughout the study, and Dr Digby Queded and Dr Peter Sargent for their role on the steering committee. We would also like to thank Dr Kerry Kershaw for her advice on the psychometric instrumentation used to assess memory performance. We thank referees of previous versions for their helpful comments.

Author note

This article presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. A subset of this data was presented in poster format in July 2011 for the BAP summer meeting. It was also presented in poster format at Imperial College London in June 2013 for the one day seminar “A discussion on scientific research with psychedelic drugs”.

Conflict of interest

The authors declare no conflict of interest.

Funding

This work was funded by the NIHR under its RfPB Programme (grant number PB-PG-0408-16030).

References

- Aan het Rot M, Collins KA, Murrough JW, et al. (2010) Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry* 67: 139–145.

- Aan het Rot M, Zarate CA Jr, Charney DS, et al. (2012) Ketamine for depression: where do we go from here? *Biol Psychiatry* 72: 537–547
- Beck AT and Beamesderfer A (1974) Assessment of depression: the depression inventory. *Mod Probl Pharmacopsychiatry* 7: 151–169.
- Berman RM, Cappiello A, Anand A, et al. (2000) Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 47: 351–354.
- Cunje A, Molloy DW, Standish TI, et al. (2007) Alternate forms of logical memory and verbal fluency tasks for repeated testing in early cognitive changes. *Int Psychogeriatr* 19: 65–75.
- DiazGranados N, Ibrahim L, Brutsche NE, et al. (2010) A randomized add-on trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 67: 793–802.
- Dritschel BH, Williams JM, Baddeley AD, et al. (1992) Autobiographical fluency: a method for the study of personal memory. *Mem Cognit* 20: 133–140.
- First M, Anthony JC, Tepper S, et al. (1997): *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/NP, Research Version, Non-patient Edition)*. New York: New York State Psychiatric Institute.
- Hamilton M (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23: 56–62.
- Kershaw KF (2010) *The effects of depression and electroconvulsive therapy on autobiographical memory and cognitive function*. PhD Thesis. Goldsmiths, University of London, UK.
- Larkin GL and Beautrais AL (2011) A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int J Clin Neuropsych* 14: 1127–1131.
- Lisanby SH, Maddox JH, Prudic J, et al. (2000) The effects of electroconvulsive therapy on memory of autobiographical and public events. *Arch Gen Psychiatry* 57: 581–590.
- McElhiney M, Moody B and Sackeim H (1997) *The Autobiographical Memory Interview—Short Form*. New York: New York State Psychiatric Institute.
- Morgan CJA and Curran HV (2006): Acute and chronic effects of ketamine upon human memory: a review. *Psychopharmacology* 188: 408–424.
- Murrough JW, Iosifescu DV, Chang LC, et al. (2013) Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry* 170: 1134–1142.
- Murrough JW, Perez AM, Pillemer S, et al. (2013a) Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry* 74: 250–256.
- Overall JE and Gorham DR (1962) The Brief Psychiatric Rating Scale. *Psychol Rep* 10: 799–812.
- Powell JH, Pickering AD, Wyke M, et al. (1993): The effects of three anti-hypertensive medications on learning and memory. *Br J Pharmacol* 35: 105–113.
- Price RB, Nock MK, Charney DS, et al. (2009) Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry* 66: 522–526.
- Rush A, Trivedi M, Wisniewski S, et al. (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 163: 1905–1917.
- Sackeim HA (2001) The definition and meaning of treatment-resistant depression. *J Clin Psych* 62(16): 10–17.
- Valentine GW, Mason GF, Gomez R, et al. (2011) The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [(1)H]-MRS. *Psychiatry Res Neuroimaging* 191: 122–127.
- Zarate CA Jr, Brutsche NE, Ibrahim L, et al. (2012) Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry* 71: 939–946.
- Zarate CA Jr, Singh JB, Carlson PJ, et al. (2006) A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 63: 856–864.