Cognitive behavior therapy may sustain antidepressant effects of intravenous ketamine in treatment-resistant depression

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Abstract

Introduction—Ketamine has shown rapid though short-lived antidepressant effects. The possibility of concerning neurobiological changes following repeated exposure to the drug motivate the development of strategies that obviate or minimize the need for longer-term treatment with ketamine. In this open-label trial, we investigated whether cognitive behavioral therapy (CBT) can sustain or extend ketamine's antidepressant effects.

Methods—Patients who were pursuing ketamine infusion therapy for treatment-resistant depression (TRD) were invited to participate in the study. If enrolled, the subjects initiated a 12-session, 10-week course of CBT concurrently with a short 4-treatment, 2-week course of intravenous ketamine (0.5mg/kg infused over 40 mins) provided under a standardized clinical protocol.

Results—Sixteen participants initiated the protocol, with 8 (50%) attaining a response to the ketamine and 7 (43.8%) achieving remission during the first two weeks of protocol. Among ketamine responders, the relapse rate at the end of the CBT course (8 weeks following the last ketamine exposure) was 25% (2/8). On longer-term follow up, 5 of 8 subjects eventually relapsed, the median time-to-relapse being 12 weeks following ketamine exposure. Among ketamine remitters, 3 of 7 retained remission until at least 4 weeks following the last ketamine exposure, with 2 retaining remission through 8 weeks following ketamine exposure. Ketamine non-responders did not appear to benefit from CBT.

Conclusions—CBT may sustain the antidepressant effects of ketamine in TRD. Well-powered randomized controlled trials are warranted to further investigate this treatment combination as a way to sustain ketamine's antidepressant effects.

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Keywords

Cognitive behavior therapy; major depressive disorder; relapse; treatment-resistant depression; cognition; ketamine

Introduction

Several small trials have shown that ketamine is capable of producing rapid antidepressant effects in both unipolar and bipolar depression [1-5]. Unfortunately, these effects are time-limited, even following cessation of repeated administrations [1, 2, 5-7]. As animal models and studies of ketamine abusers demonstrate concerning structural and functional brain changes associated with prolonged ketamine exposure [8, 9], identifying adjunctive/maintenance strategies could be of great value in limiting the duration and number of ketamine treatments necessary to maintain clinical benefit.

In contrast to studies suggesting long-term ketamine exposure negatively impacts cognition [10, 11], limited exposure may enhance cognitive abilities or at least resolve depression-related cognitive impairment in the short-term [12]. Sub-anesthetic doses of ketamine has been shown to induce neuroplastic changes [13, 14] over periods of hours to days following exposure in rodent models. Evidence suggests that ketamine may also enhance synaptic potentiation in humans [15]. Therefore, it may be possible to exploit this critical period of induced plasticity to initiate attempts at modifying cognitions and behaviors that require synaptic plasticity.

In light of existing data showing Cognitive Behavioral Therapy (CBT) to be highly effective in relapse prevention for depression [16-18] and in line with the sequential model [19], we conducted an open-label study to explore the efficacy and feasibility of combining CBT and intravenous ketamine infusions for TRD. We were interested in (1) whether CBT can prolong the antidepressant effects of ketamine in patients who respond to ketamine and (2) whether concurrent CBT improves outcomes in patients who do not have an initial robust response to ketamine. As one of the primary goals of CBT is to learn non-pathological thought patterns, we further speculated that severely depressed patients may be able to more meaningfully engage in CBT shortly following exposure to ketamine, given the drug's purported cognitive enhancing effects. Hence we investigated the effects of ketamine on cognitive performance as a secondary aim.

Methods

Participants and Procedure

Subjects ages 18-65 with Major Depressive Disorder were recruited from patients presenting for ketamine treatment at our institution. All subjects signed informed consent and the protocol was approved by the Yale IRB and registered on www.clinicaltrials.gov (NCT02289248). This openlabel trial consisted of two phases. During phase one (ketamine/CBT phase), eligible subjects underwent 4 intravenous ketamine infusions (twice weekly for two weeks, based on previous work [5]) as part of clinical care and were concurrently provided CBT under the research protocol (Figure S1). Participants were not

required to respond during the first phase prior to receiving CBT. The CBT was started 24-48 hours following the first ketamine infusion and was provided twice weekly during the first phase (concurrent with the ketamine but on separate days). Thereafter, during the second phase (CBT only phase), CBT was provided weekly for an additional 8 weeks (12 total sessions). Responders were followed for up to 3 months after study end. Concomitant psychotropic medications were not controlled. Ketamine infusions were delivered at 0.5mg/kg over 40 minutes (based on ideal body weight if BMI   30). Further details of the protocol are found in the online supplement.

Cognitive Behavioral Therapy

The CBT was based on Beck's model and focused on (1) psychoeducation, (2) cognitive restructuring, and (3) behavioral activation/modification. The therapy was delivered by therapists (MFK, LF) who received extensive training and certification at the Beck Institute for Cognitive Therapy, have 10 or more years of experience with CBT, and experience with prior CBT studies [20-22]. Homework included "Thought Records" and "Activity Charts" to help facilitate the adoption and internalization of CBT principles.

Depression Assessments

Depression severity was assessed at every visit using the Montgomery-Asberg Depression Rating Scale (MADRS) [23] and the Quick Inventory of Depression Symptomatology Self Report (QIDS-SR$_{16}$) [24]. Response was defined as   50% in MADRS score from baseline and remission was defined as a MADRS   9. Relapse was defined as an increase in MADRS scores to < 50% reduction of baseline scores for 2 consecutive weeks [6].

Cognitive Assessments

To explore ketamine's delayed effects on cognition, participants underwent repeated cognitive testing, examining attention, working and visual memory, processing speed, and verbal memory (www.cogstate.com) [25]. Further details of the cognitive assessments are found in the online supplement.

Data Analytic Method

Data analysis followed strategies of a similar protocol [6]. Changes between two time-points for depression severity were calculated using paired t-tests. Time-to-relapse among responders was calculated using the Kaplan-Meier method. Survival analyses were performed for all patients who received at least one CBT session. A general linear mixed-model analysis was used to compare cognitive measures over time within subjects, using changes in depression severity over time as a covariate. Further details of the analytic approach are found in the supplement.

Results

Demographic and Baseline Clinical Variables

Among the 16 subjects who initiated the protocol (Figure S2), the mean age was 42.7 (SD 13.7) and the mean number of years of education was 16.3 (SD 2.4). Most were female

(75%) and Caucasian (93.8%). Most participants (68.8%) had a history of hospitalization, a melancholic depression subtype (68.8%), and a substantial minority (37.5%) had a history of ECT. Ketamine responders had lower baseline MADRS scores compared to non-responders (29.6 v. 33.9, t=2.34, p=0.035), however baseline QIDS-SR[16] scores were not different between responders and non-responders (19.9 v. 19.4, t=-0.169, p=0.869). Ketamine responders and non-responders did not differ in other clinical or demographic variables (Table 1). Details of subject retention are found in the online supplement.

Clinical Response and Remission to Ketamine

Of the total sample, 8 (50%) subjects achieved response, while 7 (43.8%) achieved remission. Among those who achieved response, most (6/8, 75%) did so after the initial infusion, while the others responded following the fourth infusion. Among those who remitted, four (57.1%) did so after the first infusion, two did so following the second infusion, and one did so following the fourth infusion.

Among ketamine responders, MADRS gains were generally maintained, with significant differences compared to baseline at all time points throughout the study, even when using a conservative LOCF approach (Figure S3A). A similar pattern emerged as assessed by the QIDSSR$_{16}$ (Figure S3B). Ketamine non-responders showed significant improvements during the first three weeks of the protocol but then showed no difference compared to baseline following week 3 (Figure S3A).

Relapse and Retention of Remission

Among responders, 2 (25%) had relapsed by 8 weeks following the last infusion (Figure 1). On longer-term follow-up, the median time to relapse was 12 weeks. Among the 7 ketamine remitters, 3 had retained remission until at least 4 weeks following the final ketamine infusion and 2 had retained remission by 8 weeks following last infusion (study end), though 5/7 had retained a response at this time point.

Cognition

There were no differences between ketamine responders and non-responders in cognition measures at baseline (data not shown). After adjusting for changes in depression severity, there was a significant effect of time on cognitive measures in working memory (one-back [t=2.65, p=0.008] and two-back [t=2.02, p=0.043] tasks) and visual memory (t=3.73, p<0.001) through the two weeks of ketamine infusions (Figure S4). There was a slowing in processing speed over time (t= -2.93, p=0.003). There were no other significant trends over time in other domains. Details regarding concomitant medications and adverse events can be found in the online supplement.

Discussion

This is the first study examining the ability of CBT to sustain the antidepressant effects of ketamine as well as the first study to examine longer-term outcomes in a substantial cohort of ketamine treated TRD participants. Our sample was comprised of severely ill treatment-seeking patients, the majority of whom had chronic and melancholic (68.8%) forms of

depression, many who had previously received ECT (38.8%). Compared to previous reports [6, 26], this study found CBT may be effective in extending the duration of the ketamine antidepressant response. While most participants eventually relapsed, the majority did so following completion of the weekly CBT, suggesting a sustained antidepressant response with ongoing CBT. Given the concerns of repeated ketamine exposure, the relapse prevention strategy of the current study shows promise and warrants further study.

The initial clinical response and remission rates are comparable to prior studies [6, 26, 27]. Despite the open-label nature of our study, our relapse rate of 25% at 8 weeks following last ketamine infusion compares very favorably to the results of similar open-label protocols, where relapse rates at 4 weeks or earlier following 6 infusions range from 55-89% [6, 7, 26]. The median time-to-relapse in this study (12 weeks) also compares favorably to other studies explicitly designed to examine relapse pharmacotherapeutic prevention strategies where the median time-to-relapse measures were 17 and 24 days [28, 29]. Vande Voort et al. showed that the antidepressant effects of ketamine could also be extended in early remitters by repeated exposures at weekly intervals. In this study, most (4/5) remitters lost remission status at 4 weeks following the discontinuation of ketamine but all retained response at that time point; longer-term outcomes were not reported [27]. In our protocol, of 7 remitters, 3 retained remission by 4 weeks post-ketamine and 2 retained remission 8 weeks post-ketamine.

As noted, most of the ketamine responders relapsed following the conclusion of the weekly CBT phase of the study. Given that all subjects were treatment-resistant and had recurrent forms of MDD, it is possible that a longer course of CBT may have been more effective at modifying negative core beliefs and thus producing a longer relapse-free period post-ketamine. Additionally, a longer course of ketamine infusions may also contribute to longer relapse-free periods. Longer courses of both ketamine treatments and CBT should be considered in future studies. Future work with larger sample sizes should also include analyses of baseline predictors of the likelihood of experiencing adverse events as a consequence of this treatment approach [30]. Our small sample size precludes meaningful analyses of subgroups of patients most likely to benefit versus those who would incur harmful adverse events of this approach.

The results of our cognitive assessments were mixed. The improvements seen in working and visual memory replicated those from a prior study [31], though our study showed these effects over a shorter time period (24-72 hours v. 3 weeks) and survived adjustment for changes in depression severity. However, we observed an unexpected decline in processing speed over time, which is in contrast with prior research [31, 32]. This potential decline may underscore concerns in the field that repeated exposure to ketamine may produce adverse neurocognitive changes [33] and serves to emphasize the urgency for strategies to maintain wellness without continued exposure to the drug and the pressing need for research on the safety of longer-term exposure to ketamine [34]. Our small sample size, however, precludes firm conclusions of the effects of ketamine on processing speed.

Several limitations of our study require comment. First, our findings are limited by the small sample size and open-label design. Second, the lack of a control group makes it difficult to

interpret whether the antidepressant sustaining effects of psychotherapy were specific to CBT or were due to non-specific supportive effects. Additionally, the lack of control group makes it difficult to interpret whether cognitive changes were due to a specific effect of ketamine or only the result of practice effects. Third, given that concomitant medications were not controlled, it is possible that any sustained antidepressant effects were due to effects of medication changes; however, the fact that very few of the ketamine responders (25%) made changes to antidepressants during the trial argues against this explanation. Finally, administering ketamine concurrently with CBT may have confounded whether the response was specific to ketamine or was due to the combination of the two treatments; however, the relatively rapid nature of response seen in this study was more characteristic of ketamine than CBT.

Conclusions

Given the concerns of repeated exposure to ketamine, CBT may provide an effective treatment strategy to sustain ketamine's antidepressant effects. Well-powered, randomized trials are warranted to investigate whether this treatment strategy produces sustained effects and minimizes the exposure to ketamine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Depression-free survival using open label CBT following IV ketamine (n=8 responders)
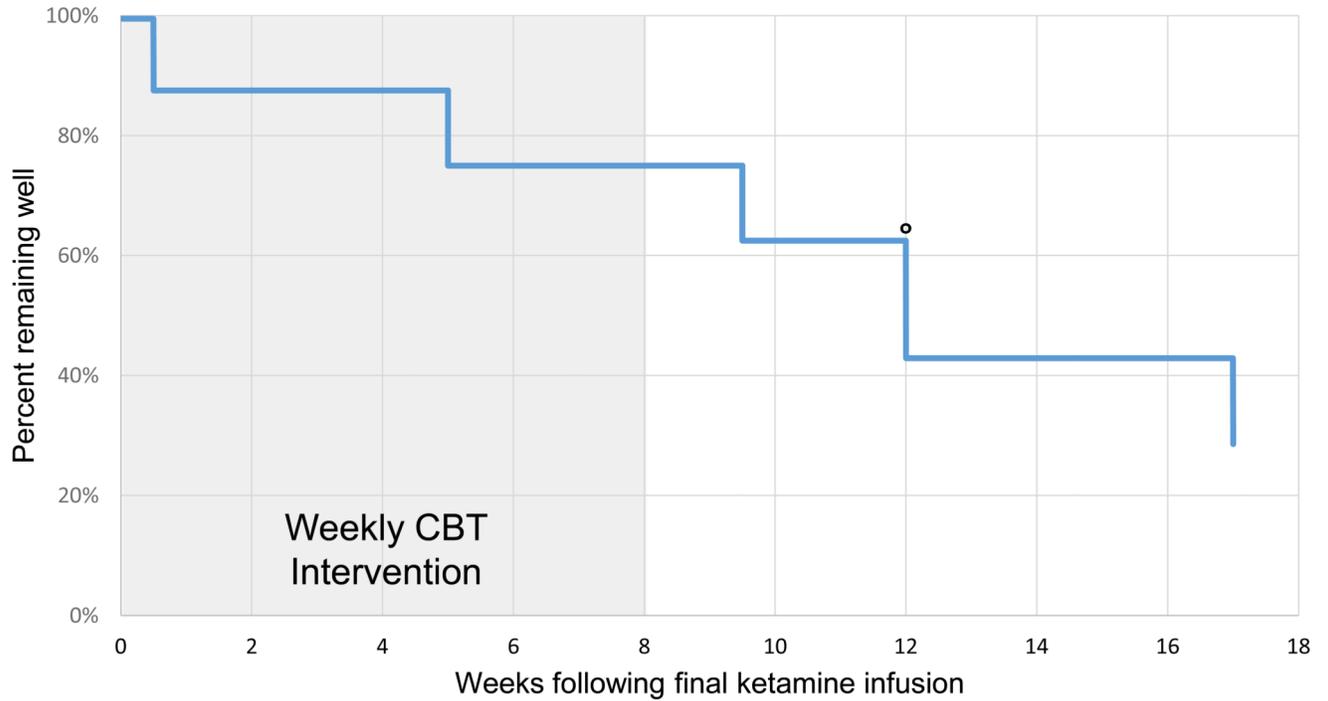

Figure 1.
Depression-free survival in responders with CBT following 4 ketamine infusions. CBT continued for 8 weeks following the final ketamine infusion.

Table 1

Demographic and clinical characteristics of participants

	Overall Sample (n=16)	Responders (n=8)	Non Responders (n=8)	
Demographic Variables		Mean/N (SD/%)		p value
Age, years	42.7 (13.7)	47.8 (11.6)	37.6 (14.5)	0.146
Male	4 (25)	2 (25)	2 (25)	1.000
Marital Status				0.158
Married	5 (31.3)	3 (60)	2 (40)	
Single	6 (37.5)	1 (16.7)	5 (83.3)	
Divorced	2 (12.5)	2 (100)	0 (0)	
Cohabitating	3 (18.8)	2 (66.7)	1 (33.3)	
Education, years	16.3 (2.4)	16.1 (2.1)	15.6 (2.1)	0.644
Clinical Variables				
Age of Onset of MDD, years	16.6 (3.76)	16.4 (3.78)	16.9 (4.02)	0.815
History of ECT	6 (37.5)	4 (50)	2 (25)	0.334
History of hospitalization	10 (62.5)	4 (50)	7 (87.5)	0.106
Melancholic subtype of MDD	11 (68.8)	5	6	0.590
Current episode length, months	46.7 (75.6)	68.1 (100.8)	20.1 (13.2)	0.203
Failed antidepressant trials, current episode	2.64 (1.98)	2.75 (2.60)	2.29 (0.95)	0.664
MADRS, Baseline	31.8 (4.14)	29.6 (3.62)	33.9 (3.64)	0.035
QIDS, Baseline	19.6 (5.76)	19.9 (5.96)	19.4 (5.95)	0.869
Baseline concomitant medications				
Antidepressant	9 (56.3)	4 (50)	5 (62.5)	0.642
Antipsychotic	7 (43.8)	2 (25)	5 (62.5)	0.149
Mood stabilizer	4 (25)	2 (25)	2(25)	1.000

MDD – Major depressive disorder, ECT – electroconvulsive therapy, MADRS – Montgomery-Asberg Depression Rating Scale, QIDS – Quick Inventory of Depressive Symptomatology. Two-sample t tests and chi square tests were used to compare continuous or categorical variables, respectively.