Effects of intranasal (*S*)-ketamine on Veterans with co-morbid treatment-resistant depression and PTSD: A retrospective case series

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Summary

Background (*S*)-ketamine is a glutamatergic drug with potent and rapid acting effects for the treatment of depression. Little is known about the effectiveness of intranasal (*S*)-ketamine for treating patients with comorbid depression and post-traumatic stress disorder (PTSD).

Methods We performed a retrospective case series analysis of clinical outcomes in 35 Veterans with co-morbid depression and PTSD who were treated with intranasal (*S*)-ketamine treatments at the VA San Diego Neuromodulation Clinic between Jan 2020 and March 2021. Veterans were not randomized or blinded to treatment. The primary outcome measured was a change in patient health questionnaire-9 (PHQ-9) and PTSD Checklist for DSM-5 (PCL-5) scores across the first 8 treatments (induction period) using a repeated measures analysis of variance (ANOVA). In a smaller sub-group (n = 19) of Veterans who received at least 8 additional treatments, we analyzed whether intranasal (*S*)-ketamine continued to show treatment effects. Finally, we performed a sub-group and correlation analyses to understand how changes in PHQ-9 and PCL-5 scores were related across treatments.

Findings During the induction phase of treatment there was an absolute reduction of 5.1 (SEM 0.7) on the patient health questionnaire-9 (PHQ-9) rating scale for depression, from 19.8 (SEM 0.7) at treatment 1 to 14.7 (SEM 0.8) at treatment 8 (week 4) ($F(7238) = 8.3$, p = 1e-6, partial η^2 = 0.2). Five Veterans (14%) showed a clinically meaningful response (50% reduction in PHQ-9 score) at treatment 8. There was an absolute reduction of 15.5 +/- 2.4 on the patient checklist 5 (PCL-5) rating scale for PTSD, from 54.8 (SEM 2) at treatment 1 down to 39.3 (SEM 2.5) at treatment 8 ($F(7238) = 15.5$, p = 2e-7, partial η^2 = 0.31). Sixteen Veterans (46%) showed a clinically meaningful response (reduction in PCL-5 of > 30%) in PTSD. Change in PHQ-9 correlated with change in PCL-5 at treatment 8 (r = 0.47, p = 0.005), but a decrease in PTSD symptoms were observable in some individuals with minimal anti-depressant response.

Interpretations While this is an open-label retrospective analysis, our results indicate that both depression and PTSD symptoms in Veterans with dual-diagnoses may improve with repeated intranasal (*S*)-ketamine treatment. The effects of (*S*)-ketamine on PTSD symptoms were temporally and individually distinct from those on depression, suggesting potentially different modes of action on the two disorders. This work may warrant formal randomized controlled studies on the effects of intranasal (*S*)-ketamine for individuals with co-morbid MDD and PTSD.

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Introduction

Post-traumatic stress disorder (PTSD) has a lifetime prevalence in Veterans of 15–20% or more.[1,2] Despite the disabling nature of PTSD and its relatively high rate of occurrence in Veterans, treatment options are limited.[3] Trauma-focused psychotherapy has high empirical support, but is often limited by tolerability and early treatment termination in clinical practice.[4,5] Response rates to selective serotonin reuptake inhibitors (SSRIs)

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Research in context

Evidence before this study

Different formulations of ketamine, including intranasal (*S*)-ketamine, have shown efficacy for the treatment of major depressive disorder. Recent placebo-controlled randomized clinical trials have been performed to evaluate the efficacy of IV ketamine for post-trauamatic-stress-disorder (PTSD) as well. Some of these have shown positive results and while others have not. There have been randomized clinical trials documenting efficacy of intranasal (*S*)-ketamine for PTSD symptoms to date.

Added value of this study

To address the lack of knowledge of the effects of intranasal (*S*)-ketamine on PTSD symptoms, we performed a retrospective analysis of clinical outcomes in Veterans treated at one clinic. We observed significant reductions in both depression (as measured using the PHQ-9 self-report scale) and PTSD symptoms (as measured using the Patient-Checklist-5, or PCL-5 self-report scale). These results, while not performed in the context of an RCT, lend support to further study of intranasal (*S*)-ketamine for the treatment of PTSD.

Implications of all evidence available

At present, intranasal (*S*)-ketamine is approved for treatment-resistant-depression (TRD). Our data suggests that it has value in treating co-morbid PTSD symptoms in individuals with TRD, with both symptom domains improving over time in some individuals.

in patients with PTSD rarely exceed 60% and only about 20–30% achieve complete remission of their symptoms,[6,7] resulting in many patients being prescribed complex pharmacologic regimens.[7–9] Further complicating PTSD treatment is comorbidity with depression. Epidemiological studies indicate more than half of US Military Veterans with PTSD also meet criteria for Major Depressive Disorder (MDD),[10,11] which can make adequate treatment of both conditions more challenging.[12–14] While distinct disorders, they do share considerable phenomenological and diagnostic overlap including changes in mood, anhedonia, guilt, sleep disturbance, and difficulty concentrating.[15] In addition, recent structural equation (SEM) models leveraging large genome wide association studies (GWAS) indicate a roughly 0.40 genetic correlation between MDD and PTSD.[16] Research also indicates this comorbidity increases risk of psychosocial role impairment, chronic health problems, suicidality, and decreased quality of life relative to either disorder alone.[17] Taken together, this research indicates sizable etiological and phenomenological overlap, suggesting that treatments with good efficacy for treating one disorder may show common/overlapping benefits for the other – particularly in the negative mood and cognition as well as the arousal and reactivity sub-domains of PTSD symptoms.[18]

Racemic (R,S)-Ketamine has been utilized for decades as a rapid acting, dissociative anesthetic.[19] In the early 2000s, intravenous racemic (R,S)-ketamine was discovered to have rapid antidepressant effects at sub-anesthetic doses.[20] Since then, numerous randomized controlled trials have replicated the antidepressant effects of various formulations of ketamine.[21–25] Given the overlap in diagnostic domains noted above, intravenous racemic ketamine has been studied in both open-label and randomized trials for possible effectiveness in PTSD.[26–31] An early, randomized, double-blind crossover study of 41 civilian patients observed a significant reduction in PTSD symptoms 24 h after a single infusion of ketamine (0.5 mg/kg) compared with IV administration of midazolam.[27] A follow-up study, using six repeated infusions of either ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) in civilians,[28] showed a greater decrease in Clinician Administered PTSD Scale for DSM-5 (CAPS-5) scores in patients who received ketamine compared to those who received midazolam. Of participants in the IV ketamine group, 67% were treatment responders (> 30% improvement in CAPS5 scores), compared with only 20% in the midazolam group. Individuals receiving ketamine showed a significant improvement in depression symptoms, measured using the Montgomery-Åsberg Depression Rating Scale (MADRS).

The relevance of these results in civilians to Veterans is tempered by a recent large, multi-center placebo-controlled study investigating the efficacy of 8 bi-weekly treatments over 4 weeks of either low (0.2 mg/kg) or standard dose (0.5 mg/kg) IV ketamine in Veterans or active-duty service members with PTSD. In this trial, an inactive placebo was compared with a low (0.2 mg/kg) and standard (0.5 mg/kg) dose of IV (R,S)-ketamine.[29] The primary endpoint of this trial (a significant effect of treatment group x time on PTSD scores) was negative, indicating that the groups receiving ketamine did not separate significantly from the placebo arm. However, post-hoc tests revealed that subjects receiving the lower dose of IV ketamine (0.2 mg/kg) may have separated more from placebo at the long-term (4 week) time point on PCL-5, CAPS-5, and MADRS.[29] While preliminary, it is thus possible that lower-doses of ketamine, over longer time-periods, may be required to see a significant effect on PTSD symptoms in Veterans.

In recent years an intranasal formulation of the (*S*)-enantiomer of ketamine was shown to be moderately effective for treatment resistant depression (TRD, generally defined as failure to respond to at least two different antidepressant trials).[24,25,32,33] Based on these studies, intranasal (*S*)-ketamine was FDA-approved to be used for TRD, and an effort was made to offer this treatment at various VA facilities. To date, no randomized study has been published measuring the effects of

intranasal (*S*)-ketamine in patients with comorbid depression and PTSD. Intranasal (*S*)-ketamine differs from standard IV racemic ketamine in two important ways. First, important differences at both molecular and systems-levels have been described for the (S) and (R) enantiomers suggesting possibly differential modes of action.[34–36] Second, the pharmacodynamics of intranasal dosing is clearly different compared to standard IV dosing.[37] For these reasons, we retrospectively analyzed clinical outcomes in 35 Veterans with co-morbid depression and PTSD symptoms treated with intranasal (*S*)-ketamine at the San Diego VA Medical Center. All Veterans included in this analysis had both MDD and PTSD as determined by clinical diagnosis and elevated scores on both symptom scales (> 15 for PHQ-9, > 33 for PCL-5). Though this study was neither randomized nor blinded, we were interested in understanding whether intranasal (*S*)-ketamine improved either depression or PTSD symptoms.

Gender	25 M, 10F
Age	45.4 +/- 10 (yrs)
Treatment Severity / Refractoriness	
# adequate antidepressants	2.7 +/−1.5
Duration illness	15.5 +/- 7.9 (yrs)
Hospitalizations	2.2 +/- 4 (yrs)
Suicide Attempts	1.3 +/- 1.9
History of ECT	8(23%)
History of rTMS	5 (14%)
Pre-treatment PHQ-9	19.6 +/- 4
Pre-treatment PCL-5	54.4 +/- 12
Co-Morbid Diagnoses	
Axis II	4 (11%)
Bipolar Spectrum	13 (37%)
Chronic Pain	25 (71%)
Tobacco	18 (51%)
Marijuana	9 (26%)

***Table 1*: Patient information. Veterans (*n* = 35) included in this analysis, who received at least two doses of (*S*)-ketamine treatment. Data reported as *n* (%), or as mean +/- standard deviation.**

Methods

Data reported following STROBE guidelines.

Veterans included in analysis

This study was approved as an institutional review board (IRB)-exemption by the VA San Diego Medical Center IRB committee. We conducted a chart review of patients referred to the VA San Diego neuromodulation program who, after consultation, were deemed appropriate for a trial of (*S*)-ketamine. Veterans were included for analysis in this analysis if they were administered at least two doses of (*S*)-ketamine within our clinic between the dates of Jan 2020 and March 2021, had a comorbid diagnosis of depression and PTSD (established on the basis of prior diagnoses in the chart, during the initial consultation by the clinician, or with an elevated PCL-5 score measured at base-line > 33), and for whom we had base-line PHQ-9/PCL-5 scores prior to their first treatment. Veterans who had previous trials of ketamine or (*S*)-ketamine prior to coming to our clinic were excluded from this analysis in order to prevent potential bias or expectation from prior exposure to ketamine (either positive or negative) in treatment outcomes. Data from 35 Veterans was included in this analysis (see Table 1) for more details.

All Veterans were initially referred to the VA San Diego neuromodulation program by their primary psychiatrists for an evaluation and recommendations for patients withTRD. Possible treatments that could be offered were repetitive transcranial magnetic stimulation (rTMS), intranasal (*S*)-ketamine or electroconvulsive therapy (ECT). After consultation, physicians in the program made a joint decision with the Veteran about which of the above treatments would be most appropriate to try. Veterans included in this retrospective analysis may thus have been started on (*S*)-ketamine upon initial referral to this program or could have been switched to (*S*)-ketamine after first trying, and not responding adequately to rTMS and/or ECT. Eligibility criteria for (*S*)-ketamine generally required a failure of at least 2 antidepressants within the past 5 years and a PHQ-9 score of at least 15 at the time of initial consultation. Exclusion criteria included the absence of serious medical contra-indications, such as (known aneurysmal vascular disease, intracranial hemorrhage, history of seizures, recent delirium, cardiac decompensation, severe hepatic disease, cystitis), comorbid psychosis, neurocognitive disorder, or active/history of abuse of ketamine. (*S*)-ketamine dosing in the San Diego VA (*S*)-ketamine clinic is generally performed twice/week for 4 weeks (a total of 8 treatments) during the induction phase. (*S*)-ketamine was always started at 56 mg at the first treatment, with flexible dosing increases or decreases on subsequent treatments based on tolerability and efficacy. By the 8th treatment (i.e., end of induction), one Veteran was taking the lowest dose (28 mg), two were taking the medium dose (56 mg), while the rest were on the maximum dose (84 mg). Veterans who chose to continue receiving (*S*)-ketamine after 8 treatments were then transitioned to once/week or less frequent dosing.

Assessments

All data analyzed in this manuscript were gathered during normal clinical care. Veterans were administered a Patient Health Questionnaire-9 (PHQ-9) to track depression and a Patient Check List-5 (PCL-5) to track PTSD symptoms prior to each treatment within the

clinic. Treatment 1 (T1) scores reflect the patient's baseline PHQ-9/PCL-5 scores immediately before their first (*S*)-ketamine dose, and Treatment 8 (T8) scores reflect symptoms immediately before their 8th (*S*)-ketamine induction dose. The PHQ-9 was first developed and validated as a tool for screening for depression in primary care settings, but has been tested and validated in both psychiatric populations more generally[38] and as a tool to measure depression-related symptoms at the VA.[39] While it would have been optimal to validate these measures of self-report with a clinically administered, rather than self-report scale, we did not collect such data in a standardized method that facilitates chart review. The PCL-5, a DSM-V updated version of the PCL, is one of the most widely used self-reported measures of post-traumatic-stress disorder. It has been validated for use in Veterans,[40] and is often deployed clinically within the VA system as an easy measure of PTSD severity. In the DSM-5, PTSD has been broken into 4 clusters or sub-domains of symptomatology.[41] This includes cluster B (re-experiencing symptoms), which includes nightmares, intrusive thoughts/memoires, flashbacks and strong arousal; cluster C (avoidance symptoms), which includes avoidance of thoughts/memories and feelings associated with the traumatic event; Cluster D (mood and cognition symptoms), i.e. persistent negative beliefs about oneself, distorted cognitions, detachment and estrangement, negative emotional state and inability to experience positive emotions; and, Cluster E (hyperarousal symptoms), i.e. hypervigilance, reckless, exaggerated startle response and sleep/concentration problems.[41] In addition to the summary PCL-5 score, we also analyzed and reported changes in cluster scores.

We performed a chart review to gather auxiliary data that included age, gender, years in mental health treatment (based on first mental health treatment note in the VA records), number of suicide attempts and number of hospitalizations. We reviewed medical record diagnosis codes, along with Neuromodulation clinician's initial consultation note, to determine diagnostic history including Axis II diagnosis, Unipolar v Bipolar Depression, diagnosis of PTSD, the presence of chronic pain, alcohol, tobacco and substance use disorders. We also reviewed treatment history including past trials of (*S*)-ketamine/IV ketamine, ECT and history of adequate/inadequate antidepressant trials (as defined by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire), using data from the chart to fill in details. Data used had been documented within the patient chart within the last 5 years, accessible via CPRS, the VA electronic medical record system.

Statistical analyses

We focused on two primary outcomes of interest: whether there was a significant change in either the PHQ-9 or the PCL-5 summary score across the treatment induction phase (treatments 1 through 8). To analyze this, we performed a repeated-measures Analysis of Variance (rmANOVA) test with scores prior to each treatment (from 1 through 8) entered into the model as the repeated measure. There were a total of 25 missing PHQ-9 values and 81 missing PCL-5 values across the first 8 treatments. Following recent recommendations,[42] based on the pattern of missing data we observed, multiple imputation would be the recommended approach for handling missing data. We tested both single-imputation (last-observation-carried-forward) and multiple-imputation (using a regression method implemented within the statistical software SPSS) and found generally similar results (at the level of significance, p-values, etc.) on the data reported here. For this reason, we report the multiple imputation results implemented using linear regression within SPSS.

Secondary outcomes

Treatment response. A reduction in PHQ-9 of 50% of greater was used to denote a meaningful clinical response in depression. A reduction of PCL-5 scores of 30% or greater was considered a meaningful clinical response in PTSD.

Maintenance of effect. To understand whether there was a maintenance of the antidepressant/anti-PTSD effects, we analyzed data from the 19 Veterans who continued treatment for at least an additional 8 sessions (i.e., Treatment 9 (T9) to Treatment 16 (T16)). We performed a repeated-measures ANOVA test on both the PHQ-9 and PCL-5 data from these Veterans. Missing data was handled using multiple imputation (linear regression) within SPSS.

PTSD cluster sub-scores. We analyzed changes across treatments in the 4 symptom domains/clusters of PTSD symptomatology, as noted above, using a repeated-measures-ANOVA model. These are represented within the PCL-5 weekly as cluster sub-scores.

Relationship between change in PHQ-9 and PCL-5. We performed a linear regression between the percentage change in PHQ-9 ([T1 − T8]/T1) and the percentage change in PCL-5 scores ([T1 − T8]/T1). We performed a similar correlation between this and percentage changes in the PCL-5 sub-scores as well.

Statistical analyses and reporting. For all ANOVA analyses reported here, we followed the following steps: (1) Normality of score distributions was tested prior to

performing further statistical testing using the Shapiro-Wilk test ($p > 0.05$ suggestive of normal distribution). (2) Greenhouse-Geisser correction was applied to p-values prior to interpretation in repeated-measures ANOVA models. (3) All ANOVA and linear regression models were interpreted using a significance level (alpha) of 0.05. (4) Bonferroni tests were applied to analyze and interpret post-hoc tests if the omnibus ANOVA model was significant. (5) For ANOVA models we report the following: the F-statistic (F), which represents the variance between sample means / variances within sample means; p-values, which represent the probability for a given statistical model that, if the null hypothesis is true, we would have observed the values observed. For regression models, we report the Pearson correlation value (r), which reflects the strength of the linear association between two variables, and p-values as noted above.

Role of funding. Funding provided time for investigators to work on data analyses and writing of manuscript.

Results

A summary of the base-line characteristics of Veterans included in this analysis is reported in Table 1. Patients who were given a trial of (*S*)-ketamine were all treatment resistant, judging by the average duration of treatment, antidepressant / electroconvulsive therapy (ECT) /repetitive Transcranial Magnetic Stimulation (rTMS) trials previously. Tobacco use disorder and chronic pain were the most common comorbidities in this patient population.

Effects of (*S*)-ketamine on depression symptoms

The induction phase of treatment involves 8 bi-weekly treatments delivered over 4 weeks. Using a repeated-measures ANOVA model for PHQ-9 scores across these treatments we observed a significant reduction in PHQ-9 over time (Figure 1A, F(7, 238) = 8.3, p = 1e-6, η^2 = 0.2). There was a mean/SEM reduction of 5.1 (SEM = 0.7) on PHQ-9 scores (post-hoc Bonferroni corrected p = 2e-6), from 19.8 (SEM = 0.7) at treatment 1 (T1) to 14.7 (SEM = 0.8) at treatment 8 (T8). By the eighth treatment, five Veterans (14%) showed a 50% reduction in the PHQ-9 score, and only 2 Veterans had achieved remission (PHQ9 < 5). However, 18 Veterans (51%) showed a reduction in PHQ-9 scores of greater than 6, a less strict metric for denoting clinically meaningful changes in symptoms. We next examined the time-course of these changes. Post-hoc tests revealed that a significant symptom reduction occurred after only one treatment; (mean-difference between Treatment 1 (T1) and Treatment 2 (T2) was 2.8 (SEM = 0.8, p = 0.04, Bonferroni corrected post-hoc test). Between T2 and T8, there was a non-significant reduction of 2.3 points on the PHQ-9 (SEM = 0.8, p = 0.28 Bonferroni corrected). After the initial 8 bi-weekly treatments, Veterans could continue with maintenance treatment (typically weekly or every other week) if they desired. During this maintenance phase, we included individuals (n = 19) who had data for both PHQ-9 and PCL-5 scales for an additional 8 treatments. In these Veterans, we observed stable effects over time (Figure 1B, F(7, 126) = 0.7, p = 0.6). PHQ-9 scores in this group changed from a mean of 15 (SEM = 1.1) at treatment 9 to a mean of 14.2 (SEM = 1.2) at treatment 16.

Effects of intranasal (*S*)-ketamine on PTSD symptoms

We next examined the effects of intranasal (*S*)-ketamine on PTSD symptoms by analyzing changes in the PCL-5 over time. A repeated measures analysis across time points demonstrated a significant effect of treatment on the overall PCL-5 score (F(7, 238) = 15.5, p < 2e-7, partial η^2 = 0.3). There was a mean reduction of 15.5 (SEM = 2.4) on the PCL total score, from 54.8 (SEM = 2) at treatment 1 to 39.3 (SEM = 2.9) at treatment 8 (Figure 1A, p-7e-6, Bonferroni corrected). A meaningful clinical response (> = 30% reduction in the PCL-5) was seen in 16/35 of these Veterans (46%) by the 8th treatment. Five Veterans (15%) dropped below the diagnostic cut-off score (< = 33) indicating remission. Changes in PTSD symptoms occurred slowly and progressively across treatments. There was a significant reduction of 5.5 points (SEM = 1.3) in the PCL-5 between treatment 1 and 2 (p = 0.005, Bonferroni corrected). PCL-5 scores continued to show a significant reduction with continued treatment. Even between treatments 4 and treatment 8, Veterans showed a mean 5 point (SEM 2) reduction in PCL-5 scores (p = 0.03, Bonferroni corrected). Moreover, there was a continued significant reduction in the PCL-5 scores during the maintenance period as well, from a mean of 39.3 points (SEM 3.2) to a mean of 33.2 (points SEM 2.9) (Figure 1B, F(7, 126) = 2.7, p = 0.03, partial η^2 = 0.13). By the 16th treatment, 12 Veterans (34% of the total that initially started treatment), had achieved remission in PTSD (PCL-5 scores < = 33). We next analyzed the PCL-5 sub-scales by symptom cluster. Significant treatment effects were observed across all sub-domains of PTSD (Figure 2A −D) including a mean 3.6 (SEM 0.7) point reduction in Cluster B (intrusion/re-experiencing symptoms, F(7, 238) = 7.9, p = 3.5e-5), a mean 1.6 (SEM 0.4) point reduction in Cluster C (avoidance symptoms, F(7, 238) = 6.6, p = 0.0007), a mean 6.5 point reduction in Cluster D (mood and cognition symptoms, F(7, 238) = 18.3, p = 3e-8) and a mean 5 point reduction in Cluster E (arousal symptoms, F(7, 238) = 14, P = 2e-8).

Relationship between PTSD and depression responses

To examine the relationships between improvements in PTSD and depression symptoms, we performed a linear

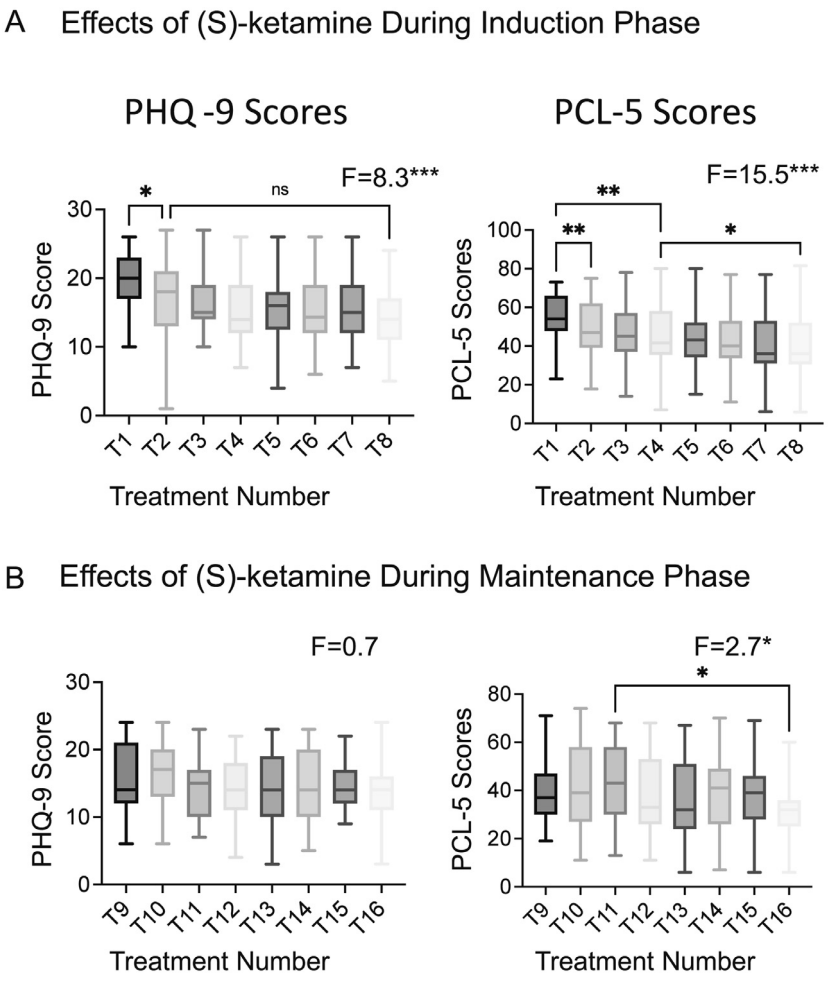

Figure 1. Effects of Esketamine on Depression and PTSD. A. The induction phase of treatment consisted of 8 treatments delivered twice/week. A repeated-measures ANOVA was performed was performed for both PHQ-9 and PCL-5 scales across these treatments ($n = 35$). We observed a significant effect of intranasal (*S*)-ketamine on both PHQ-9 scores and PCL-5 scores across treatments. Post-hoc Bonferroni tests (corrected for all treatment comparisons) revealed a significant reduction in scores was observed after the first treatment session ($p < 0.05$) for both PHQ-9 and PCL-5. PHQ-9 scores did not show significant improvements after the second treatment. PCL-5 scores showed continued improvement over time (with improvements observed as late as between the 4th and last treatment).

B. After induction, subjects who continued treatment were transitioned to a weekly or every other week schedule for maintenance. We collected PHQ-9/PCL-5 scores from 19 subjects for an additional 8 maintenance treatment sessions. PHQ-9 scores did not show a significant improvement during this time period. PCL-5 scores showed a continued improvement during the maintenance period ($p < 0.05$).

Box and whisker plots show the minimum score, first (lower) quartile, median, third (upper) quartile, and maximum score. *$p < 0.05$; **$p < 0.01$, ***$p < 0.001$.

regression between the percentage change in each Veteran's PHQ-9 score [(T1 − T8)/T1] with the percentage change in their PCL-5 scores [(T1 − T8)/T1]. These changes in the PHQ-9 and PCL-5 scores was significantly positively correlated (Figure 3A, $r = 0.47$, $p = 0.005$). We next measured how changes in PHQ-9 correlated with changes in each of the Cluster scores measured on the PCL-5. We found a significant correlation between percent change in PHQ-9 scores and percent changes in the re-experiencing scores (Cluster B, $r = 0.36$, $p = 0.035$) and in the mood/cognition scores (Cluster D, $r = 0.4$, $p = 0.018$). Correlation values between percent change in the PHQ-9 and percent change in the avoidance ($r = 0.1$, $p = 0.6$), and arousal ($r = 0.16$, $p = 0.4$) clusters were non-significant.

Despite the overall significant correlation between the percentage change in PHQ-9 and percentage change in PCL-5 with treatment, we noted that several individuals showed a meaningful reduction in PCL-5 scores with only a minimal antidepressant response (i.e., a small reduction in PHQ-9). To better illustrate this point, we categorized Veterans based on the degree

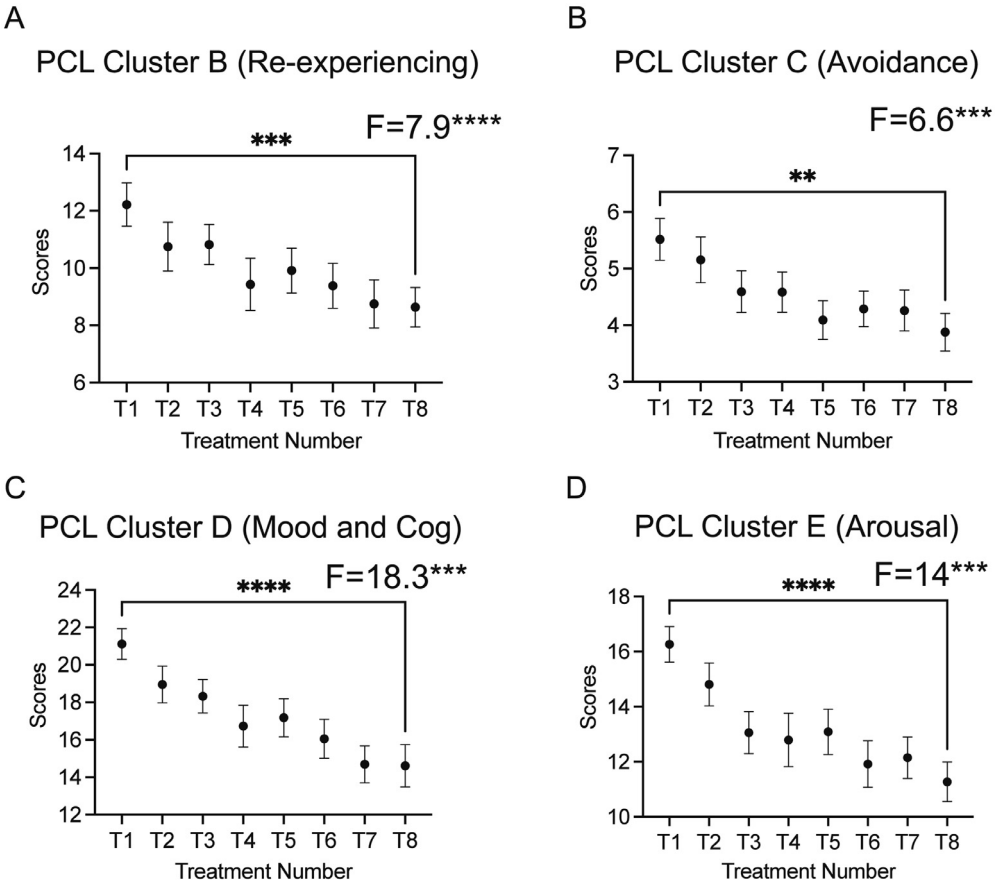

Figure 2. Effects of Esketamine on PTSD Sub-domains.

The PCL-5 has sub-scores related to the 4 major clusters of symptoms in PTSD. We analyzed changes in each sub-score using a repeated-measures ANOVA across treatments, followed by a Bonferroni post-hoc test for significant differences between treatments. Significant effects were observed across all 4 cluster sub-scores. Plots show mean +/- SEM. *$p < 0.05$; **$p < 0.01$, ***$p < 0.001$. ****$p < 0.0001$.

of anti-depressant response that occurred during between treatments 1 and 8: a large antidepressant response (a reduction of PHQ-9 by > = 50% by treatment 8, $n = 5$); medium antidepressant response (reduction in PHQ-9 of 20–50%, $n = 16$), or a small antidepressant response (< 20% reduction in PHQ-9, $n = 14$), and evaluated changes on PCL-5 scores in each of these groups. Surprisingly, we observed a significant reduction in PCL-5 scores even in individuals with small/non-significant antidepressant responses. These individuals showed a mean 11.2 (SEM = 3.6) point reduction in PCL-5 scores (one-sample *t*-test, t(13) = 3.1, $p = 0.008$, compared to the null hypothesis of no change) from T1 to T8 (Figure 3B). This change was comparable to participants with a medium antidepressant response, who showed a mean 12.5 (SEM = 2.2) reduction in PCL-5 scores, (one-sample *t*-test, t(15) = 5.8, $p = 4e\text{-}5$). Participants with a large antidepressant response group did show a large reduction in PCL-5 symptoms (mean/SEM = 36.7 (SEM = 6.1) points, one sample *t*-test, t(4) = 4.3, $p = 0.004$). While there was a significant difference between the three groups in the change in PCL-5 scores (overall ANOVA between the three groups, F(2, 34) = 10.1, $p = 0.0004$), this was driven solely by the large changes in the large anti-depressant group. The small/medium anti-depressant groups did not show any difference in the magnitude of their reduction in PCl-5 scores (mean difference = 1.4 (SEM 4.1), $p = 1$, Bonferroni corrected).

Discussion

In Veterans with comorbid depression and PTSD, we observed a significant reduction in both PHQ-9 and PCL-5 scores during the initial 8 treatment induction period of intranasal (*S*)-ketamine treatment. The effects observed on the PHQ-9 are similar, though of a smaller magnitude, to what has been previously observed in randomized control trials (RCTs).[24,25] In a previous RCT of intranasal (*S*)-ketamine,[43] 85% of the subjects who

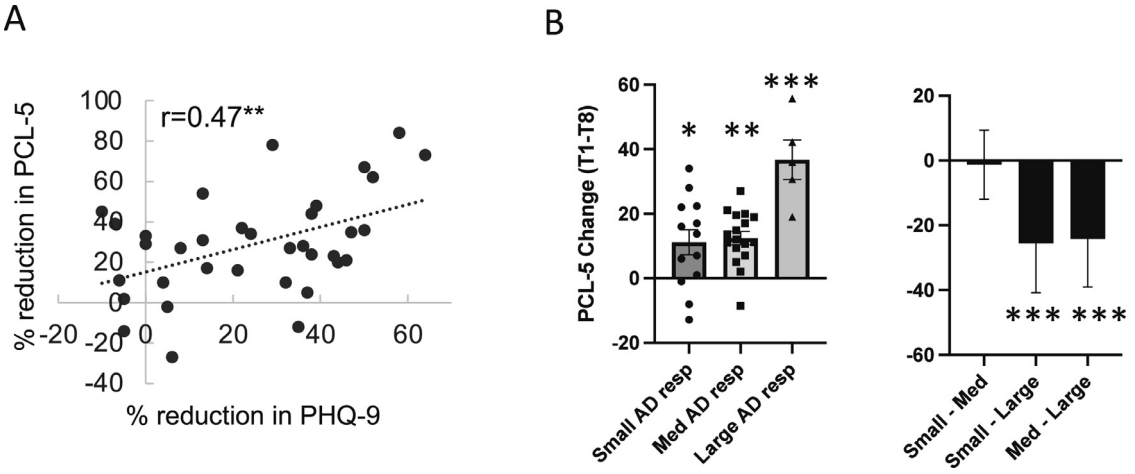

Figure 3. Decoupling of Depression and PTSD. (A) Significant correlation between %reduction in PHQ-9 scores ([T1-T8]/T1) and % reduction in PCL-5 scores ([T1-T8]/T1. Despite a significant correlation, we observed that some Veterans received a meaningful reduction in PCL-5 scores (with a very limited reduction in PHQ-9 scores. (B) To further understand this, we split Veterans into three groups based on their antidepressant response: large (> 50% reduction in PHQ-9, n = 6), medium (20−50% reduction in PHQ-9, n = 13) and small (< 20% reduction in PHQ-9, n = 16). All groups showed a significant reduction in PCL-5 scores. Moreover, there was no difference in the reduction in PCL-5 scores comparing the small/medium antidepressant response groups. Bar plots show mean +/- SEM. *$p < 0.05$; **$p < 0.01$, ***$p < 0.001$.

received treatment showed a change of at least 6 points in the PHQ-9 whereas we found here 51% of Veterans we administered treatment to showed that level of change. This replicates a common finding that Veterans often have lower response rates to antidepressant medications compared to non-Veteran populations,[44] and may also be related to greater treatment-resistance in our naturalistic cohort compared to those recruited for a clinical trial. Interestingly, and somewhat surprisingly, we found a larger effect size in the overall reduction in PCL-5 scores, a higher percentage of Veterans classified as responders and with remission of symptoms for PTSD compared to depression. In addition, while there was a significant correlation between changes in PCL-5 and PHQ-9 scores across treatments, there were also meaningful differences in how these two symptom clusters changed. PHQ-9 symptoms generally show a rapid response (after the first/second treatments) followed by relative stability. By contrast, we observed a steady drop in PCL-5 symptoms across treatments that continued even through the maintenance period. Additionally, we found that some individuals showing a significant reduction in PCL-5 scores evidenced only a minimal change in PHQ-9 scores.

There are important qualifications to these results. First, and most importantly, this is a retrospective analysis of outcome data from a clinical program and thus randomization and blinding were not used. As such, we cannot determine whether outcomes described above were driven by non-specific factors of treatment (repeated visits to the clinic, supportive environment, expectation / placebo effects, etc.) versus actual pharmacologic effects. Next, it is possible that the effects of intranasal (*S*)-ketamine on PTSD symptoms we observed may not be related to a direct pharmacologic effect on brain circuits involved in PTSD. In particular, it is possible that the modest reduction in depression symptoms that occurred early in treatment precipitated a set of behavioral or life-style changes that resulted in a delayed improvement in PTSD symptoms that unfolded over time. This scenario would suggest that our results are specific to those with co-morbid MDD and PTSD, and may not generalize to individuals with only a PTSD diagnosis.

There are several hypotheses regarding how racemic ketamine (and by proxy (*S*)-ketamine) acts as an antidepressant.[45] Initial theories of how ketamine promotes rapid antidepressant actions were focused on action on N-Methyl-D-Aspartate (NMDA) receptors.[23] However, other NMDA antagonists have failed to find an effect for depression,[23] resulting in other potential molecular targets that could explain ketamine's rapid efficacy, including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor modulation by a metabolite of (*R*)-ketamine,[35,36,46] action on mu-opioid receptors[47–50] and intracellular effects on brain derived neurotrophic factor (BDNF) / mammalian target of rapamycin (mTOR) / methyl-CpG binding protein 2 (MeCP2) signal cascades.[51,52] The ketamine metabolite, hydroxynorketamine, has also been found to have anti-inflammatory effects, which may provide another pathway for improving symptoms.[53] Ketamine has also been found to lead to rapid electrophysiological changes including increased gamma power, perhaps a proxy of its effects on glutamatergic signaling.[54,55] Finally, the effects of ketamine may depend on modulating synaptic

plasticity in prefrontal neurons[56] and/or changing activity within the lateral habenula.[50,57] Which of these effects are mediated by (*R*)-ketamine and which by (*S*)-ketamine are still being worked out, and further research is needed.[34,36,58] It is even less clear which of these mechanisms may be helpful for improving symptoms of PTSD. Ketamine has been shown to accelerate fear extinction and reconsolidation.[59,60] From a phenomenological perspective, qualitative data acquired from Veterans receiving treatment in our clinic has indicated what many described as an "uncoupling' or "loosening" of the emotional salience to traumatic memories and painful thoughts during the acute effects of ketamine. The perceived emotion-cognition uncoupling may have served to interrupt maladaptive patterns of rumination and avoidance providing veterans the opportunity to evaluate, process/reframe, and reintegrate thoughts and memories more objectively and effectively.

It is currently unclear to what degree intranasal (*S*)-ketamine may be more or less effective than IV (R,S)-ketamine for PTSD symptoms in particular. The bioavailability of intranasal ketamine has been estimated to be between 30 and 50% of IV formulations. While not obvious, it is possible that this lower effective dose is more beneficial for PTSD symptoms than a higher dose that is traditionally used in IV formulations. Notably, in the recently reported negative trial of IV ketamine for PTSD symptoms in Veterans/active service members,[29] the lower dose of IV ketamine (0.2 mg/kg) showed a larger response and slightly delayed response at the end of 6 treatments than the higher dose. Thus, even in light of their report of negative primary outcome, our work argues for a reassessment of effects on Veterans with more severe PTSD co-occurring with depression, and potentially for a larger RCT on the effects of (*S*)-ketamine in the treatment resistant Veteran population. Finally, we found that PTSD symptoms may take longer to respond than those of depression suggesting longer trial designs may be needed to maximize power to see an effect in individuals with PTSD.

Declaration of interests

The views expressed here are our own and do not represent the opinion of the VA.

Contributors

HA, SB, EM, FL, KS, AB, DP, EL, BM, SDP, DGB, JM, DR... aided in design and collection of the data, conceptualized the key analyses that should be performed and / or aided in interpretation of the data. HA, SB, EM, FL AB, EL, DGB, JM and DR... co-wrote manuscript. All authors revised manuscript and gave final approval for publication. DR... accessed and takes full responsibility for the set of raw data associated with this study.

Data sharing statement

De-identified data used for analyses will be shared on request.

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