Psychopharmacology
https://doi.org/10.1007/s00213-021-05939-z

ORIGINAL INVESTIGATION

Age affects temporal response, but not durability, to serial ketamine infusions for treatment refractory depression

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Received: 7 December 2020 / Accepted: 14 July 2021

Abstract

Rationale Ketamine is a novel, rapid-acting antidepressant for treatment refractory depression (TRD); however, clinical durability is poor and treatment response trajectories vary. Little is known about which patient characteristics predict faster or more durable ketamine responses. Ketamine's antidepressant mechanism may involve modulation of glutamatergic signaling and long-term potentiation (LTP); these neuroplasticity pathways are also attenuated with older age.

Objective A retrospective analysis examining the impact of patient age on the speed and durability of ketamine's antidepressant effects in 49 veterans receiving serial intravenous ketamine infusions for TRD.

Method The relationship between age and percent change in Beck Depression Inventory (BDI-II) scores was compared across six serial ketamine infusions (twice-weekly for 3 weeks) using a linear-mixed model.

Results A significant Age-X-Infusion number interaction ($F = 3.01$, $p = .0274$) indicated that the relationship between age and treatment response depended on infusion number. Follow-up tests showed that younger age significantly predicted greater clinical improvement at infusion #4 ($t = 3.02$, $p = .004$); this relationship was attenuated at infusion #5 ($t = 1.95$, $p = .057$) and was absent at infusion #6. Age was not a significant predictor of treatment durability, defined as percent change in BDI-II 3 weeks following infusion #6.

Conclusions These data preliminarily suggest that younger age is associated with a faster response over six serial ketamine infusions; by infusion #6 and subsequent weeks of clinical follow-up, age no longer predicts ketamine's antidepressant activity. Age may mediate the speed but not the durability or total efficacy of ketamine treatment, suggesting that dissociable mechanisms may underlie differing aspects of ketamine's antidepressant activity.

Keywords Ketamine · Psychopharmacology · Geropsychiatry · Aging · Depression

Introduction

Treatment-refractory depression (TRD), commonly defined as failure to respond to at least 2 antidepressant trials of adequate dose and duration, affects up to one-third of patients with major depressive disorder (MDD) and is associated with greater rates of relapse, prolonged disability, higher medical costs, and lower life quality then treatment-responsive MDD (Dunner et al. 2006; Fekadu et al. 2009; Judd et al. 2000).

The dissociative anesthetic ketamine has garnered increasing enthusiasm as a highly effective and rapidly acting antidepressant with a novel mechanism of action (Monteggia and Zarate 2015; Sanacora et al. 2017). A single sub-anesthetic infusion of ketamine results in significant reductions in depressive symptoms in 40 to 80% of TRD patients within 3 to 72 h of treatment (Fava et al. 2020; Zarate et al. 2006). However, these impressive antidepressant effects are ephemeral with a majority of patients fully relapsing within 1 week of treatment (Berman et al. 2000; Zarate et al. 2006). While providing multiple infusions in series can prolong treatment

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Published online: 07 August 2021

efficacy to an extent (Murrough et al. 2013; Shiroma et al. 2014), antidepressant durability remains a significant limitation of ketamine therapy as a treatment modality. Furthermore, the parameter space of ketamine delivery for MDD (i.e., optimizing dosing, number of treatments, treatment interval, etc.) has been largely unexplored (Sanacora et al. 2017), with most multi-infusion studies examining the effects of six serial ketamine infusions (Murrough et al. 2013; Shiroma et al. 2014; Singh et al. 2016). Among other important directions, a more complete understanding of the individual factors that moderate treatment response is a critical step towards improving, optimizing, and ultimately personalizing ketamine therapy for TRD.

Ketamine's rapid and highly effective antidepressant action is unique amongst existing antidepressant therapies. While ketamine's precise mechanism of action is unclear, current research supports the likely importance of its action as an inhibitor of the *N*-methyl-D-aspartate receptor (NMDAR) (Cornwell et al. 2012; Muthukumaraswamy et al. 2015; Newport et al. 2015; Sanacora et al. 2008), which is necessary for glutamatergic signaling, long-term potentiation (LTP), and neuroplasticity (Citri and Malenka 2008). Impairments in LTP and NMDAR functioning are increasingly recognized as a potential common pathophysiological mechanism for numerous psychiatric disorders including schizophrenia, anxiety disorders, addiction, and mood disorders, including MDD (Cantone et al. 2017; Citri and Malenka 2008).

Numerous lines of preclinical and clinical evidence support impaired glutamatergic signaling, NMDAR functioning, and LTP in MDD (Sanacora et al. 2008). This glutamatergic view has challenged the classical "monoamine hypothesis" of MDD, in which reductions in monoamine neurotransmitter levels (e.g., serotonin, dopamine) are central to the pathophysiology of depression (and corrected by SSRI administration) (Cantone et al. 2017). Instead, derangements in glutamate signaling leading to attenuated LTP-based neuroplasticity in mood-regulation networks may represent a more fundamental, downstream pathophysiological mechanism, and therefore a more direct target for antidepressant therapeutics such as ketamine (Monteggia and Zarate 2015; Sanacora et al. 2008).

Age has been shown to be a moderating factor of response to numerous antidepressant treatments, including SSRIs and intranasal esketamine (Ochs-Ross et al. 2020; Whyte et al. 2004). Furthermore, advancing age has also been shown to attenuate LTP and related neural plasticity mechanisms in preclinical models (Lynch 1998), and these findings have been extended to humans, showing reduced cortical plasticity as measured by both motor-evoked potentials (Lynch 1998; Muller-Dahlhaus et al. 2008) and EEG-based measures (Porto et al. 2015; Spriggs et al. 2017). Ketamine also activates and upregulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, as well as synaptogenic signaling pathways (Aleksandrova et al. 2017). This is notable, given that AMPA receptor downregulation and decreased synaptogenesis are associated with aging(Henley and Wilkinson 2013).

Given the strong implication of LTP-like and associated glutamatergic signaling underlying ketamine's antidepressant mechanism, as well as evidence of age-related decline in neuroplasticity, we examined relationships between patient age and treatment response trajectories and response durability in a case-series retrospective analysis of 49 veterans with TRD treated with a series of six ketamine infusions at a VA medical center. Prior studies examining the impact of age on ketamine's antidepressant efficacy represent a modest literature mostly consisting of small case series and case reports with some conflicting results. Several, but not all (Szymkowicz et al. 2014), case series examining ketamine's efficacy in older patients report antidepressant efficacy similar to non-geriatric patients (Medeiros da Frota Ribeiro and Riva-Posse 2017; Srivastava et al. 2015; Wilkinson et al. 2018), and a small randomized-controlled trial of subcutaneous ketamine also demonstrated significant effects of ketamine in geriatric patients (George et al. 2017). However, the Transform-3 trial, a large multi-site RCT that assessed the efficacy of intranasal esketamine in patients over 65 with TRD, failed to show separation from placebo following 4 weeks of twice-weekly treatment, although post hoc analysis of patients between 65 and 74 did demonstrate efficacy at this time-point, suggesting possible effects of age on esketamine treatment response and/or response trajectory (Ochs-Ross et al. 2020).

Together, these data suggest that age may be an important factor to consider when using ketamine to treat TRD in older patients, but that additional studies are needed to fully explore this important issue. We therefore examined this question in our retrospective sample and hypothesized that age would be a significant predictor of treatment response in veterans with TRD receiving a course of six serial ketamine infusions; specifically, we used a mixed model analysis approach to assess whether age predicted treatment response, and also whether the hypothesized age-treatment response relationship depended on treatment number within the infusion series.

Methods

Participants and procedures

We examined retrospective treatment outcome data of 49 consecutive veterans treated with intravenous ketamine for TRD at the San Francisco VA Medical Center. Inclusion criteria included two or more failed antidepressant trials,

moderate-to-severe current depression severity, and ability to give informed consent to the clinical treatment; exclusion criteria included DSM-5 Psychotic Disorders or current or recent (within 30 days) substance use, other than cannabis. Patients received six infusions of ketamine (0.5 mg/kg over 40 min) twice weekly for 3 weeks in the post-operative care unit (PACU) of the San Francisco VA Medical Center. Patients with a body mass index (BMI) of > 30 kg/m^2 were dosed via their adjusted body weight (ideal body weight + 0.4 (actual body weight – ideal body weight) to account for differences in acute IV drug distribution in obese patients. The majority of patients received the 0.5 mg/kg dose for all 6 infusions. However, seven patients had their ketamine dose increased to 0.6 mg/kg ($n = 6$) or 0.7 mg/kg ($n = 1$) over the six infusion courses. Ketamine infusions were provided under the care of both an anesthesiologist and psychiatrist and with standard vital sign monitoring (heart rate, blood pressure, and oxygen saturation monitoring). Beck Depression Inventory-II (BDI-II) data were collected immediately prior to each infusion (e.g., BDI-II for infusion #1 was collected just prior to infusion #1, BDI-II score at infusion #2 was collected just prior to infusion #2, etc.).

Following the initial induction phase of six infusions, 36 of the 49 patients progressed to a maintenance phase of treatment consisting of one ketamine infusion every 3 weeks. Thirteen of the 49 patients in this case series did not follow up at the 3-week time point for booster infusion. Eight received their initial index treatment as inpatients and were lost to follow-up following discharge from the hospital and the remaining five elected not to continue with maintenance therapy following the initial six infusions for other reasons (e.g., logistical challenges, perceived lack of efficacy).

This case series study was approved by the University of California, San Francisco's Institutional Review Board (# 18–25,566).

Statistical analysis

Linear mixed model*:* To test our central hypothesis that trajectories of clinical response vary as a function of patient age, we employed a linear mixed model in SAS (v9.4), with BDI-II percentage change from baseline as the dependent variable, time (infusions #2–6) as a repeated measure, age as continuous covariate, and subject as a random factor. We considered compound symmetric, auto-regressive (AR-1), and unstructured covariance structures to account for the correlated nature of the BDI-II percent change repeated measure, with the final model selected based on best Bayesian Information Criteria (BIC) (Schwarz 1978). We first examined the main effect of time (with Tukey–Kramer adjusted follow-up comparisons), in order to characterize the clinical response trajectory of the entire cohort, over the infusion series. Next, our main effect of interest, the age × time interaction effect was parsed with planned follow-up tests assessing the relationship between BDI-II percent change and age at each time point. For all follow-up tests, type 1 error was controlled at $p < 0.05$, familywise.

Treatment durability: To investigate the antidepressant durability of the initial induction phase of six ketamine infusions, we also examined follow-up BDI-II data collected directly prior to the first maintenance infusion, which was 3 weeks following the final (sixth) of the initial infusion series (3-week follow-up). The durability of response to ketamine was assessed with a paired t-test examining the difference in BDI-II percent change from infusion #6 versus the change at 3-week follow-up (both relative to pre-infusion #1 BDI-II). Lastly, to further examine age effects in our data, age was correlated with the durability of treatment response.

Results

Demographic and clinical characteristics

The mean age of the patient cohort was 52.5 with a range from 24 to 77 years old. Forty-five of the 49 patients were diagnosed with treatment-resistant MDD and four patients with bipolar disorder, currently in a depressive episode. Treatment resistance was determined by chart review of the electronic medical record assessing number, efficacy, length, and dosing ranges for all antidepressant medication trials to ensure trials were of adequate dose and duration; per the clinic's protocol, all patients treated with ketamine were required to fail at least 2 antidepressant trials of adequate dose and duration. The patients were largely male (75%) and had a high rate (34%) of comorbid post-traumatic stress disorder (PTSD), consistent with patient demographics of the veteran population. The sample also had a high rate of treatment resistance, with 9.2 mean failed med trials and 35% having previously failed ECT. Adverse events were rare. One patient was given ondansetron and scopolamine secondary to nausea and vomiting. One patient did not finish the six-infusion series due to dysphoria during the treatment. Patient demographic information is summarized in Table 1.

Age effects on clinical response pattern and durability

For the final linear mixed model, an unstructured covariance matrix was selected, based on BIC (Schwarz 1978). The model revealed a significant age × time interaction effect ($F(4,47) = 3.01$, $p = 0.027$), a main effect of time ($F(4,47) = 3.49$, $p = 0.0142$) but no main effect of age ($F(1,47) = 3.04$, $p = 0.0876$). We first examined the main effect of time to establish the pattern of clinical treatment response across the entire sample, collapsed across age.

Table 1 Demographic and clinical data

Clinical data	Patients
n	49
Age (years; range 24 to 77)	52.6 ± 14.4 (SD)
Gender (% Male)	75 (37/49)
Comorbid PTSD (%)	34 (17/49)
Bipolar, diagnosis (%)	8.2 (4/49)
BDI-II score pre-ketamine	35.5 ± 11.3
BDI-II score at infusion #6	16.8 ± 11.7
# of prior antidepressant medication trials	9.2 ± 4.5
Prior ECT (%)	35 (17/49)
Concurrent medications (%)	
SRI (SSRI, SNRI)	46.8 (23)
TCA	8.2 (4)
Lithium	6.1 (3)
Lamotrigine	6.1 (3)
Benzodiazepine	34.7 (17)
Stimulant	14.3 (7)
Antipsychotic (augmentation)	51.0 (25)
Other AD (e.g., bupropion, mirtazapine)	38.8 (19)

Abbreviations: *AD*, antidepressant; *BDI-II*, Beck Depression Inventory version 2; *ECT*, electroconvulsive therapy; *PTSD*, post-traumatic stress disorder; *SD*, standard deviation; *SRI*, serotonin reuptake inhibitor; *SSRI*, selective serotonin reuptake inhibitor; *SNRI*, serotonin-norepinephrine reuptake inhibitor; *TCA*, tricyclic antidepressant

The BDI-II assessed at (i.e., just prior to) infusion #1 was used as the reference to calculate percent change scores with each subsequent infusion (i.e., percent change score for infusion #2 would represent the change score from infusion #2 to #1, thus reflecting the effects of a single infusion, and so on for the six-infusion series). The main effect of time across the infusion series was parsed with Tukey–Kramer adjusted follow-up comparisons. Figure 1 shows key comparisons of these BDI-II percent change scores, including significantly greater reduction at infusion #2 compared to infusion #1, and at infusion #6 compared to infusion #1, reflecting significant clinical response after both the first and final infusion (corrected $p < 0.001$).

Next, we examined the age × time interaction effect. Planned follow-up tests parsed the significant interaction effect by assessing the BDI-II percent change relationship with age at each time point. Scatter plots showing the relationship between percent change in BDI-II and age at each infusion are shown in Fig. 2A and statistical analyses from the mixed model are summarized in Table 2. There was a significant effect of age on BDI-II percent change at infusion #4 ($B = 0.88\% +/- 0.29\%$, $t = 3.02$, $p = 0.004$) and a trend towards significance at infusion #5 ($B = 0.62\% +/- 0.31\%$, $t = 1.95$, $p = 0.057$) with older patients showing less percent change (i.e., older age is associated with less reduction in depression severity at infusion #4). For example, a decade increase in age corresponds to a model predicted 8.8% less percent reduction in BDI-II score at infusion #4. Notably, there was no significant effect of age at infusion #6 ($B = 0.37\% +/- 0.3\%$, $t = 1.23$, $p = 0.225$) indicating that patient age did not affect the total antidepressant response to the infusion series. Example modeled estimates of BDI-II response trajectories by various ages representative of the sample are shown in Fig. 2B. BDI-II response trajectories plotted by age quartiles of the cohort are shown in Supplementary Information (Figure S1).

Additional models were run to consider effects of participant sex, body mass index, and variations in ketamine dose and produced the same pattern of effects suggesting

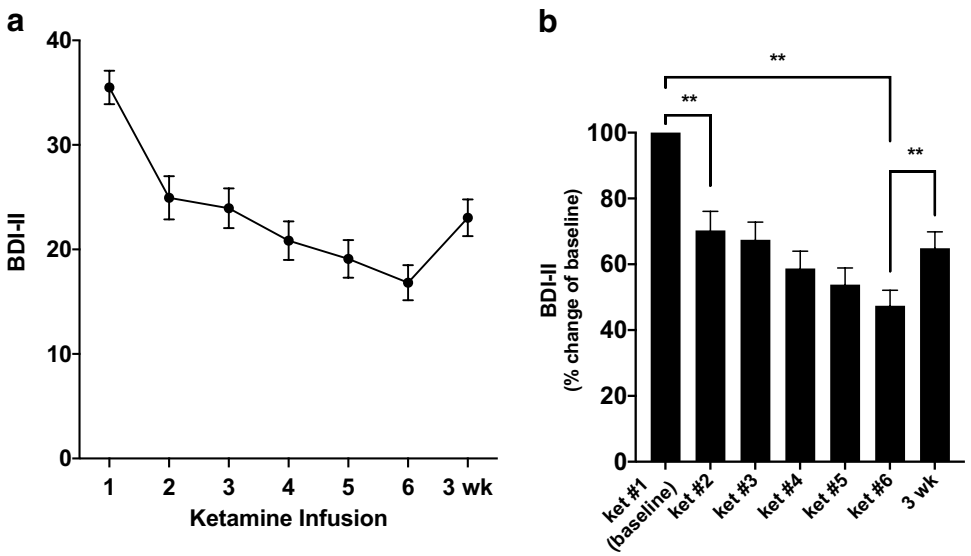

Fig. 1 Cohort-level clinical response trajectory to the series of six ketamine infusions. **A** Mean BDI-II scores collected prior to each ketamine infusion (#1–6) and at 3-week follow-up (3 wk). **B** Bar graphs of % change in BDI-II score (from ket#1/baseline) at each infusion (ket #2 through ket #6) and 3-week follow-up (3 wk). BDI-II scores: Ket #1: 35.5 +/− 1.6, Ket #2: 24.9 +/− 2.09, Ket #6:16.8 +/− 1.6, 3 wk: 23 +/− 1.7. Error bars: SEM. ** $p < 0.001$

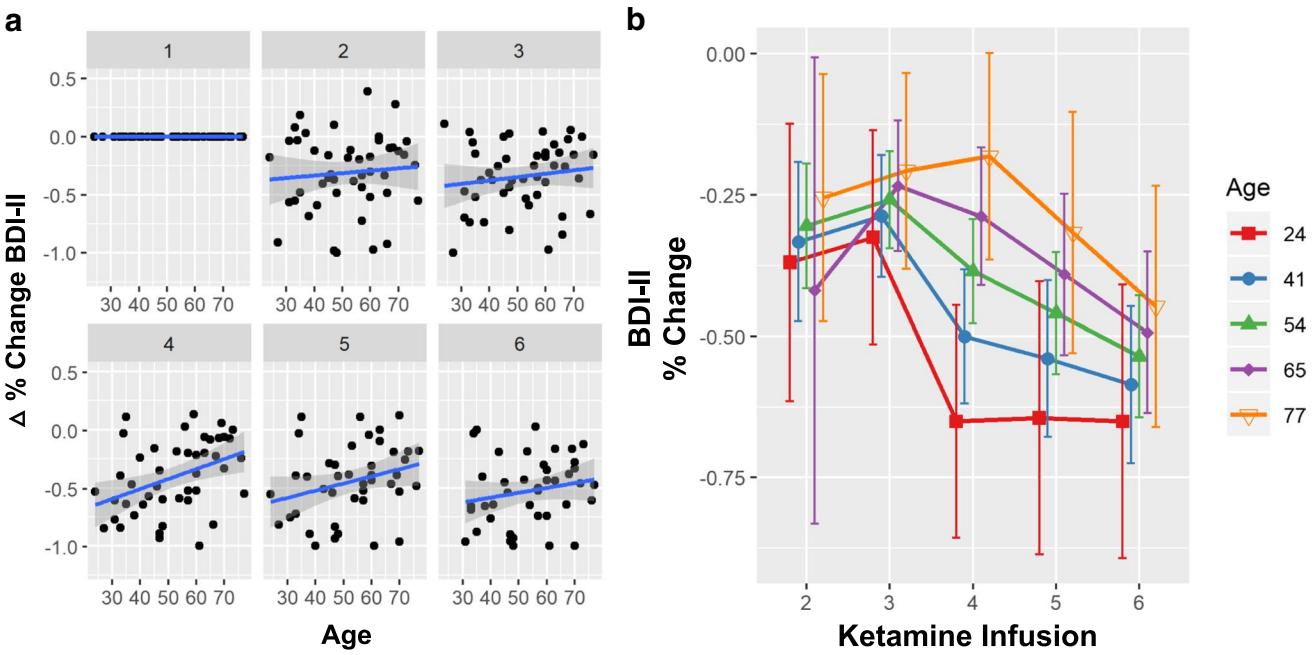

Fig. 2 Relationship between age and antidepressant response over six ketamine infusions. **A** Scatterplots of age × Δ percent change (decimated) in BDI-II from infusion #1 at each infusion (plots numbered 1 to 6). Blue shading: 95% confidence interval. Correlation at infusion #4: $p < 0.01$; correlation at infusions 2,3,5,6: *n.s.* **B** Sample response trajectories (% change in BDI-II (decimated)), as estimated by the linear mixed model, over the ketamine infusion series at select ages representing the minimum (24), maximum (77), and quartiles (41, 54, 65) of the patient cohort. Error bars: standard error. See Table 2 for statistical analysis

Table 2 Model estimates of effects of age on BDI-II percent change at each infusion

Estimates								
Label	**Estimate**	**SE**	**DF**	***t* value**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
1 year change in age at infusion 2	0.2225%	0.3745%	47	0.65	0.5163	0.05	−0.4620%	0.9071%
1 year change in age at infusion 3	0.2207%	0.5923%	47	0.37	0.7111	0.05	−0.9710%	1.4120%
1 year change in age at infusion 4	0.8861%	0.2929%	47	3.02	0.004	0.05	0.2968%	1.4750%
1 year change in age at infusion 5	0.6202%	0.3176%	47	1.95	0.0568	0.05	−0.0190%	1.2590%
1 year change in age at infusion 6	0.3745%	0.3049%	47	1.23	0.2254	0.05	−0.2390%	0.9878%

that the age × time effects observed were not driven by these factors (see Supplementary Information).

Treatment durability effects

In contrast to the significant age interaction effect observed across the six-infusion series, there was no significant correlation between change in BDI-II measured at ketamine infusion #6 to the BDI-II measurement at 3-week follow-up; (r (36) = 0.0005, $p = 0.997$), see Fig. 3. The lack of age relationship in treatment durability was observed in the context of a significant increase in BDI-II percent change, $t(35) = 3.55$, $p = 0.0011$ (reflecting a partial relapse in depression severity from infusion #6 to the 3-week-follow-up, see Fig. 1B). These data show that while at the cohort level there was a clinically relevant change in BDI-II from infusion #6 to the 3-week follow-up assessment, age had no effect on antidepressant durability measured 3 weeks following the completion of the infusion series.

Discussion

This retrospective analysis of the clinical response of 49 veterans receiving six serial ketamine infusions shows that older age moderated ketamine's antidepressant effects at infusion #4 (with a trend towards significance at infusion #5), but had no effect on the efficacy of infusions earlier or later in the treatment course, nor on antidepressant durability at a 3-week follow-up assessment. In sum, these

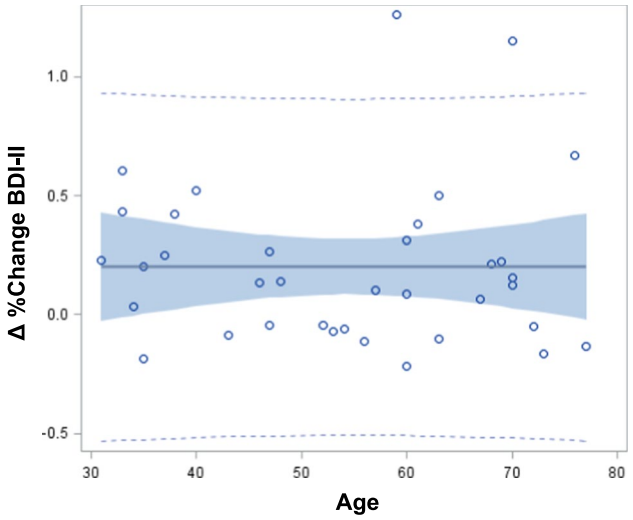

Fig. 3 Age effects on the durability of antidepressant response. Scatterplot of age × Δ percent change (decimated) in Beck Depression Inventory (BDI-II) from infusion #6 to 3-week follow-up (percent change at infusion # 6 from baseline − percent change at 3 weeks from baseline) representing the durability of the antidepressant response at 3 weeks following the completion of the infusion series. Blue shading: 95% confidence interval. Correlation n.s. ($p = 0.997$), $n = 36$

results suggest that age affects the trajectory of antidepressant response to serial ketamine infusions, such that older patients may respond later in the treatment course, but ultimately experience the same degree of improvement as younger patients following the completion of the six-infusion series. Elucidating this delayed-efficacy phenomenon in older patients receiving serial ketamine infusions for TRD has important implications for personalizing treatment as well as counseling patients appropriately concerning how quickly they can expect to receive benefit over the course of multi-infusion ketamine treatment.

Furthermore, these data reveal several interesting observations that could have implications concerning ketamine's mechanisms of action that may inform future mechanistic studies. Based on the trajectories of response described in this study, we propose three distinct response features to an index treatment of six serial ketamine infusions: early infusion responses, late infusion responses, and durability of response at a 3-week follow-up. Furthermore, we propose that the clinical phenomenology described here suggests that these three phases of response to ketamine may have distinct mechanisms.

Age had no effect on the clinical response to infusions early in the treatment series. It is of interest to note that ~ 30% of the total group clinical response to the six-infusion series occurred following ketamine infusion #1 (with the remaining response evolving more slowly over the subsequent infusions) (see Fig. 1A, B). This is both broadly consistent with the extensive literature examining the efficacy of a single ketamine infusion and with existing literature showing antidepressant response trajectories to a six-infusion series (Murrough et al. 2013; Shiroma et al. 2014; Singh et al. 2016). In contrast to prior studies, we found a negative correlation between patient BMI and antidepressant response to ketamine and this interaction did not impact or change the pattern of any other of our reported effects. However, it is important to note that prior work (Freeman et al. 2020; Niciu et al. 2014) demonstrating positive correlations between BMI and ketamine response did not use adjusted body weight in their dosing protocols, complicating comparisons to the current study. Furthermore, while age was shown to moderate the efficacy of intranasal esketamine (Ochs-Ross et al. 2020), a case series of serial ketamine infusions published by Wilkinson et al. in 54 patients failed to find an age × time interaction (Wilkinson et al. 2018). There were potentially significant demographic differences between the Wilkinson et al. cohort and our own that could explain the discrepant findings with respect to age as a treatment moderator, including our cohort being largely male, older, higher rates of comorbid PTSD as well as potentially higher degrees of treatment resistance. Another difference between the two studies is that the Wilkinson study examined patients treated with between one and four ketamine infusions, whereas our cohort received a six-infusion series. The different patient characteristics and treatment protocols may explain the discordant findings.

The fact that the first ketamine infusion drives ~ 30% of the total clinical response (i.e., percent change in BDI-II scores) in our cohort to the infusion series and that age only moderates antidepressant efficacy to infusions later in the treatment course suggests that distinct mechanisms may drive effects of early versus later ketamine infusions in the treatment series. For example, as existing lines of evidence demonstrate reductions in neural plasticity with advancing age (Henley and Wilkinson 2013; Lynch 1998; Spriggs et al. 2017), one possible interpretation of our data is that LTP and glutamatergic mechanisms are more important later in the infusion course as compared to earlier infusions. What mechanisms would then be predominant for earlier infusions? Recent work by Williams et al. (2018) showed that pre-treatment with opioid receptor antagonist naltrexone resulted in attenuated efficacy of a single ketamine infusion, arguing that ketamine's antidepressant mechanisms may be largely mediated via the opioidergic system. Interestingly, other published case series data, including work from our group, showed no effect of concurrent opioid receptor modulator use or naltrexone on the response to serial ketamine infusions (Marton et al. 2019; Yoon et al. 2019). Perhaps ketamine's antidepressant mechanism is more opioid-dependent early in treatment, and plasticity mechanisms contribute more with successive infusions (or as a function

of time). Our results contribute to a body of work that suggests a possible framework with which to design mechanistic studies to parse the relative contributions of neural plasticity and opioidergic signaling in ketamine's antidepressant action.

Our finding that age has no effect on the durability of ketamine's antidepressant response (at 3 weeks) is also informed by recent literature and raises further mechanistic questions. D-Cycloserine is a partial agonist at the glycine site of the NMDAR and has been shown to have pro-plasticity effects in preclinical models and in clinical studies (Brown et al. 2020; Rouaud and Billard 2003). However, D-cycloserine administration following a single ketamine infusion failed to extend antidepressant durability in a recent study (but did extend the durability of anti-suicidal effects) (Chen et al. 2019). A similar lack of effect on ketamine' antidepressant durability has also been shown in 2 studies that used glutamatergic modulator riluzole after a ketamine infusion (Ibrahim et al. 2012; Mathew et al. 2010). Broadly, as plasticity is attenuated by age, our results showing no effect of age on ketamine's antidepressant durability are consistent with these reports showing no improvement of durability with the administration of pharmacologic agents targeting the NMDAR and presumably NMDAR-dependent plasticity mechanisms.

Interestingly, a recent study examining the use of the mTORC1 inhibitor rapamycin following ketamine infusion did extend clinical durability effects, although the mechanistic implications of this phenomenon are unclear (Abdallah et al. 2020). mTORC1 is a critical downstream signaling molecule of glutamatergic signaling via AMPA receptors resulting in synaptogenesis; several preclinical studies show that ketamine increases mTORC1 signaling (Li et al. 2010; Zhou et al. 2014). The authors initially hypothesized that rapamycin would block ketamine's antidepressant action (via blockade of mTORC1), but instead surprisingly reported both no effect of rapamycin administration on ketamine's antidepressant efficacy and that rapamycin pretreatment actually lead to superior antidepressant durability. Thus, the existing literature as well as the current study suggest that plasticity mechanisms may be less important for maintaining ketamine's antidepressant durability and that other mechanistic targets (e.g., inflammation, genetics, ketamine metabolites) may be of greater import.

Our study had several important limitations. We conducted a retrospective case-series analysis of veterans receiving clinical care at a VA ketamine clinic. As such, we are limited by the demographic and diagnostic heterogeneity of the sample and lack the rigor of a randomized, controlled, prospective study design. Other demographic and treatment variables that may have covaried with age could have contributed to our reported effects. For example, removal of the 7 patients from the model who had modest ketamine dose adjustments (from 0.5 to 0.7 mg/kg) during the treatment course actually strengthened the age × infusion number interaction (demonstrating significant effects at both infusions #4 and #5) suggesting that ketamine dose could be an important covariate in this analysis. Additionally, it is possible that with more power, we would have demonstrated statistically significant age-dependent effects for infusions #5 and #6, which would affect the interpretation of these results (namely showing that older patients had reduced total clinical response to the six infusion ketamine series). Follow-up analyses with a larger controlled sample are needed to help to clarify these points, including examining patient sex as a biological variable of interest. Including sex in our model indicated that age × time interaction effects were not explained by participant sex, though these analyses are hindered by the small female sample ($n = 12$) and warrant replication in a study designed to fully power examination of age-by-sex interactions relevant to ketamine's antidepressant effects.

It is also important to note that this naturalistic case series study examined patients receiving adjunctive ketamine treatment in the context of their ongoing regular psychiatric care. As such, patients were on a number of differing medication regimens and augmentation strategies (Table 1), and this study was neither designed nor powered to account for all possible sources of variance attributable to the concurrent medication. For example, lamotrigine can attenuate ketamine's acute neuropsychiatric affects (Anand et al. 2000); future work in a larger sample using a randomized controlled design is warranted to address the impact of concurrent medication on ketamine treatment response, including lamotrigine, SRIs, benzodiazepines, and antipsychotics. As BDI-II data were collected prior to each infusion, we do not have BDI-II outcome data reflecting the effects of the sixth infusion in the series. While this does impact to an extent our reported group-level clinical outcomes for total response and durability effects, we do not expect the additional clinical improvement resultant from infusion #6 would manifestly change our reported correlations, particularly with respect to response durability at 3 weeks. Finally, our sample was highly treatment refractory (averaging ~ 9 failed antidepressant trials) which may affect the generalizability of these results to less treatment-resistant populations.

Despite these limitations, this is the largest case series to date examining the effects of patient age on antidepressant response trajectories and durability to six serial ketamine infusions in patients with TRD. These results inform the current literature focusing on characterizing the different phases of clinical response to serial ketamine infusions and possible mechanisms underlying ketamine's antidepressant activity. This work contributes to efforts informing personalization and optimization of ketamine delivery parameters, as well as in developing mechanistic studies that can better capture the

nuances of ketamine's antidepressant action across a treatment course.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00213-021-05939-z.

Author contribution *SP* made significant contributions to data collection, analysis, and manuscript preparation. *BJR* contributed key statistical analyses and critical review for intellectual content. *SLF* contributed to the drafting of the manuscript as well as key intellectual contributions. *AB* made contributions to data collection and analyses. *AW* contributed to the interpretation of key results and critical review for intellectual content. *DHM* assisted with analytical methods and critical review for intellectual content. *TFM* made key contributions to data collection, data analysis, manuscript preparation, and final approval of the version to be published.

Drs. Fryer, Wallace, Mathalon, and Marton are US Government employees. The content is solely the responsibility of the authors and does not necessarily represent the views of the Department of Veterans Affairs.

Declarations

Conflict of interest The authors declare no competing interests.

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