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Intravenous ketamine for postmenopausal women with treatment-resistant depression: Results from the Canadian Rapid Treatment Center of Excellence

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ABSTRACT

Women are disproportionately represented amongst samples of adults with treatment-resistant depression (TRD). Ketamine has demonstrated rapid and robust efficacy in adults with TRD. Herein, we sought to determine whether the effectiveness of intravenous (IV) ketamine was influenced by menopausal status in women with TRD. We defined premenopausal women as those under the age of 45 ($n = 52$), while postmenopausal women ($n = 54$) were those over the age of 51. Participants received four IV ketamine infusions over one-to-two weeks at a community-based center for adults with TRD. The primary outcome of interest was the change in depressive symptom severity as measured by the Quick Inventory of Depressive Symptomatology Self-Report 16 (QIDS-SR_{16}) following four infusions, compared to pretreatment. The secondary outcomes were improvements in suicidal ideation (SI; i.e., QIDS-SR_{16} SI item), anxiety (i.e., Generalized Anxiety Disorder-7 scale), anhedonic severity (i.e., Snaith-Hamilton Pleasure Scale), and workplace and psychosocial function (i.e., Sheehan Disability Scale). Menopausal status did not influence overall treatment response, $F(4, 280) = 1.83$, $p = .123$, $\eta_p^2 = 0.025$. Both premenopausal and postmenopausal participants demonstrated similar response rates (30% and 26%, respectively) and remission rates (both 13%) to IV ketamine treatment following four infusions. Premenopausal women experienced improvements in social function more rapidly than postmenopausal women, $F(2, 174) = 1.65$, $p = .047$, $\eta_p^2 = 0.019$. Postmenopausal women experienced reduction in SI more rapidly than premenopausal women, $F(4, 280) = 2.72$, $p = .030$, $\eta_p^2 = 0.037$. These preliminary *post-hoc* findings provide the impetus for future studies to investigate the moderational role of menopausal status, as defined by hormone levels, on response to IV ketamine for TRD.

1. Introduction

Women are differentially affected by major depressive disorder (MDD), and are 1.7 times more likely to experience a major depressive episode in their lifetime than men (Kessler et al., 1993). Additionally, women are more likely to be prescribed antidepressants and have a higher likelihood of meeting criteria for treatment-resistant depression (TRD; McAllister-Williams et al., 2020, Thunander Sundbom and Hedborg, 2019). Menopause is a particularly vulnerable developmental period for women, and approximately 20% of women experience

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depression during the menopausal transition (Soares, 2004). Furthermore, postmenopausal women with MDD are more likely to report suicidal ideation (SI) when compared to premenopausal and perimenopausal women (Kornstein et al., 2010). However, it remains unclear to what extent menopausal status influences patient response to conventional monoamine-antidepressants (Sloan and Kornstein, 2003; Sramek and Cutler, 2011). Extant studies have suggested that postmenopausal women experience a poorer response to monoamine-based antidepressants than premenopausal women (Pae et al., 2009).

During the perimenopause period, gonadal hormones are in flux. In particular, the steroid hormone estrogen, which has central nervous system activity, fluctuates and declines during perimenopause (Bromberger and Epperson, 2018; Dalal and Agarwal, 2015). Estrogen plays a role in increasing levels of serotonin and norepinephrine, which are commonly implicated in the pathophysiological cause of depression (Halbreich, 1997; Spinelli, 2004). As estrogen levels decrease during the menopausal transition, it is suspected that serotonin and norepinephrine levels decrease as well, which may be associated with the increased prevalence of depression during this period (Halbreich, 1997; Ryan et al., 2009; Spinelli, 2004; Steiner et al., 2003).

The dissociative anesthetic and N-methyl D-aspartate (NMDA) receptor antagonist, ketamine, has demonstrated rapid and robust efficacy in adults with depression, including TRD (aan het Rot et al., 2010; Coyle and Laws, 2015; Phillips et al., 2019; Rosenblat et al., 2019; Wilkinson et al., 2018). Extant literature has focused on the relationship between menopausal status and response to conventional monoamine-based antidepressants, but there is a lack of replicated evidence identifying whether patient sex or menopausal status influences the efficacy of intravenous (IV) ketamine for TRD. A preliminary *post-hoc* analysis of a randomized, double-blinded, placebo-controlled trial examining sex differences between men and women reported that within the female cohort, there were no significant differences in efficacy or tolerability between premenopausal ($n = 30$) and postmenopausal ($n = 16$) women (Freeman et al., 2019).

Estrogen receptors are protective against glutamate-induced neurotoxicity (Lan et al., 2014). Moreover, preclinical data suggests estrogen enhances NMDA receptor function through upregulation of the receptor subtypes (Gazzaley et al., 1996; Panda et al., 2018). Neuroactive steroids (e.g., allopregnanolone) affect extrasynaptic GABA receptors which indirectly influence glutamatergic signalling (Schüle et al., 2014). In addition, sex steroids, as well as their binding globulins, are relevant to mood and cognitive symptoms (Kleeblatt et al., 2017; McIntyre et al., 2005; Takayanagi et al., 2015). During menopause, the loss of these protective factors may increase the risk of developing depressive symptoms (Marsh et al., 2017).

Taken together, the physiology linking glutamate and sex steroid activity in the central nervous system (e.g., estrogen) provides the impetus to ascertain whether the effectiveness of ketamine, a putative glutamatergic agent, in TRD is affected by menopausal status. Herein, we primarily compared the effectiveness of repeat-dose IV ketamine in premenopausal versus postmenopausal women with TRD. In addition, we compared the two groups on measures of suicidality, anxiety, anhedonia, workplace function, and psychosocial function.

2. Method

2.1. Participants

All participant data included in these *post-hoc* analyses were derived from patients at the Canadian Rapid Treatment Center of Excellence (CRTCE) in Mississauga, Ontario, Canada, which is an outpatient clinical and research facility specializing in the administration of IV ketamine for adults with TRD in the context of MDD or BD. The CRTCE follows the best practices for safe and appropriate ketamine administration guidelines, as outlined by the Consensus Statement for the American Psychiatric Association Council of Research Task Force (Sanacora et al., 2017). All participants who received treatment at the CRTCE provided informed consent. This study was approved by a community institutional review board (IRB#00000971) and is registered on clinicaltrials.gov (NCT04209296).

2.2. Inclusion/exclusion criteria

To be eligible for IV ketamine treatment, participants had to meet criteria for a *Diagnostic and Statistical Manual of Mental Disorders* (5th edition) - defined mood disorder and Stage 2 treatment resistance or higher (i.e., inadequate response to at least two different trials of antidepressants; American Psychiatric Association, 2013; Thase and Rush, 1997). This diagnosis was confirmed by a staff psychiatrist at the CRTCE. A small subpopulation of participants met criteria for TRD secondary to a primary diagnosis of obsessive-compulsive disorder (OCD) or post-traumatic stress disorder (PTSD; Table 1). Participants with comorbid psychiatric conditions and/or active SI were eligible for IV ketamine at CRTCE.

Participants with substance-use or alcohol-use disorders were required to have a minimum of three months of abstinence from these substances before being able to receive ketamine treatment. However, participants presenting with psychosis or dementia, pregnancy, were over 275 lbs., reported a history of traumatic brain injury, or who had uncontrolled hypertension (as assessed by a staff anesthesiologist) were not eligible for IV ketamine.

2.3. Treatment protocol

2.3.1. Treatment and assessment timeline

Participants were referred to the CRTCE by their primary care physician, nurse practitioner, or psychiatrist. Participants who were approved for ketamine treatment by both the psychiatrist and

Table 1
Pre-treatment (baseline) participant characteristics and Chi-Square or independent samples *t*-tests of between group differences.

Characteristic	Premenopausal ($n = 52$)	Postmenopausal ($n = 54$)	*p*
Age in Years, *M* (SD)	32.77 (7.98)	60.31 (6.70)	<.0001
Primary Diagnosis, *n* (%)			
MDD	40 (76.92)	44 (81.48)	.568
BD	7 (13.46)	8 (14.81)	
PTSD	4 (7.69)	1 (1.85)	
OCD	1 (1.92)	1 (1.85)	
Pre-treatment Symptom Severity, *M* (SD)			
QIDS-SR_{16} Total	19.60 (4.75)	18.78 (4.83)	.404
QIDS-SR_{16} SI Item	1.87 (1.03)	1.39 (1.06)	.444
GAD-7	15.64 (4.24)	13.26 (6.00)	.028
SHAPS	8.64 (3.45)	8.84 (4.36)	.804
SDS Workplace Function	8.63 (2.47)	7.20 (3.88)	.054
SDS Social Function	8.93 (1.34)	8.67 (2.26)	.509
SDS Family Function	8.13 (1.73)	8.18 (2.58)	.914
Number of Previous Antidepressant Trials, *M* (SD)	7.89 (4.60)	10.06 (6.09)	.136
Number of Concomitant Antidepressants During IV Ketamine Treatment, *M* (SD)	2.40 (1.40)	3.53 (3.40)	.098

Abbreviations: MDD: major depressive disorder; BD: bipolar disorder; PTSD: post-traumatic stress disorder; OCD: obsessive compulsive disorder; *SD*: standard deviation; QIDS-SR_{16}: Quick Inventory for Depressive Symptomatology – Self Report-16; SI: suicidal ideation; GAD-7: Generalized Anxiety Disorder – 7; SHAPS: Snaith-Hamilton Pleasure Scale; SDS: Sheehan Disability Scale; IV: intravenous.

anesthesiologist received acute IV ketamine treatment, consisting of four infusions over a one-to-two week period (i.e., the initiation treatment), and a post-treatment follow-up assessment with the clinic psychiatrist following infusions (i.e., post-initiation treatment follow-up). There were a total of five assessment points during the treatment period. Data were collected before infusion 1 (i.e., baseline), post-infusion 1, post-infusion 2, post-infusion 3, and at the post-initiation treatment visit. Post-infusion data were collected within 2 days of the infusion, and post-initiation treatment visits were scheduled within 7–14 days after the fourth infusion.

2.3.2. Concomitant medications

Participants were permitted to use adjunctive medications during the course of ketamine treatment. However, participants were instructed to refrain from the use of naltrexone during the course of the infusions, monoamine oxidase inhibitors beginning two-weeks prior to the first infusion, and benzodiazepines within 12 h preceding each infusion.

2.3.3. Ketamine infusions

All participants began the four-infusion treatment course with a dose of 0.5 mg/kg of ketamine hydrochloride, diluted in 0.9% saline solution. If participants did not experience a sufficient response to the two initial treatments (as measured by a $\leq$20% reduction in Quick Inventory of Depressive Symptomatology Self-Report-16 [QIDS-SR_{16}] total score from baseline), and they had sufficient tolerability to IV ketamine, they were eligible to receive a dose optimization to 0.75 mg/kg for the third and fourth infusions. Total doses were calculated at each infusion based on the participant's actual body weight at that time. Ideal body weight was used to calculate the dose if the participant's body mass index exceeded 35 kg/$m^{2.}$ All treatments were infused over a period of 40–45 min. Following each infusion, participants were monitored at the clinic for up to 2 h by clinic nursing staff and were then escorted home by a responsible adult known to the patient.

2.4. Measures

2.4.1. Menopausal status

The CRTCE does not routinely collect biochemical evidence indicative of menopausal status (e.g., follicle stimulating hormone [FSH]). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial proxied premenopause as under 40 years of age (Kornstein et al., 2013). We elected to dichotomize individuals under 45 (i.e., premenopausal) and those over 51 (i.e., postmenopausal). The rationale for this was pragmatic, insofar as 51 is the mean age of natural menopause in North America (Costanian et al., 2018). We elected to exclude participants between the ages of 45 and 51 as our aim was to achieve specificity (as opposed to sensitivity) in ensuring that the majority of participants were categorized properly, even without biochemical evidence of menopausal status.

2.4.2. Symptom response

The primary outcome of depressive symptoms was measured using the QIDS-SR_{16} (Rush et al., 2003). The secondary outcome measures of suicidality, anxiety, anhedonic severity, and psychosocial and workplace function were operationalized using the QIDS-SR_{16} SI item, the Generalized Anxiety Disorder-7 (GAD-7) scale (Spitzer et al., 2006), the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995), and the Sheehan Disability Scale (SDS) (Sheehan et al., 1996), respectively. The QIDS-SR_{16} is scored on a scale of 0–27, the QIDS-SR_{16} SI item is scored on a scale of 0–3, the GAD-7 is scored on a scale of 0–21, and the SHAPS is scored on a scale of 0–14. We used the SDS subdomain scores, rather than the total score, to retain data from patients who were not currently working. Each of the SDS subdomain scales (workplace, social, and family function) are scored on a scale of 0–10. On all of the scales, a score of 0 indicated absence of symptoms while higher scores indicated greater symptom severity. Participants completed the QIDS-SR_{16} at all five timepoints, while the GAD-7, SHAPS, and SDS were completed at baseline, post-infusion 3, and at the post-initiation treatment visit.

2.4.3. Data collection and analysis

All scales were completed by participants on a tablet device while at the CRTCE. Data were de-identified and stored on Research Electronic Data Capture (REDCap) (Obeid et al., 2013).

Retrospective analyses were conducted using SPSS Statistics Version 23 to identify whether premenopausal and postmenopausal women had differential responses to IV ketamine treatment. Mixed models with compound symmetry covariance matrices were used to accommodate for missing data. Restricted Maximum Likelihood (REML) and an alpha level of 0.05 were applied. Bonferroni corrections were applied to follow-up pairwise comparisons in order to adjust for multiple comparisons.

Seven hierarchical models were run, with the model terms *number of infusions*, *menopausal status* (i.e., premenopausal vs. postmenopausal), and a *number of infusions by menopausal status* interaction in each model. The primary outcome measure was QIDS-SR_{16} total score. Secondary outcome measures were QIDS-SR_{16} SI score, GAD-7 score, SHAPS score, SDS workplace function, SDS social function, and SDS family function, respectively. Pretreatment symptom severity was controlled for in each model (e.g., baseline SI was included as a covariate in the suicidality model).

Response and remission rates with IV ketamine were also calculated. Response rates were defined as a 50% decrease in QIDS-SR_{16} total score compared to pretreatment QIDS-SR_{16} score, and remission was operationalized as a total score less than or equal to five on the QIDS-SR_{16}.

3. Results

A total of 228 participants received treatment at the CRTCE from July 2018 to December 2019, of which 126 were female. Within our sample ($N = 106$), 52 participants were categorized as premenopausal and 54 participants were categorized as postmenopausal. The remaining 20 participants were between the ages of 45 and 51, and therefore did not fit into either the premenopausal or postmenopausal groups. In the depressive symptoms, suicidality, and anhedonic severity analyses, 47 premenopausal women were included, and 49 postmenopausal women were included. In the anxiety analysis, 47 premenopausal and 47 postmenopausal women were included. Forty premenopausal women and 41 postmenopausal women were included in the workplace function analysis, and 45 premenopausal and 45 postmenopausal women were included in the psychosocial function analyses. Participants were excluded from the analyses due to missing data at all timepoints. Missing data on some scales did not exclude participant data from analyses for which data were available. Demographic information of the sample is described in Table 1. In the included sample, 30 premenopausal women and 20 postmenopausal women received a dose increase to 0.75 mg/kg at infusion 3.

3.1. Symptom improvement in premenopausal versus postmenopausal participants

Premenopausal and postmenopausal women did not exhibit significantly different responses to repeat-dose IV ketamine as measured by changes in total depressive symptoms (Fig. 1a), anxiety (Fig. 2a), anhedonic severity (Fig. 2b), workplace function (Fig. 3a), and family (Fig. 3c) function. Overall, regardless of menopausal status, all of the aforementioned symptoms improved with repeated ketamine infusions (Table 2).

Interaction analyses revealed that menopausal status differentially affected response to IV ketamine infusions as measured by changes in social function (Table 2). Postmenopausal women were slower to respond to IV ketamine treatment, such that while premenopausal women experienced significant improvements in social function after

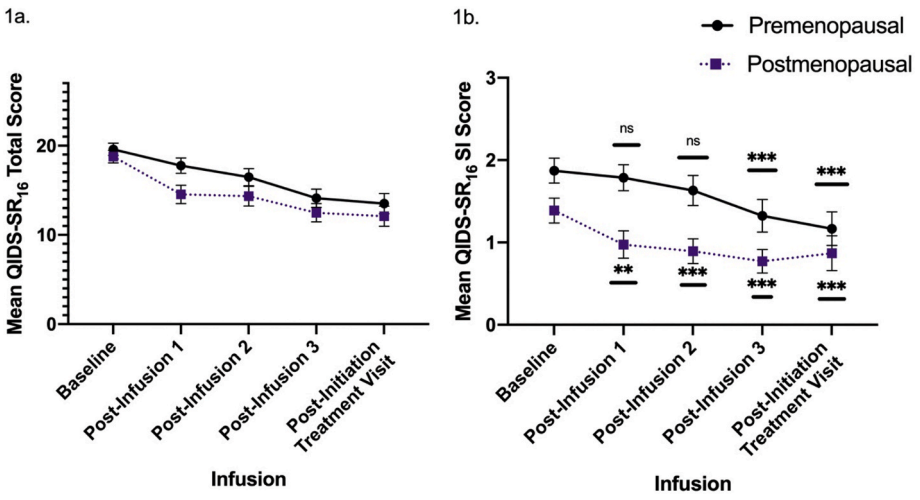

Fig. 1. Changes in depressive symptoms (1a) and suicidal ideation (SI; 1 b) in premenopausal ($n = 47$) and postmenopausal ($n = 49$) women, as measured by the Quick-Inventory of Depressive Symptomatology-Self Report 16 (QIDS-SR_{16}) (mean and standard error). *Note:* ns: not significant. $^{*}p \leq .05$; $^{**}p \leq .01$; $^{***}p \leq .001$ compared to pretreatment.

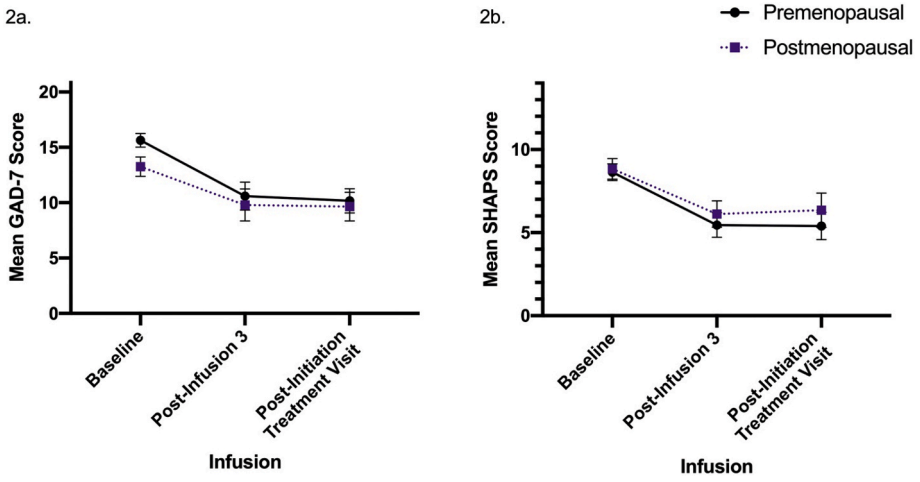

Fig. 2. Changes in anxiety (2a) and anhedonic severity (2 b) with repeated ketamine infusions in premenopausal ($n = 47$) and postmenopausal women (anxiety $n = 47$, anhedonic severity $n = 49$) (mean and standard error).
Abbreviations: GAD-7: Generalized Anxiety Disorder-7; SHAPS: Snaith-Hamilton Pleasure Scale.

the third ketamine infusion, postmenopausal women did not experience a significant improvement in social function symptoms until after the fourth infusion (Table 3; Fig. 1b). Additionally, postmenopausal women experienced anti-SI effects of ketamine more rapidly than premenopausal women (Table 2). While postmenopausal women reported significant reductions in suicidality at each infusion compared to pretreatment SI, premenopausal women did not report significant improvements from baseline until after the third infusion (Table 3; Fig. 3b).

3.2. Response and remission rates with IV ketamine

Nine premenopausal women (17%) and eight postmenopausal women (15%) reported remission (i.e., QIDS-SR_{16} score $\leq$ 5) of depressive symptoms at some point during the course of treatment (Table 4). No premenopausal women reported remission at more than one timepoint, whereas four postmenopausal participants reported remission at multiple timepoints. At the post-initiation treatment visit, four premenopausal participants (13% of premenopausal women with data at the post-initiation treatment visit) reported remission and 3 postmenopausal women (13% of postmenopausal women with data at the post-initiation treatment visit) reported remission. Additionally, while response rates to IV ketamine were similar between premenopausal and postmenopausal women at the post-initiation treatment visit (approximately 30%), postmenopausal women reported treatment response more rapidly than premenopausal participants.

4. Discussion

4.1. Commensurate response in premenopausal and postmenopausal women

Our findings provide preliminary suggestive evidence that both premenopausal and postmenopausal women experience comparable reductions in overall depressive symptoms with repeat-dose IV ketamine. Furthermore, menopausal status did not attenuate improvement in anxiety, anhedonia, workplace, and family function. Both premenopausal and postmenopausal women experienced significant improvement of these secondary measures with IV ketamine treatment.

The commensurate antidepressant effect of IV ketamine in premenopausal and postmenopausal women comports with results from Freeman et al. (2019), who also did not observe significant differences in the efficacy of IV ketamine as a function of menopausal status. Our

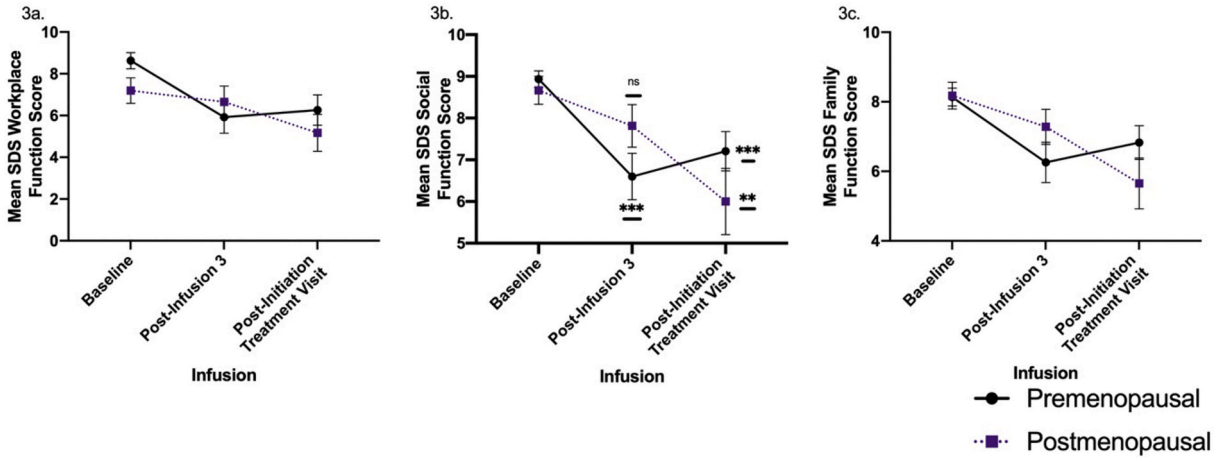

Fig. 3. Changes in workplace (3a), social (3 b), and family (3c) function with repeat-dose IV ketamine based on menopausal status, as measured by the Sheehan Disability Scale (SDS; mean and standard error). Forty premenopausal women and 41 postmenopausal women were included in the workplace function analysis. Forty five premenopausal women and 45 postmenopausal women were included in both psychosocial function analyses.
Note: ns: not significant. *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$ compared to pretreatment.

Table 2
Model effects of all outcome measures, controlling for baseline symptom severity. Significant main effects and interaction effects, at a $p < .05$ threshold, are denoted by †.

	df	*F*	*p*	η_p^2
Model 1: Depressive Symptoms (QIDS-SR$_{16}$ Total Score)				
Number of Infusions†	4, 280	36.46	<.001	.342
Menopausal Status	1, 100	0.49	.486	.005
Number of Infusions * Menopausal Status	4, 280	1.83	.123	.025
Model 2: Suicidality (QIDS-SR$_{16}$ Suicidality Item)				
Number of Infusions†	4, 280	19.10	<.001	.214
Menopausal Status	1, 101	2.57	.112	.025
Number of Infusions * Menopausal Status†	4, 280	2.72	.030	.037
Model 3: Anxiety Symptoms (GAD-7 Total Score)				
Number of Infusions†	2, 160	37.91	<.001	.322
Menopausal Status	1, 106	2.02	.158	.019
Number of Infusions * Menopausal Status	2, 160	1.94	.147	.024
Model 4: Anhedonic Severity (SHAPS Total Score)				
Number of Infusions†	2, 153	22.64	<.001	.228
Menopausal Status	1, 103	2.98	.087	.028
Number of Infusions * Menopausal Status	2, 152	1.28	.282	.017
Model 5: Workplace Function (SDS Workplace Function Item)				
Number of Infusions†	2, 141	14.48	<.001	.170
Menopausal Status	1, 83	1.38	.244	.016
Number of Infusions * Menopausal Status	2, 141	2.09	.127	.029
Model 6: Social Function (SDS Social Function Item)				
Number of Infusions†	2,174	2.18	<.001	.024
Menopausal Status	1, 80	16.98	.202	.175
Number of Infusions * Menopausal Status†	2, 174	1.65	.047	.019
Model 7: Family Function (SDS Family Function Item)				
Number of Infusions†	2, 165	14.70	<.001	.151
Menopausal Status	1, 89	1.48	.227	.016
Number of Infusions * Menopausal Status	2, 165	2.49	.086	.029

Abbreviations: *df*: Degrees of Freedom; QIDS-SR$_{16}$: Quick Inventory of Depressive Symptomatology - Self Report $_{16}$; GAD-7: Generalized Anxiety Disorder-7; SHAPS: Snaith-Hamilton Pleasure Scale; SDS: Sheehan Disability Scale.

results replicate and extend their randomized, double-blind, placebo--controlled study, insofar as our sample was a clinical sample, highly representative of patients typically encountered with TRD. Moreover, Freeman et al. (2019) compared a single, variable-dose infusion (i.e., 0.1–1.0 mg/kg) of IV ketamine to a single fixed-dose of IV midazolam (0.045 mg/kg). Our study was a repeat-dose study, which is the most common method of delivering IV ketamine in clinical practice.

4.2. Rapid anti-suicidal ideation effects in postmenopausal women

In contrast to Freeman et al. (2019), we found that reductions in SI and improvement in social function differed by menopausal status. Postmenopausal women reported significant reductions in SI earlier than premenopausal women. When compared to pretreatment SI, postmenopausal women reported significant reductions in SI following the first infusion, while premenopausal women did not report statistically significant reductions in SI until after the third infusion. The discrepancy between our findings and the findings reported by Freeman et al. (2019) may be due to the larger sample size reported on in the present study. In the previous study, only 16 participants were categorized as postmenopausal, which may have been too small to detect an effect. Additionally, we observed that a higher percentage of postmenopausal women met criteria for treatment response and remission earlier on than premenopausal women, however by the post-initiation treatment visit the response and remission rates were commensurate between the two groups. Importantly, the magnitude of these findings are relatively small and not necessarily robust, and must be replicated.

4.3. Rapid social function improvements in premenopausal women

Interestingly, it was observed that premenopausal women experienced a more rapid improvement in social function compared to postmenopausal women. While premenopausal women experienced a statistically significant improvement in social function compared to pretreatment following the third infusion, postmenopausal women did not report a significant social function improvement until the post-initiation treatment visit. The transition in social roles that often occurs during the menopausal transition has been attributed as a possible contributor to the onset of a depressive episode during this period (Dalal and Agarwal, 2015). This stressor may contribute to the delayed response of social function observed in postmenopausal women

Table 3
Within-subjects pairwise comparisons and pairwise comparisons of interaction effects. All pairwise comparisons were two-tailed, and Bonferroni corrections were applied to all *p*-values to correct for multiple comparisons.

	Baseline to Post-Infusion 1		Baseline to Post-Infusion 2		Baseline to Post-Infusion 3		Baseline to Post-Initiation Treatment Visit	
Depressive Symptoms	<.001		<.001		<.001		<.001	
Suicidality	.010		<.001		<.001		<.001	
Anxiety Symptoms	N/A		N/A		<.001		<.001	
Anhedonic Severity	N/A		N/A		<.001		<.001	
Workplace Function	N/A		N/A		.003		<.001	
Social Function	N/A		N/A		<.001		<.001	
Family Function	N/A		N/A		<.001		<.001	
Menopausal Status	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Suicidality	>.999	.003	.291	<.001	<.001	<.001	<.001	.001
Social Function	N/A	N/A	N/A	N/A	<.001	.255	<.001	.002

Abbreviations: Pre: Premenopausal; Post: Postmenopausal; N/A: Not Applicable.

Table 4
The number of participants who reported remission of depressive symptoms (QIDS-SR16 score ≤ 5) and response to IV ketamine treatment (50% decrease in QIDS-SR16 score from baseline) following each infusion.

	Baseline	Post-Infusion 1	Post-Infusion 2	Post-Infusion 3	Post-Initiation Treatment Visit
Sample Size					
Premenopausal	47	42	38	37	30
Postmenopausal	49	39	38	35	23
Remission, *n* (%)					
Premenopausal		1 (2.38)	1 (2.63)	3 (8.11)	4 (13.3)
Postmenopausal	N/A	3 (7.69)	2 (5.26)	7 (20.0)	3 (13.0)
Response, *n* (%)*					
Premenopausal		6 (14.3)	2 (5.26)	4 (10.8)	9 (30.0)
Postmenopausal	N/A	8 (20.5)	9 (23.7)	10 (28.6)	6 (26.1)

**Note*. Percentages are calculated based on sample size of participants with available data at both baseline and at the post-infusion assessment. Participants who were missing data at either of the two timepoints were excluded from the treatment response analysis since both datapoints were needed to calculate percent change in symptom severity.

receiving IV ketamine. This finding is similar to that observed with other antidepressants. Kornstein et al. (2015) reported a greater improvement in overall function (i.e., total SDS score) in perimenopausal women compared to postmenopausal women following treatment with desvenlafaxine. However, this study did not separately analyze subdomains of function (i.e., workplace, social, and family function) and did not control for pretreatment differences in function between the two groups (Kornstein et al., 2015). The observed effects presented herein were relatively small, and although statistically significant, may not necessarily be important. Furthermore, in the present study, both premenopausal and postmenopausal women reported significant improvements in social function by the post-initiation treatment visit compared to pretreatment social function.

A previous study indicated that postmenopausal status attenuated efficacy of monoamine-based antidepressants, especially selective serotonin reuptake inhibitors (Kornstein et al., 2000). A subsequent study, however, did not replicate these initial findings (Kornstein et al., 2014). A separate body of literature indicates that the menopausal transition may increase the risks for the onset of first-episode and the recurrence of depression (Soares, 2017). Women are more likely than men to be prescribed antidepressants and disproportionately exhibit treatment resistance, providing the impetus to investigate whether menopausal status influences patient response to evidence-based interventions (e.g., ketamine) for TRD.

4.4. Strengths and limitations

There are several methodological aspects of our study that affect inferences and interpretations of our findings. We proxied menopausal status using age cut-offs and could not confirm individual menopausal status using a biochemical assay. Furthermore, our study was open-label and, consequently, susceptible to expectancy and confirmation biases. We did not attempt to evaluate fixed doses of ketamine, and most participants (i.e., approximately 90%) received ketamine as an adjunctive treatment to other prescribed medications for their TRD. Consequently, we cannot rule out the possibility that other adjunctive medications may have contributed to the observed symptom reduction over time. However, participants were asked not to change their medications during the course of treatment. Additionally, it is noted that we did not have a control group as a comparison. Moreover, although we included validated measures of depression, anxiety, anhedonia and function, we did not have a comprehensive measure of suicidality (e.g., Columbia Suicide Severity Rating Scale (Posner et al., 2008)). Due to the relatively small number of responders and remitters in the included sample, we also did not perform exploratory analyses to determine if any baseline characteristics predicted response in premenopausal or postmenopausal participants. Possible characteristics such as level of treatment resistance and depression severity may be interesting factors to consider with larger sample sizes that have greater statistical power.

The strengths of our study include the use of a large, well-characterized sample of pre- and postmenopausal women with TRD receiving IV ketamine in a community-based clinic. Moreover, the participants in this study had multiple treatment trials and received IV ketamine as an adjunctive treatment, which reflects the most common approach in real-world clinical practice. We did not exclude participants on the basis of suicidality, which also increases the generalizability of our findings to real-world patients. Our study is also strengthened by the use of validated assessment tools for measuring symptoms of depression, anxiety, anhedonic severity, and psychosocial and workplace function. Moreover, to our knowledge, our sample is the largest sample studied to date evaluating IV ketamine's effectiveness as a function of menopausal status.

5. Conclusion

In summary, both premenopausal and postmenopausal women with TRD reported experiencing significant symptom relief with IV ketamine treatment. However, the reported effects are relatively small in size, and therefore there remains uncertainty in the results presented herein. Future research should endeavor to evaluate menopausal status using biochemical measures (e.g., FSH) or self-report measures of menopausal status. It is also important to determine whether more robust findings are detected with a sample that is defined by hormone level. Whether estrogen-augmentation of IV ketamine in postmenopausal women is safe

and/or synergistically effective is a testable hypothesis and would be an interesting investigatory avenue. Moreover, evaluating IV ketamine's safety and efficacy in hormone-related mood changes, notably peripartum and postpartum depression and premenstrual dysphoric disorder (PMDD), would be especially valuable given the urgency for rapid symptom relief.

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Declaration of competing interest

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All other authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.08.002.

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