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Exploring Predictors of Ketamine Response in Adolescent Treatment-Resistant Depression

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Abstract

Objective: Ketamine has proved effective as a rapid-acting antidepressant agent, but treatment is not effective for everyone (approximately a quarter to a half of patients). Some adult studies have begun to investigate predictors of ketamine's antidepressant response, but no studies have examined this in adolescents with depression.

Methods: We conducted a secondary data analysis of adolescents who participated in a randomized, single-dose, midazolam-controlled crossover trial of ketamine for adolescents with treatment-resistant depression. We examined the relationship between 19 exploratory demographic and clinical variables and depression symptom improvement (using the Montgomery-Åsberg Depression Rating Scale [MADRS]) at 1 and 7 days postinfusion.

Results: Subjects who had fewer medication trials of both antidepressant medications and augmentation treatments were more likely to experience depression symptom improvement with ketamine. Subjects with shorter duration of their current depressive episode were more likely to experience depression symptom improvement with ketamine. Subjects currently being treated with selective serotonin reuptake inhibitor medications, and not being treated with serotonin–norepinephrine reuptake inhibitor medications, also experienced greater symptom improvement with ketamine. When receiving the midazolam control, less severe depressive symptoms, as measured by the Children's Depression Rating Scale (CDRS) (but not MADRS), and a comorbid attention-deficit/hyperactivity disorder diagnosis were associated with increased response.

Conclusions: Findings should be viewed as preliminary and exploratory given the small sample size and multiple secondary analyses. Identifying meaningful predictors of ketamine response is important to inform future therapeutic use of this compound, however, considerably more research is warranted before such clinical guidance is established. The trial was registered in clinicaltrials.gov with the identifier NCT02579928.

Keywords: ketamine, clinical trial, predictors, major depression, adolescent

Introduction

Ketamine has emerged as an effective treatment for depression, demonstrating robust antidepressant (Newport et al., 2015; Price et al., 2022) and antisuicidal (Ballard et al., 2014; Wilkinson et al., 2018) properties. More recently, research has begun investigating ketamine for the treatment of severe, treatment-resistant depression (TRD) in pediatric populations. Case reports first documented the potential of a single intravenous (IV) ketamine infusion for adolescents with TRD (Dwyer et al., 2017; Zarrinnegar et al., 2019). An open-label study similarly evidenced the success of multiple IV ketamine infusions, with 5 out of 13 patients meeting criteria for clinical response, 3 of whom sustained remission at 6 weeks (Cullen et al., 2018).

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A randomized, placebo-controlled (RCT) single-dose trial investigated the use of IV ketamine in 17 adolescents aged between 13 and 17 years with severe TRD (Dwyer et al., 2021). The trial demonstrated significant improvement of depressive symptoms with ketamine compared to midazolam. Subjects received a dose of ketamine (dosed at 0.5 mg/kg over 40 minutes), or midazolam, (the active comparator; dosed at 0.045 mg/kg over 40 minutes), and the alternate compound 2 weeks later. Findings demonstrated that a single ketamine infusion resulted in significantly reduced depressive symptoms at 1-day post-infusion, compared with midazolam, and that these treatment gains remained, on average, for up to 14 days following treatment.

However, not everyone experiences depressive symptom relief with ketamine. Across adult depression trials, a single dose of IV ketamine typically results in a 50%–70% response rate, with a varying duration of symptom response (Aan Het Rot et al., 2012; Murrough et al., 2012). The single adolescent RCT evaluating ketamine has suggested similar levels of response with a significant proportion (77%) of the sample responding to ketamine (8 participants responded only to ketamine; 5 evidenced symptom relief with both ketamine and midazolam out of the 17 participants), but several other participants experienced no symptom relief (3 participants did not respond to either compound; 1 participant responded only to midazolam) (Dwyer et al., 2021).

Thus, although ketamine treatment may improve depressive symptoms, ketamine is not effective for everyone (approximately a quarter to a half of patients) and the identification of subpopulations that are more or less likely to benefit from ketamine is a priority.

Limited adult research has begun examining clinical predictors that could help identify subsets of depressed individuals who may be more likely to respond to ketamine (Rong et al., 2018). Individuals' studies have suggested that several predictors may be indicative of an antidepressant response to ketamine, including body mass index (BMI) (Freeman et al., 2020; Niciu et al., 2014), a positive family history of alcohol use disorder (Luckenbaugh et al., 2012; Niciu et al., 2014; Pennybaker et al., 2017; Phelps et al., 2009), intrainfusion dissociation levels (Luckenbaugh et al., 2014; Sos et al., 2013), anxious depression subtypes (Ionescu et al., 2014; Wang et al., 2019), lesser treatment resistance as evidenced by fewer previous antidepressant trials (Jesus-Nunes et al., 2022), as well as the absence of prior suicide attempts (Niciu et al., 2014).

A recent individualized participant data meta-analysis suggested that greater depression treatment-resistance at a study level and using a crossover study design were associated with greater measured treatment benefits of ketamine (Price et al., 2022). This individual patient meta-analysis also suggested that individuals that had greater treatment resistance to prior medications, had a primary diagnosis other than major depressive disorder (MDD) (e.g., had bipolar disorder, post-traumatic stress disorder), were enrolled in the United States, and had a higher BMI tended to have greater improvement in response to ketamine relative to placebo. However, all these moderators had, at most, small effects on outcome (Price et al., 2022). Research has also begun investigating potential biomarkers (e.g., genetics, neuroimaging, peripheral measures) predictive of ketamine response (Gadad et al., 2018; Haile et al., 2014; Zarate et al., 2013), although these are of less relevance to the present study.

Within the adolescent population, save for one article reporting no association between intrainfusion dissociation levels (Clinician Administered Dissociative States Scale [CADSS]) and therapeutic efficacy (Lineham et al., 2023), very limited literature exists examining potential predictors of ketamine's antidepressant response. The current study represents a secondary analysis of the only published RCT investigating ketamine for the treatment of adolescent TRD (Dwyer et al., 2021). We will investigate19 exploratory variables with the aim of identifying predictors of antidepressant response after a single dose of IV ketamine in adolescent TRD subjects.

Methods

Secondary data were used for this study. A full description of the methods and results are available from the original trial (Dwyer et al., 2021).

Participants

Seventeen participants, all aged 13–17 years (76% female), were recruited via physician referral. All participants had a DSM-5 diagnosis of MDD, as determined by the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) and scored >40 (severe) on the Children's Depression Rating Scale-Revised (CDRS-R) (Mayes et al., 2010). All participants were either treatment-resistant (having failed 1 selective serotonin reuptake inhibitor [SSRI] of adequate dose and duration), or treatment-refractory (failing 2 or greater serotonin reuptake inhibitors [SRI] medications of adequate dose and duration).

Exclusion criteria included a lifetime history of psychotic disorder, mania, autism spectrum disorder, intellectual disability (intelligence quotient <70), and drug or alcohol dependence/abuse (excluding tobacco). All participants were outpatients with no active suicidal or homicidal ideations. All participants were ketamine-naive, meaning that they had no prior treatment with ketamine for TRD or prior recreational use of ketamine. Participants remained on their standard medication regimens for the 4 weeks before and throughout the 4-week trial period. However, those who did not respond to antidepressant medication, or whom had significant side effects to past medications, were not required to be on medication during the trial.

Ethical approval was granted by The Institutional Review Board at Yale School of Medicine. As participants were minors, all had to be accompanied by at least one parent or guardian. Adults provided written informed consent and adolescents provided written informed assent. Inability to provide this written informed consent, according to the Yale Human Investigation Committee (HIC) guidelines, resulted in study exclusion.

Design and procedure

The original trial consisted of a 4-week randomized midazolam-controlled crossover trial, in which adolescents received a single IV infusion of either ketamine (0.5 mg/kg over 40 minutes) or midazolam (0.045 mg/kg over 40 minutes), and the alternate compound 2 weeks later (Dwyer et al., 2021). The following measures were put in place to protect the blind. All participants, investigators, anesthesiologists, and data analysts were blinded to drug randomization and treatment sequence. The Yale Investigational Drug Service were the only study personnel aware of drug identity. Separate raters were used to score depression (Montgomery-Åsberg Depression Rating Scale [MADRS]) and subjective effects (dissociation; CADSS) measures. MADRS raters were not present during infusions and did not meet with participants until after the final intrainfusion ratings were completed and subjective effects had subsided. Midazolam was used as an active control, based on a similar pharmacokinetic profile, and similar behavioral effects to ketamine.

Measures

Montgomery-Åsberg Depression Rating Scale. The primary outcome measure was depression symptom response assessed

using the MADRS (Montgomery and Asberg, 1979). We utilized baseline, day 1 (24 hours following infusion), and day 7 MADRS scores to calculate response outcomes. Individuals were defined as being a responder if they experienced a reduction >50% in MADRS score at any time point in the first 3 days following infusion. The MADRS was chosen as the primary outcome measure due to its previously demonstrated sensitivity to the acute antidepressant effects of ketamine (Ballard et al., 2018), and its evidenced reliability and validity for depression screening with adolescent patients (Ntini et al., 2020).

Subject-level predictors of antidepressant response. A variety of baseline sociodemographic and clinical variables were explored as potential predictors of depression symptom response. Included were age, gender, BMI, baseline CDRS-R (Mayes et al., 2010), baseline MADRS (Montgomery and Asberg, 1979), baseline Multidimensional Anxiety Scale for Children (MASC) (March et al., 1997), age of depression onset, current depression episode duration, being on a current SSRI, antipsychotic or SRI (SSRI and venlafaxine, duloxetine or desvenlafaxine), having TRD versus having Treatment Refractory Depression, and comorbid conditions, including attention-deficit/hyperactivity disorder (ADHD), and Anxiety, a Family History of Depression. Intrainfusion Dissociation levels were collected from the CADSS (Bremner et al., 1998) data administered at 60 minutes postinfusion.

Analysis

Data management and statistical analysis were performed using STATA/BE v17 (StataCorp). Two sample *t*-tests and chi-square tests were performed for continuous and categorical variables, respectively, to examine if any clinical characteristics were associated with response to ketamine and midazolam at day 1 and 7 following infusion. Correlation analyses were performed to examine the association between baseline clinical characteristics and depression symptom improvement at day 1 and 7 following ketamine and midazolam infusions. Relevant statistical assumptions underlying tests for correlation analyses were assessed, including level of measurement, related pairs, absence of outliers, and normal distribution. Every participant had a pair of values, specifically a clinical characteristic total and a depression outcome score.

Regarding level of measurement, all variables included (each clinical characteristic and depression scores) were continuous, indicating the use of a Pearson parametric correlation test, rather than a nonparametric alternative. The 19 clinical characteristics examined were as follows: sex, age, BMI, baseline CDRS, baseline MADRS, baseline MASC, CADSS, age of onset of depression, duration of current depressive episode, number of previous pharmacological treatments, number of previous antidepressant treatments, number of previous augmentation treatments, treatment resistance versus treatment refractory depression, current use of SSRI, current use of serotonin and norepinephrine reuptake inhibitors (SNRI), current use of other antidepressant, comorbid ADHD or anxiety disorder diagnosis, and family history of depression.

We also conducted linear models to assess whether baseline clinical characteristics were associated with depression symptom improvement with ketamine infusion (compared to midazolam) at day 1 and 7 after infusion. In linear regression models, MADRS rating at day 1 or 7 following ketamine infusion was the dependent variable, with the baseline predictor variables entered as the independent variable in the model. Each linear regression model included additional variables to adjust for (1) treatment order, (2) baseline MADRS score, and (3) MADRS score at day 1 or 7 following midazolam infusion. All 17 participants were utilized for the analyses involving ketamine only and 16 subjects were used for the analysis involving midazolam only and exploring moderators of response as 1 subject dropped out from the crossover trial after receiving ketamine in the first phase (thus never received midazolam infusion).

Results

Clinical characteristics associated with response to ketamine and midazolam

Table 1 depicts the clinical characteristics of responders and nonresponders to both ketamine and midazolam infusions separately. Responders to ketamine had significantly shorter duration of current depressive episode, had fewer previous antidepressant and augmentation treatments, were more likely to be currently taking an SSRI, and less likely to be currently taking an SNRI or other antidepressant than ketamine nonresponders. By contrast, responders to midazolam infusion had a significantly lower baseline CDRS depression score and were more likely to have comorbid ADHD than nonresponders to midazolam. No baseline clinical characteristics demonstrated significant association with both ketamine and midazolam treatment response.

Clinical characteristics correlated with depression symptom improvement with ketamine and midazolam infusion

Table 2 presents the correlation coefficients for the associations between baseline clinical characteristics and magnitude of symptom improvement at day 1 and 7 following ketamine and midazolam infusion. Fewer previous antidepressant medication trials was significantly associated with greater depression symptom improvement at both day 1 postinfusion ($r = 0.711$, $p < 0.01$) and day 7 ($r = 0.546$, $p < 0.05$) following ketamine infusion. Fewer number of previous pharmacological augmentation trials was significantly associated with greater depression symptom improvement at day 1 ($r = 0.507$, $p < 0.05$) following ketamine infusion (but not significantly at day 7). Lesser baseline depression severity, as measured by the CDRS (but not MADRS), was significantly associated with greater depression symptom improvement following midazolam at day 1 ($r = 0.526$, $p < 0.05$) but not day 7.

Comorbid ADHD was significantly associated with response to midazolam at day 1 ($\beta = -16.18$, $p < 0.01$) but not day 7 and having a family history of depression was significantly associated with response to midazolam at day 1 ($\beta = -14.00$, $p < 0.05$) but not day 7. No baseline clinical characteristics were significantly associated with depression symptom improvement to both midazolam and ketamine.

Moderators associated with depression symptom response to ketamine compared to midazolam infusion

Table 3 depicts the moderator analysis examining baseline clinical characteristics associated with ketamine infusion (as opposed to midazolam) at day 1 and 7 following infusion. Fewer number of past medication treatments was associated with significantly greater depression improvement at day 1 ($\beta = 1.46$, 95% confidence interval [CI] = 0.23–2.70, $p = 0.024$) and at day 7 ($\beta = 2.46$, 95% CI = 0.73–4.19, $p = 0.010$) following infusion. Fewer number of previous antidepressant treatments was significantly associated with greater depression symptom improvement with ketamine (compared to midazolam) on day 1 ($\beta = 3.43$, 95% CI = 1.74–5.13, $p = 0.001$) following infusion.

Table 1. Clinical Characteristics Associated with Response to Ketamine and Midazolam

	Ketamine			*Midazolam*		
	Responders (n = *12*)	*Nonresponders* (n = *5*)	p	*Responders* (n = *6*)	*Nonresponders* (n = *11*)	p
Sex, female, *n* (%)	10 (83)	3 (60)	0.30	4 (67)	9 (82)	0.48
Age (years), mean (SD)	15.33 (1.50)	16.00 (1.00)	0.38	15.00 (1.26)	15.82 (1.40)	0.25
BMI, mean (SD)	32.39 (31.92)	27.45 (7.51)	0.74	22.01 (5.18)	35.81 (32.63)	0.33
Baseline CDRS, mean (SD)	61.00 (19.03)	68.60 (11.35)	0.42	**50.83 (14.16)**	**70.00 (15.07)**	**0.022**
Baseline MADRS, mean (SD)	31.42 (10.03)	37.40 (6.15)	0.24	29.50 (9.14)	35.18 (9.17)	0.24
Baseline MASC, mean (SD)	53.17 (18.15)	64.40 (23.32)	0.30	59.67 (17.74)	60.90 (22.60)	0.91
CADSS at 60 minutes, mean (SD)	18.33 (12.14)	18.80 (9.18)	0.94	2.33 (2.07)	2.90 (2.28)	0.63
Age of depression onset (years), mean (SD)	13.17 (2.08)	13.00 (3.24)	0.90	13.00 (1.67)	13.18 (2.75)	0.89
Current episode duration (months), mean (SD)	**13.67 (6.61)**	**38.40 (27.36)**	**0.008**	16.17 (8.82)	23.55 (22.44)	0.46
Number of past treatments, mean (SD)	3.92 (2.71)	7.00 (4.00)	0.082	4.33 (2.73)	5.09 (3.73)	0.67
Number of antidepressant therapies, mean (SD)	**1.75 (0.75)**	**5.00 (1.41)**	**<0.001**	2.00 (1.26)	3.09 (1.97)	0.24
Number of augmentation therapies, mean (SD)	**1.08 (1.16)**	**4.60 (4.22)**	**0.015**	1.00 (0.89)	2.73 (3.38)	0.24
Current SSRI, *n* (%)	**9 (75)**	**0 (0)**	**0.005**	5 (83)	4 (36)	0.064
Current other antidepressants, *n* (%)	**2 (17)**	**5 (100)**	**0.001**	2 (33)	5 (45)	0.63
Current SNRI, *n* (%)	**1 (8)**	**3 (60)**	**0.022**	0 (0)	4 (36)	0.091
Treatment resistant depression, *n* (%)	5 (42)	0 (0)	0.086	3 (50)	2 (18)	0.17
Treatment refractory despression, *n* (%)	7 (58)	5 (100)		3 (50)	9 (82)	
Comorbid conditions, *n* (%)						
ADHD	4 (33)	2 (40)	0.79	4 (67)	2 (18)	0.046
Anxiety	8 (67)	3 (60)	0.79	3 (50)	8 (73)	0.35
Family history of depression	6 (50)	3 (60)	0.71	5 (83)	4 (36)	0.064

Significant findings are highlighted in bold.

ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CADSS, Clinician Administered Dissociative States Scale; CDRS, Children's Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MASC, Multidimensional Anxiety Scale for Children; SD, standard deviation; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor.

Table 2. Correlation Between Clinical Characteristics and Depression Symptom Improvement Following Ketamine and Midazolam Infusion

	Ketamine		*Midazolam*	
	Day 1	*Day 7*	*Day 1*	*Day 7*
Age	0.263	0.414	0.488	0.483
BMI	–0.038	–0.018	0.227	–0.025
Baseline CDRS	0.054	0.053	**0.526***	0.495
Baseline MADRS	0.195	0.280	0.338	0.500
Baseline MASC	0.224	0.200	–0.025	–0.150
CADSS at 60 minutes	0.231	0.220	–0.032	–0.254
Age of depression onset	0.122	0.338	0.228	0.451
Current episode duration (months)	0.375	0.272	0.037	0.035
Number of past treatments	0.241	0.438	0.185	0.243
Number of antidepressant therapies	**0.711****	**0.546***	0.187	0.321
Number of augmentation therapies	**0.507***	0.453	0.214	0.320
Treatment refractory versus Treatment resistant depression	6.45	4.30	9.78	8.35
Comorbid conditions				
ADHD	–2.38	–2.55	–16.18**	0.75
Anxiety	3.10	2.75	–3.80	–8.67
Family history of depression	–0.38	0.71	–14.00*	–4.57

Significant findings are highlighted in bold. Asterisks denote *p*-value. Coefficients for continuous predictors are presented as *r* and for categorical predictors are presented as β-coefficients.

**$p < 0.01$, *$p < 0.05$.

ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CADSS, Clinician Administered Dissociative States Scale; CDRS, Children's Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MASC, Multidimensional Anxiety Scale for Children.

Table 3. Moderators Associated with Depression Symptom Response to Ketamine Compared to Midazolam Infusion

	Day 1			*Day 7*		
	β coefficient	*95% CI*	p	*β coefficient*	*95% CI*	p
Age	2.08	−1.82 to 5.98	0.266	4.28	−1.18 to 9.74	0.111
Female versus male	−4.70	−16.15 to 6.76	0.386	−10.84	−27.42 to 5.74	0.176
BMI	0.01	−0.18 to 0.19	0.931	0.01	−0.28 to 0.29	0.964
Baseline MADRS	−0.04	−0.59 to 0.52	0.89	0.11	−0.72 to 0.94	0.779
CADSS at 60 minutes	−0.23	−0.79 to 0.33	0.385	−0.28	−1.17 to 0.60	0.492
Age of depression onset	0.33	−2.02 to 2.68	0.760	1.79	−1.53 to 5.11	0.258
Current episode duration (months)	0.22	−0.12 to 0.55	0.187	0.18	−0.36 to 0.72	0.479
Baseline MASC	0.22	−0.12 to 0.55	0.187	0.26	−0.32 to 0.84	0.343
Number of past treatments	**1.46**	**0.23 to 2.70**	**0.024***	**2.46**	**0.73 to 4.19**	**0.010***
Number of antidepressant therapies	**3.43**	**1.74 to 5.13**	**0.001****	3.44	−0.17 to 7.04	0.060
Number of augmentation therapies	**1.85**	**0.62 to 3.08**	**0.007****	**2.23**	**0.08 to 4.37**	**0.043***
Current SSRI	−6.89	−17.83 to 4.06	0.193	−11.01	−27.17 to 5.15	0.160
Current SNRI	**13.11**	**4.71 to 21.52**	**0.006****	13.89	−1.57 to 29.36	0.073
Treatment refractory versus Treatment resistant depression	7.91	−2.32 to 18.14	0.117	7.53	−10.44 to 25.50	0.373
Comorbid conditions						
ADHD	−2.40	−16.24 to 11.44	0.710	−3.16	−25.73 to 19.40	0.761
Anxiety	0.35	−10.39 to 11.09	0.07	1.15	−15.41 to 17.72	0.880
Family history of depression	0.27	−11.86 to 12.41	0.962	1.86	−16.67 to 20.40	0.827

Significant findings are highlighted in bold. Asterisks denote *p*-value.
$^{**}p < 0.01$, $^{*}p < 0.05$.
ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CADSS, Clinician Administered Dissociative States Scale; CDRS, Children's Depression Rating Scale; CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; MASC, Multidimensional Anxiety Scale for Children; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

Fewer previous pharmacological augmentation treatments were associated with greater depression symptom improvement with ketamine (as opposed to midazolam) at day 1 ($\beta = 1.85$, 95% CI = 0.62–3.08, $p = 0.007$) and day 7 ($\beta = 2.23$, 95% CI = 0.08–4.37, $p = 0.043$) following infusion. Subjects currently on an SNRI medication experienced significantly less depression symptom improvement with ketamine (as opposed to midazolam) at day 1 following infusion ($\beta = 13.11$, 95% CI = 4.71–21.52, $p = 0.0006$).

Discussion

This analysis represents the first study to examine predictors of ketamine depression symptom response in adolescents with depression. Subjects who had fewer medication trials of both antidepressant medications and augmentation treatments were more likely to experience depression symptom improvement with ketamine. In addition, subjects with shorter duration of their current depressive episode were more likely to experience improvement with ketamine. Subjects currently being treated with SSRI medications, and not being treated with SNRI medications, also experienced greater symptom improvement with ketamine. By contrast, less severe depressive symptoms, as measured by the CDRS (but not MADRS), and comorbid ADHD and having a family history of depression, was associated with increased response to the midazolam control. These findings should be viewed as preliminary and exploratory and require further replication given the small sample size and multiple secondary analyses.

Overall, several findings suggest that adolescent subjects were more likely to experience depressive symptom improvement if they were treated earlier in the course of their depressive episode. Specifically, shorter duration of the current depressive episode, as well as fewer previous medication trials, was associated with improved ketamine response. This corroborates previous adult literature evidencing that number of previous treatment failures and severity of illness were predictors of fewer remissions and responses of depressive symptoms to either ketamine or esketamine treatment in a randomized controlled trial (Jesus-Nunes et al., 2022). However, it also contrasts with a recent individual patient-data meta-analysis in adults which found that greater treatment resistance was associated with a greater moderating effect of ketamine (compared to control conditions) in randomized controlled trials (Price et al., 2022).

If current findings can be replicated, this would suggest that pediatric predictors and moderators of ketamine response may differ from adults and also that pediatric patients could benefit from ketamine treatment at an earlier stage in their depressive disease course and potentially prevent individuals from progressing into later, more chronic, and persistent forms of major depression. However, our data are both preliminary and exploratory and based on a small number of subjects compared to the much greater evidence-base from the adult individual patient-data meta-analysis, so we urge caution against over generalizing the interpretation of our findings.

Subjects taking SSRI and not taking SNRI medications (or other antidepressants) were more likely to respond to ketamine treatment. We believe that this association is most likely explained by the correlation between current medication use and degree of treatment-resistance as SSRI medications are routinely prescribed as first-line pharmacological treatment in preference to SNRI medications for pediatric depression. The strong preference of SSRI before SNRI medications in pediatric depression is in contrast to the treatment algorithms for adult depression, where both medication classes (as well as some other agents) are considered first-line.

Another potential explanation that we cannot entirely discount is that interactions with individuals' current medications may be having augmenting effects when used alongside ketamine. For

example, it is possible that SSRI's work to harness the potential efficacy of ketamine, and SNRI's do the opposite. Further investigations in adult populations where SSRIs are not preferentially prescribed over other antidepressants (SNRI, bupropion, mirtazapine) could definitively exclude this possibility.

Investigating clinical predictors of ketamine within a pediatric population is important for several reasons. Pediatric depression often differs considerably from adult depression, manifesting in distinct symptom profiles (e.g., irritability as cardinal symptom). Neurotransmitter systems implicated in depression (e.g., the glutamate system) have not reached full maturity before adulthood (Arain et al., 2013), and brain networks implicated in depression (e.g., default mode network) are continuing to grow in complexity (Fan et al., 2021; Power et al., 2010). Differences in other biological systems, such as those regulating pharmacological mechanisms, are also likely of relevance given that any minute differences in how the drug interacts with the body has the potential to result in varying effects and thus implicate different markers of response.

We additionally demonstrated that lesser depression symptom severity was associated with increased likelihood of response to the midazolam control condition. There exists an extensive literature linking milder levels of depression symptoms with increased placebo response and decreased measured efficacy of proven antidepressant treatments (Khan and Brown, 2001; Stein et al., 2006; Wilcox et al., 1992).

Conclusion

These findings provide initial evidence suggesting characteristics of adolescents with MDD who may be more likely to respond to ketamine treatment, specifically patients with less treatment-resistance and shorter duration of current depressive episode. We currently reserve ketamine treatment for adolescent patients who have not responded to previous trials of an SSRI of adequate dose and duration, as well as an evidence-based psychotherapy (Dwyer et al., 2020). That said, the vast majority of adolescents we currently treat with ketamine are required to fail an additional SSRI trial as well as an augmentation treatment (and possibly an alternative antidepressant) before we typically consider ketamine. However, these data are suggesting that adolescents of lesser treatment-resistance are more likely to benefit from ketamine. If these findings are replicated, it is plausible that these recommendations be reconsidered.

Given the potential clinical implications of our findings, we believe that it is important to be transparent about the significant limitations of the current analysis. Our small sample size gives us limited power to detect predictors of ketamine response and so it is possible that we did not uncover meaningful predictors of ketamine response. In addition, all the analyses were secondary analyses of a clinical trial that were not corrected for multiple comparisons and thus should be regarded as exploratory for the purposes of hypothesis generation. In clinical practice, most patients receive repeated ketamine treatments, and it is unclear how these predictors of ketamine response in a single-dose crossover study will generalize to repeated dose paradigms.

Clinical Significance

Given that trials with ketamine are still in early stages with younger patients, considerably more work will be needed before any clinical characteristics should be used to guide clinical decision-making in the treatment of adolescent depression. Identifying predictors of ketamine response is important as there are many other alternative treatments for depression (at least in adults), which have considerably greater safety and efficacy data. The efficacy of repetitive transcranial magnetic stimulation and electroconvulsive therapy specifically deserves further evaluation as a potential treatment for severe, treatment-refractory depression in adolescent populations given the morbidity and mortality associated with the condition. Further research is needed to examine predictors of ketamine response in both pediatric and adult populations. Given the absence of clinical predictors identified other than duration of current depressive episode and number of failed medication trials, other potential modalities should be examined such as neuroimaging biomarkers and blood metabolites of ketamine.

Disclosures

Dr. Bloch has served as associate editor of *The Journal of Child Psychology and Psychiatry* and on the editorial boards of the *Journal of Child and Adolescent Psychopharmacology* and the *Journal of the American Academy of Child and Adolescent Psychiatry*. He has received royalties from Wolters Kluwer for Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook, Fifth Edition. He has received moonlighting pay from the Veteran's Administration. He serves on the Scientific Advisory Board of the Tourette Association of America and the TLC Foundation for Body-Focused Repetitive Behaviors.

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