


# Efficacy of repeated intravenous esketamine in adolescents with anxious versus non-anxious depression

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## ABSTRACT

**Background** Patients with anxious major depressive disorder (MDD) are more likely to have poorer outcomes than those with non-anxious MDD. However, the effect of esketamine on adolescents with anxious versus non-anxious MDD has remained unknown.

**Aims** We compared the efficacy of esketamine in adolescents with MDD and suicidal ideation, both anxious and non-anxious.

**Methods** Fifty-four adolescents with anxious (n=33) and non-anxious (n=21) MDD received three infusions of esketamine 0.25 mg/kg or active-placebo (midazolam 0.045 mg/kg) over 5 days, with routine inpatient care and treatment. Suicidal ideation and depressive symptoms were assessed using the Columbia Suicide Severity Rating Scale and the Montgomery-Åsberg Depression Rating Scale. Multiple-sample proportional tests were used to compare the differences between groups on treatment outcomes 24 hours after the final infusion (day 6, primacy efficacy endpoint) and throughout the 4-week post-treatment (days 12, 19 and 33).

**Results** In subjects who received esketamine, a greater number of patients in the non-anxious group than the anxious group achieved antisuicidal remission on day 6 (72.7% vs 18.8%,  $p=0.015$ ) and day 12 (90.9% vs 43.8%,  $p=0.013$ ), and the non-anxious group had a higher antidepressant remission rate compared with the anxious group on day 33 (72.7% vs 26.7%,  $p=0.045$ ). No significant differences in treatment outcomes were observed between the anxious and non-anxious groups at other time points.

**Conclusions** Three infusions of esketamine as an adjunct to routine inpatient care and treatment had a greater immediate post-treatment antisuicidal effect in adolescents with non-anxious MDD than in those with anxious MDD; however, this benefit was temporary and was not maintained over time.

**Trial registration number** ChiCTR2000041232.

## INTRODUCTION

Patients with major depressive disorder (MDD) report that co-occurring anxiety symptoms or anxiety disorders are common, with approximately 50% reporting at least one-lifetime anxiety disorder.<sup>1</sup> In children and adolescents, the co-occurrence of anxiety with depression seems equally common.<sup>2</sup>

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with anxious depression are more likely to experience poorer responses to antidepressant treatment; however, it is unclear whether anxious depression is associated with the treatment response to esketamine for adolescents with major depressive disorder (MDD).

## WHAT THIS STUDY ADDS

⇒ Three low-dose esketamine infusions as an adjunct to routine inpatient care and treatment affected a greater antisuicidal remission rate in adolescents with MDD without anxiety compared with those with anxiety.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study results may inform potential strategies for the treatment of adolescents with MDD and suicidal ideation.  
⇒ Clinicians should be aware of these populations because anxious depression is associated with the treatment response to esketamine.

Patients with anxious depression are more likely to experience recurrent depressive episodes and have higher levels of suicidal ideation, greater depression severity, more severe insomnia, poorer response to medication, lower remission rates and higher readmission rates than those with MDD alone.<sup>3,4</sup>

Low-dose ketamine has been proven repeatedly to exhibit rapid antidepressant and antisuicidal effects for treatment-resistant depression (TRD).<sup>5–7</sup> Intranasal esketamine was approved by the Food and Drug Administration in the USA for adults with TRD and adult MDD with acute suicidal ideation/behaviour.<sup>8,9</sup> Several studies have examined the difference in the antidepressant effects of ketamine in patients with TRD with and without anxiety but have shown mixed findings.<sup>10–13</sup> Our previous study administered six infusions of ketamine to patients with TRD or suicidal ideation who were classified



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into four subtypes: melancholic, anxious, melancholic-anxious and non-melancholic-anxious, and showed that patients with melancholic or melancholic-anxious features had less response or remission and took longer to achieve response/remission than those with anxious or non-melancholic-anxious features.<sup>14</sup> In addition, we also found cognitive improvement in patients with anxious depression after ketamine treatment but not in patients with non-anxious depression.<sup>15</sup>

Given the safety and success of ketamine and its enantiomers in treating depression in adults, clinical trials to explore their efficacy and safety in adolescents are also ongoing. Recently, a randomised controlled trial (RCT) of a single ketamine infusion in 17 adolescents with TRD suggested that ketamine might be well tolerated and effective in reducing depressive symptoms.<sup>16</sup> Other data from two small open-label trials and three case reports also suggested that low-dose ketamine had a rapidly acting antidepressant effect and was well tolerated in adolescents.<sup>17–19</sup> However, the potential role of anxious depression in the treatment response to ketamine or its enantiomer (esketamine) has remained unknown for this adolescent population.

Recently, we conducted a double-blind RCT of three low-dose intravenous esketamine infusions in adolescents with MDD and suicidal ideation, where the esketamine treatment yielded a superior response compared with midazolam. We then conducted a secondary analysis to compare the efficacy of repeated intravenous esketamine for resolving suicidal ideation and depressive symptoms in adolescents with anxious MDD with those with non-anxious MDD. Based on our previous data from adults, we hypothesised that adolescents with anxious MDD would have a higher likelihood of achieving a rapid and robust treatment effect to esketamine than those with non-anxious MDD.

## METHODS

In this secondary analysis, data were from the trial examining three low-dose infusions of esketamine for the treatment of depression with suicidal ideation.<sup>20</sup> This trial was registered in the Chinese Clinical Trials Registry (registration number: ChiCTR2000041232).

### Participants

Adolescents with MDD and suicidal ideation were recruited from the inpatient ward of the Affiliated Brain Hospital of Guangzhou Medical University between December 2020 and April 2022. Eligible patients were males and females aged 13–18 years with a diagnosis of MDD without psychotic features according to the Diagnostic and Statistical Manual of Mental Disorders-5 criteria.<sup>21</sup> The inclusion criteria also included moderate-to-severe depressive symptoms with a total score of  $\geq 17$  as measured by the 17-item Hamilton Depression Rating Scale (HAM-D-17),<sup>22,23</sup> suicidal ideation for  $\geq 3$  months with an Ideation score of  $\geq 1$  as measured by a clinician-rated

Columbia Suicide Severity Rating Scale (C-SSRS)<sup>24</sup> and a score of  $\geq 2$  for items 4 or 5 of the self-report Beck Scale for Suicide Ideation.<sup>25</sup> The exclusion criteria were as follows: current or previous alcohol or substance use disorder; primary psychotic, bipolar disorder, pervasive developmental, post-traumatic, obsessive-compulsive or non-psychiatric neurological disorders; a significant medical illness or an active suicidal attempt on presentation or in the preceding 6 months.

### Study design

The original trial was a randomised, double-blind, active placebo-controlled study, which consisted of a 24-hour to 48-hour screening phase (day 0), followed by a 6-day double-blind infusion phase (days 1–6) and then a 4-week post-treatment follow-up phase (days 7–33). The potential participants were admitted to the hospital due to suicide risk and/or severe depressive symptoms. Routine antidepressant medication was initiated or optimised immediately, as determined by their clinicians. Thus, there was no washout period before infusion. Given the vulnerability of the participants, who had current suicidal ideation, they were provided routine inpatient nursing care and treatment with antidepressant monotherapy or combination therapy by their clinicians, and the types and doses of medications were maintained during the double-blind infusion phase. During the naturalistic follow-up phase, the participants were treated with necessary medications (monotherapy or antidepressant plus augmentation therapy) that their clinicians managed. Structured psychotherapy, electroconvulsive therapy and repetitive transcranial magnetic stimulation were not permitted throughout the study.

The participants were randomised to receive three infusions of either esketamine (0.25 mg/kg) or midazolam (0.045 mg/kg) via a computer-generated randomisation scheme. The study drugs were administered on days 1, 3 and 5. The raters and participants were blinded to the assigned treatment at randomisation. In the present study, midazolam was used as an active control, in keeping with its similar pharmacokinetic profile and precedent as a reasonable comparator for esketamine's non-specific behavioural effects.

### Anxious depression definition

We defined anxious depression with a factor of the HAM-D-17 anxiety-somatisation (AS) score, which includes psychic anxiety, somatic anxiety, somatic symptoms-gastrointestinal, somatic symptoms-general, hypochondriasis and insight.<sup>26</sup> Categorical anxious depression was defined as an AS score  $\geq 7$ , and non-anxious depression was defined as an AS score  $< 7$ . This definition and classification have been used widely and proven useful in assessing anxious depression in clinical studies of antidepressant treatment.<sup>4,10,12,15</sup>

### Outcomes and evaluations

The primary outcome was rates of suicidal remission, defined as C-SSRS Ideation score = 0 at 24 hours after the

final infusion (day 6, as the primacy efficacy endpoint).<sup>21</sup> Secondary outcomes included rates of antisuicidal response (defined as an improvement  $\geq 50\%$  from baseline in the C-SSRS Ideation score), rates of antidepressant response (defined as an improvement  $\geq 50\%$  in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline) and remission (defined as MADRS total score  $\leq 12$ ) on day 6. Other secondary outcomes included changes in suicidal ideation, depressive symptoms, psychotomimetic and dissociative symptoms and cognitive function from baseline to 4 weeks post-treatment (day 33, as the secondary endpoint).

Suicidal ideation was assessed using the Chinese version of the C-SSRS Ideation and Intensity scale,<sup>27</sup> which can reflect the severity of suicidal ideation and the intensity of suicidal ideation. The first five items of the scale refer to the severity of suicide ideation and have binary yes/no responses (yes=1, no=0): wish to be dead, non-specific active suicidal thoughts, suicidal thoughts with methods, suicidal intent and suicidal intent with a plan—with a total range from 0 to 5. The following five items refer to the intensity of suicidal ideation: frequency, duration, controllability and deterrents of ideation, and reasons for ideation, and each item scales 0 (suicidal ideation denied) to 5 (suicidal ideation with a plan, ie, severe suicidal ideation) for a total range from 0 to 25. The C-SSRS was administered at baseline (day 0, with past-week recall), then at 24 hours after each infusion (days 2, 4 and 6, modified for past 24-hour recall), and again at 1, 2 and 4 weeks after the final infusion (days 12, 19 and 33, with past-week recall).

The severity of depressive symptoms was assessed via the MADRS<sup>28,29</sup> at the same time points and with the same recall period as the C-SSRS.

The psychotomimetic effects were measured with five items (hallucinations, grandiosity, suspiciousness, unusual thought content, conceptual disorganisation) from the Brief Psychiatric Rating Scale (BPRS-5)<sup>30</sup> at baseline, then at 30 min and 24 hours after each infusion (days 1, 2, 3, 4, 5, 6) and again on days 12, 19 and 33. At the same time, dissociative symptoms were assessed by the Clinician-Administered Dissociative Symptoms Scale (CADSS).<sup>31</sup>

Cognitive function was assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (MCCB)<sup>32,33</sup> at baseline and on days 6 and 12. Four cognitive domains were selected in the present study, including processing speed, working memory, visual learning and verbal learning; learning and memory impairment are often associated with depression and have been measured by multiple ketamine clinical studies.<sup>15</sup>

The raters were psychiatrists trained by the National Drug Clinical Trial Institution of the Affiliated Brain Hospital of Guangzhou Medical University. The assessment of inter-rater reliability for raters was in the excellent-to-good range for all the scales used, with intraclass correlations  $>0.90$ .

## Statistical analyses

All analyses were conducted in IBM SPSS Statistics V.27, with a significance level set at 0.05. Statistical analysis, including participants who lacked follow-up assessment, was performed in accordance with the intention-to-treat principle.

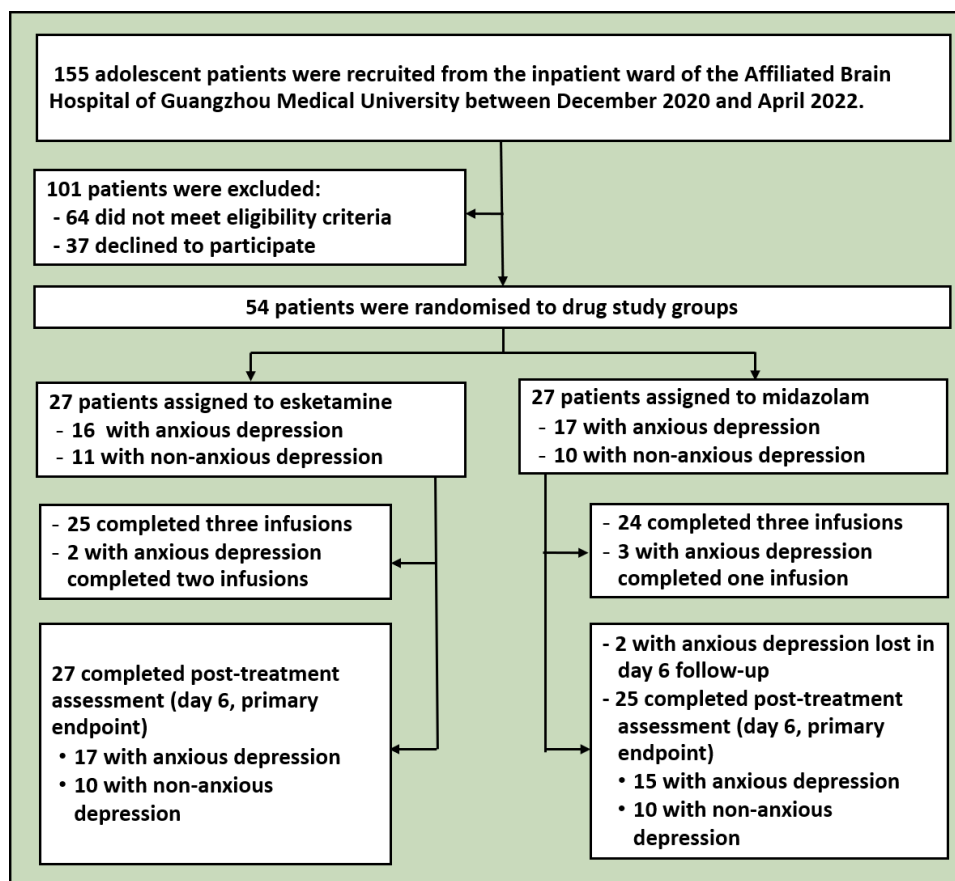
Baseline data were compared between anxious and non-anxious groups using  $\chi^2$  tests and t-tests for nominal and continuous variables. Post hoc summaries were provided for the proportions of the participants achieving clinical response and remission, and the differences between groups were compared using multiple-sample proportional tests. Factorial linear mixed models were performed to examine the roles of the study drug and depression type in the treatment outcome over time. These models used a compound symmetry covariance structure with restricted maximum likelihood estimation. The evaluation time point (from baseline to day 33 for clinical scales, and from baseline to day 12 for the MCCB), study drug (esketamine or midazolam) and group (anxious or non-anxious) were factors, and duration of illness, antidepressant class (selective serotonin reuptake inhibitor (SSRI) or non-SSRI) and augmentation therapy (yes or no) were included as the covariates. The baseline score was used as a covariate if it had statistical differences between groups. To examine differences between the anxious and non-anxious groups within subjects who received esketamine or midazolam at each time point, Bonferroni-corrected simple effects tests were used for post hoc analysis.

## RESULTS

### Participants

Of all 54 randomised subjects, 33 (61.1%) met the predefined criteria for anxious depression at baseline. In the anxious group, 16 participants received esketamine and 17 received midazolam treatment. In the non-anxious group, 11 participants received esketamine and 10 received midazolam treatment. During the infusion phase, five participants (all with anxious depression) failed to complete all three infusions; three completed one infusion of midazolam and two completed two infusions of esketamine. During the follow-up phase, five participants failed to complete the full follow-up assessment, two of them lost on day 6, one of them lost on day 12 and two of them lost on day 19. The sample sizes of each group at each follow-up time point are presented in [figure 1](#) and online supplemental tables 1–6).

Relative to the non-anxious group, the anxious group had more severe depressive symptoms at baseline according to the MADRS total score ( $t=-3.684$ ,  $p=0.001$ ) and received a higher proportion of benzodiazepines ( $\chi^2=5.129$ ,  $p=0.024$ ). Other measurements, including the C-SSRS Ideation and Intensity, BPRS-5, CADSS scores and cognitive domains, showed no significant differences between the anxious and non-anxious groups at baseline ([table 1](#)).



**Figure 1** Flowchart of participants' recruitment.

### Clinical outcomes at the acute treatment phase

Table 2 presented the rates of C-SSRS suicidal remission and response in the anxious/midazolam, non-anxious/midazolam, anxious/esketamine and non-anxious/esketamine groups. On day 6, in subjects who received esketamine, a greater number of participants in the non-anxious group than in the anxious group achieved antisuicidal remission (72.7% vs 18.8%,  $p=0.015$ ). No significant differences in antisuicidal response rates were observed in the anxious and non-anxious groups, regardless of whether they received midazolam or esketamine (all  $p>0.05$ ).

The MADRS remission and response rates in the four groups were presented in table 2. No significant differences in antidepressant remission or response rates on day 6 were observed between the anxious and non-anxious groups, regardless of whether they received midazolam or esketamine (all  $p>0.05$ ).

### Clinical outcomes at the follow-up phase

Results of antisuicidal and antidepressant outcomes during the follow-up phase were shown in table 2. In subjects who received esketamine, a greater number of participants in the non-anxious group than in the anxious group achieved antisuicidal remission on day 12 (90.9% vs 43.8%,  $p=0.013$ ), and the non-anxious group had higher antidepressant remission rates compared with the anxious group on day 33 (72.7% vs 26.7%,  $p=0.045$ ).

No significant differences in treatment outcomes were observed between the two groups at other time points.

### Results of factorial linear mixed models

For changes in the C-SSRS Ideation score, a significant time main effect ( $F=18.855$ ,  $p<0.001$ ) and a drug main effect ( $F=9.063$ ,  $p=0.004$ ) were found, but there was no significant group main effect or drug-by-group interaction effect (table 3). In subjects who received esketamine, post hoc analysis showed a reduction of C-SSRS Ideation scores was greater in the non-anxious group than in the anxious group on day 6 ( $t=-2.220$ ,  $p=0.028$ ) and day 12 ( $t=-2.518$ ,  $p=0.013$ ), but the difference faded on days 19 and 33 (figure 2, online supplemental table 1). No significant differences were found between non-anxious and anxious groups in subjects who received midazolam according to post hoc analysis.

Similar results were found in changes in the C-SSRS Intensity score, with a significant time main effect ( $F=20.809$ ,  $p<0.001$ ) and drug main effect ( $F=8.087$ ,  $p=0.007$ ), but there was no significant group main effect or drug-by-group interaction effect (table 3). Reduction of the C-SSRS Intensity score was greater in the non-anxious group than in the anxious group on day 6 ( $t=-2.182$ ,  $p=0.031$ ), but the difference faded on days 12, 19 and 33 (figure 2 and online supplemental table 2). There was no significant difference between the non-anxious



**Table 1** Demographic and baseline characteristics

	Non-anxious depression (n=21)	Anxious depression (n=33)	Statistics		
	Mean (SD)	Mean (SD)	t-test	df	P value
Age (years)	15.5 (1.0)	14.6 (1.5)	1.724	52	0.097
Duration of illness (months)	26.5 (14.3)	21.0 (12.1)	1.070	52	0.295
Body mass index (kg/m <sup>2</sup> )	21.1 (3.2)	20.9 (3.5)	0.139	52	0.891
Baseline MADRS total score	31.8 (5.7)	38.2 (6.6)	-3.684	52	0.001*
Baseline C-SSRS Ideation score	4.1 (1.2)	4.5 (0.9)	-1.626	52	0.110
Baseline C-SSRS Intensity score	17.3 (3.4)	18.9 (3.6)	-1.580	52	0.120
Baseline BPRS-5 score	5.0 (0.2)	5.3 (0.7)	-1.559	52	0.125
Baseline CADSS score	0.4 (1.2)	0.2 (0.5)	0.950	52	0.347
Baseline processing speed	43.3 (9.3)	39.7 (10.8)	1.256	52	0.215
Baseline working memory	44.8 (9.0)	42.1 (12.7)	0.863	52	0.392
Baseline verbal learning	48.2 (11.0)	42.8 (9.8)	1.892	52	0.064
Baseline visual learning	45.1 (8.8)	42.6 (8.8)	1.063	52	0.293
	N (%)	N (%)	$\chi^2$	df	P value
Gender (female)	19 (90.5)	29 (87.9)	0.088	1	0.767
Mood disorder in first-degree relatives	7 (33.3)	10 (30.3)	0.055	1	0.815
Met TRD criteria	12 (57.1)	19 (57.6)	0.001	1	0.975
First depressive episode	15 (71.4)	25 (75.8)	0.125	1	0.723
Current antidepressant	21 (100.0)	33 (100.0)	--	--	--
SSRIs	16 (76.2)	30 (90.9)	2.203	1	0.138
Escitalopram	8 (38.1)	11 (33.3)	--	--	--
Sertraline	2 (9.5)	8 (24.2)	--	--	--
Fluoxetine	5 (23.8)	9 (27.3)	--	--	--
Fluvoxamine	1 (4.8)	1 (3.0)	--	--	--
Duloxetine	3 (14.3)	1 (3.0)	--	--	--
Venlafaxine	2 (9.5)	1 (3.0)	--	--	--
Agomelatine	1 (4.8)	0 (0.0)	--	--	--
Vortioxetine	0 (0.0)	2 (6.1)	--	--	--
Current antipsychotic	13 (61.9)	20 (60.6)	0.009	1	0.924
Current mood stabiliser	8 (38.1)	6 (18.2)	2.650	1	0.104
Current benzodiazepine	12 (57.1)	28 (84.8)	5.129	1	0.024*
Study drug (esketamine)	11 (52.4)	16 (48.5)	0.078	1	0.780

\*p&lt;0.05

BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician-Administered Dissociative Symptoms Scale; C-SSRS, Columbia Suicide Severity Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; TRD, treatment-resistant depression.

and anxious groups in subjects who received midazolam, according to post hoc analysis.

For changes in the MADRS total score, a significant time main effect ( $F=30.596$ ,  $p<0.001$ ) and a drug main effect ( $F=4.903$ ,  $p=0.031$ ) were found, but there was no significant group main effect or drug-by-group interaction effect (table 3). Results of post hoc analysis at each time point were shown in figure 2 and online supplemental table 3.

No significant time main effect, group main effect, drug main effect or their interaction effect was found in the BPRS-5 score ( $p>0.05$ ). A significant main effect for time ( $F=7.342$ ,  $p<0.001$ ) and a drug main effect ( $F=5.132$ ,  $p=0.028$ ) were shown in the CADSS score (table 3). Post hoc analysis showed that anxious patients had higher CADSS scores on day 1 ( $t=-2.527$ ,  $p=0.012$ ) and BPRS-5 scores on day 6 ( $t=-2.000$ ,  $p=0.046$ ) than non-anxious patients (figure 2 and online supplemental tables 5 and 6).

**Table 2** Group difference of treatment outcome rate

	Esketamine				Midazolam			
	Non-anxious	Anxious	$\chi^2$	P value	Non-anxious	Anxious	$\chi^2$	P value
C-SSRS suicidal remission rate								
Day 6	8/11 (72.7%)	3/16 (18.8%)	–†	0.015*	2/10 (20.0%)	2/15 (13.3%)	–†	1.000
Day 12	10/11 (90.9%)	7/16 (43.8%)	6.217	0.013*	4/10 (40.0%)	4/14 (28.6%)	–†	0.673
Day 19	8/11 (72.7%)	9/15 (60.0%)	0.454	0.500	3/9 (33.3%)	6/14 (42.9%)	–†	1.000
Day 33	7/11 (63.6%)	9/15 (60.0%)	0.035	0.851	4/9 (44.4%)	6/14 (42.9%)	–†	1.000
C-SSRS suicidal response rate								
Day 6	10/11 (90.9%)	10/16 (62.5%)	2.739	0.098	7/10 (70.0%)	5/15 (33.3%)	3.232	0.072
Day 12	10/11 (90.9%)	10/16 (62.5%)	2.739	0.098	6/10 (60.0%)	8/14 (57.1%)	0.020	0.889
Day 19	9/11 (81.8%)	10/15 (66.7%)	0.740	0.390	5/9 (55.6%)	6/14 (42.9%)	0.354	0.552
Day 33	7/11 (63.6%)	11/15 (73.3%)	0.280	0.597	5/9 (55.6%)	7/14 (50.0%)	0.068	0.795
MADRS remission rate								
Day 6	4/11 (36.4%)	4/16 (25.0%)	–†	0.675	1/10 (10.0%)	1/15 (6.7%)	–†	1.000
Day 12	7/11 (63.6%)	5/16 (31.3%)	2.769	0.096	3/10 (30.0%)	1/14 (7.1%)	–†	0.272
Day 19	6/11 (54.5%)	6/15 (40.0%)	0.540	0.462	1/9 (11.1%)	2/14 (14.3%)	–†	1.000
Day 33	8/11 (72.7%)	4/15 (26.7%)	–†	0.045*	1/9 (11.1%)	3/14 (21.4%)	–†	1.000
MADRS response rate								
Day 6	5/11 (45.5%)	6/16 (37.5%)	0.171	0.679	2/10 (20.0%)	3/15 (20.0%)	–†	1.000
Day 12	8/11 (72.7%)	8/16 (50.0%)	1.395	0.238	5/10 (50.0%)	2/14 (14.3%)	–†	0.085
Day 19	7/11 (63.6%)	8/15 (53.3%)	0.276	0.599	1/9 (11.1%)	4/14 (28.6%)	–†	0.611
Day 33	8/11 (72.7%)	8/15 (53.3%)	1.008	0.315	1/9 (11.1%)	7/14 (50.0%)	–†	0.086

\*p&lt;0.05

†Fisher's exact test.

C-SSRS, Columbia Suicide Severity Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale.

For changes in the MCCB, no significant group main effect or drug-by-group interaction effect was found in any of the domains, but there were significant main time effects in the change in processing speed ( $F=13.223$ ,  $p<0.001$ ), working memory ( $F=7.154$ ,  $p=0.001$ ) and verbal learning ( $F=5.831$ ,  $p=0.004$ ), and a significant drug main effect in the change in processing speed ( $F=7.433$ ,  $p=0.009$ ; table 3). Post hoc analysis showed that improvement of verbal learning was greater in the anxious group than in the non-anxious group on day 12 ( $t=-2.362$ ,  $p=0.020$ ; online supplemental table 6).

## DISCUSSION

### Main findings

In this post hoc study of adolescents with MDD and suicidal ideation, we found that three low-dose esketamine infusions as an adjunct to oral antidepressant therapy had a greater antisuicidal effect immediately post-treatment in non-anxious patients compared with anxious patients. However, this benefit was temporary and faded rapidly over time. Anxious patients experienced similar antidepressant effects and side effects to esketamine as non-anxious patients, except that the non-anxious group showed a greater antidepressant remission rate at 4 weeks

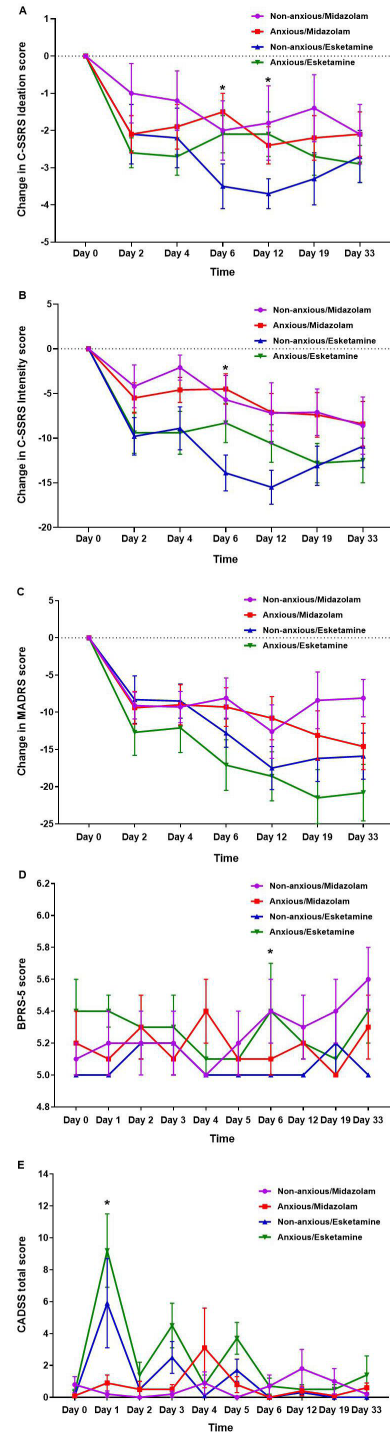
post-treatment. The current results did not support our hypothesis.

Three infusions of esketamine were significantly associated with greater antidepressant and antisuicidal efficacy according to greater reductions in MADRS and C-SSRS scores; our study team has reported these findings in detail elsewhere and they will be published soon.<sup>20</sup> Previous studies suggest that anxious depression in adolescents may have a lower response to conventional antidepressant medication than non-anxious depression in this group.<sup>3</sup> For the new drug esketamine, we found a relatively greater antisuicidal effect in adolescents with non-anxious depression than in those with anxious depression, according to the C-SSRS Ideation remission rate 24 hours immediately after treatment (72.7% vs 18.8%), and the effect persisted at 1 week after treatment (90.9% vs 43.8%). Although no statistically significant difference was found between anxious and non-anxious status on the C-SSRS Ideation response rate, it was numerically higher in the non-anxious group than in the anxious group (90.9% vs 62.5%). In addition, the post hoc analysis also showed that non-anxious patients had a greater reduction in suicidal ideation at 24 hours post-treatment. However, no significant group main effect or

**Table 3** Results of factorial linear mixed model analysis of clinical symptoms and cognitive performance

	Time main effect		Drug main effect		Group main effect		Drug×group		Drug×group×time	
	F	P value	F	P value	F	P value	F	P value	F	P value
Change in C-SSRS Ideation	18.855	<0.001*	9.063	0.004*	1.175	0.284	0.306	0.583	1.198	0.261
Change in C-SSRS Intensity	20.809	<0.001*	8.087	0.007*	0.524	0.473	0.611	0.438	1.156	0.298
Change in MADRS	30.596	<0.001*	4.903	0.031*	0.008	0.931	0.484	0.490	2.245	0.003*
BPRS-5	0.772	0.642	0.239	0.627	0.474	0.494	2.963	0.091	0.864	0.665
CADSS	7.342	<0.001*	5.132	0.028*	2.032	0.160	1.251	0.269	3.609	<0.001*
Change in processing speed	13.223	<0.001*	7.433	0.009*	0.616	0.436	0.710	0.404	1.446	0.206
Change in working memory	7.154	0.001*	0.001	0.995	0.050	0.824	0.015	0.903	0.561	0.760
Change in verbal learning	5.831	0.004*	0.355	0.554	0.613	0.438	0.043	0.836	1.753	0.117
Change in visual learning	0.340	0.713	0.261	0.612	0.047	0.829	0.232	0.632	0.311	0.930

\*p<0.05  
BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician-Administered Dissociative Symptoms Scale; C-SSRS, Columbia Suicide Severity Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale.



**Figure 2** Effect of esketamine and midazolam in anxious versus non-anxious depressed patients at baseline through day 33. Panels A–C show the change from baseline for suicidal ideation and depressive symptoms during the study period (days 0–33). Panels D–E show psychotomimetic and dissociative symptoms in anxious versus non-anxious depressed patients at baseline through day 33. Values co-varied for baseline score, duration of illness, antidepressant class and augmentation therapy. \*p<0.05. Using post hoc test between non-anxious/esketamine and anxious/esketamine groups. BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician-Administered Dissociative Symptoms Scale; C-SSRS, Columbia Suicide Severity Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale.

drug-by-group interaction was found. The sample size for each group was small, so the results are insufficient, but they can reflect potential acute treatment differences. However, this benefit was temporary and could not be maintained over time, given that there were no significant differences between the anxious and non-anxious groups at 2 and 4 weeks post-treatment.

Adult studies have shown inconsistent results of ketamine's antidepressant effect on anxious and non-anxious depression. In a placebo-controlled RCT, ketamine was administered at different doses—0.1, 0.2, 0.5 and 1.0 mg/kg—and the results showed that the antidepressant effect of ketamine did not differ between patients with TRD with anxious and non-anxious depression.<sup>12</sup> In addition, a randomised, midazolam-controlled study involving 36 patients with treatment-resistant bipolar depression who received a single infusion of ketamine showed an equally rapid and robust reduction in depressive symptoms.<sup>11</sup> However, an open-label study of 26 patients with TRD who received a single dose of ketamine showed that patients with anxiety responded better to ketamine than those without anxiety, with a significantly longer time-to-relapse.<sup>10</sup> Our previous study of adults with TRD who received repeated-dose ketamine showed that, compared with patients with pure melancholic or melancholic-anxious features, those with pure anxiety took less time to achieve response/remission and showed more improvement in depression, anxiety and suicidal ideation.<sup>14</sup> The current study is the first to examine whether the anxious subtype is associated with better treatment outcomes following repeated-dose esketamine treatment in adolescents. However, we failed to replicate our previous results from adult data.

Psychotomimetic and dissociative symptoms were common acute adverse effects during short-term treatment with low-dose ketamine, but these adverse effects were mild and transient and generally resolved within 1–2 hours following ketamine administration.<sup>34</sup> Although the mixed model revealed no significant drug-by-group interaction in the CADSS score, the post hoc analysis showed that anxious patients suffered dissociative symptoms with greater severity than non-anxious patients at 30 min postinitial esketamine infusion. Participants treated with midazolam did not show this difference between the groups. Dissociative symptoms are present in various mental disorders, including post-traumatic stress disorder, borderline personality disorder, conversion disorder, anxiety and depressive disorder.<sup>35–36</sup> It was reported that high anxiety levels were important in the development of dissociation.<sup>37</sup> Individuals with high anxiety sensitivity may experience higher peritraumatic dissociation levels, and these individuals could have a higher predisposition for post-traumatic stress disorder in the future.<sup>38</sup> In addition, patients suffering dissociative symptoms for the first time may have difficulty understanding and accepting these symptoms and may even feel fearful, especially individuals with anxiety features.<sup>39–40</sup> For example, according to the Canadian

Network for Mood and Anxiety Treatments Task Force guidelines, 50%–80% of ketamine-treated patients experience mild-to-moderate dissociative symptoms.<sup>41</sup> However, ketamine in adult TRD revealed no difference in CADSS and BPRS scores between the anxious and non-anxious groups.<sup>10–11</sup> Future studies should be conducted to determine the psychological characteristics of adolescents so that ketamine and esketamine can be used safely to help them cope with affective disorders.

No cognitive deterioration following three infusions of esketamine treatment was observed in the studied adolescents. Conversely, improvement in processing speed was observed post-infusion. Esketamine had equally short-term cognitive effects for adolescents with or without anxious depression, which was inconsistent with the observation of ketamine and traditional antidepressants in adult studies. For example, our previous study of six infusions of ketamine involving adult TRD suggested improvement in cognitive function, including processing speed and verbal learning. This was observed in the anxious group but not in the non-anxious group.<sup>15</sup> Also, better verbal learning was reported in patients with anxious depression at baseline and the end of week 8 after conventional antidepressant treatment.<sup>30</sup>

### Limitations

Several limitations should be acknowledged. First, the post hoc analysis of this study made unequal sample sizes and baseline characteristics of anxious and non-anxious groups, which may be susceptible to type I error. Second, in our study, 84.8% of patients with anxious depression were concomitantly treated with benzodiazepines, significantly more than those with non-anxious MDD. Previous studies suggested concomitant benzodiazepine use may attenuate ketamine's antidepressant outcome.<sup>42</sup> Possible interference of benzodiazepines with esketamine's effects, especially in the anxious group, cannot be ruled out. Third, other oral antidepressant medications were provided concomitantly with the study drug. Thus, a synergistic (not independent) benefit of esketamine combined with oral antidepressant medication cannot be completely ruled out as the reason for mood improvement.

### Implications

The present results suggest the possibility that, in adolescents with MDD and suicidal ideation, three infusions of low-dose esketamine as an adjunct to oral antidepressant therapy had a greater acute antisuicidal effect in individuals without anxiety than those with anxiety. However, this benefit was temporary and could not be maintained over time. Moreover, esketamine seemed to be equally antidepressant-effective and safe for treating adolescent MDD with or without anxiety.

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## REFERENCES

- Kessler RC, Sampson NA, Berglund P, *et al.* Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiol Psychiatr Sci* 2015;24:210–26.
- Essau CA. Comorbidity of depressive disorders among adolescents in community and clinical settings. *Psychiatry Res* 2008;158:35–42.
- Curry J, Rohde P, Simons A, *et al.* Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *Journal of the American Academy of Child & Adolescent Psychiatry* 2006;45:1427–39.
- Fava M, Rush AJ, Alpert JE, *et al.* Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR\*D report. *Am J Psychiatry* 2008;165:342–51.
- Murrough JW, Iosifescu DV, Chang LC, *et al.* Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry* 2013;170:1134–42.
- Wilkinson ST, Ballard ED, Bloch MH, *et al.* The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry* 2018;175:150–8.
- Zheng W, Zhou Y-L, Liu W-J, *et al.* Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. *Journal of Psychiatric Research* 2018;106:61–8.
- Canuso CM, Singh JB, Fedgchin M, *et al.* Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 2018;175:620–30.
- Daly EJ, Singh JB, Fedgchin M, *et al.* Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* 2018;75:139.
- Ionescu DF, Luckenbaugh DA, Niciu MJ, *et al.* Effect of baseline anxious depression on initial and sustained antidepressant response to ketamine. *J Clin Psychiatry* 2014;75:e932–8.
- Ionescu DF, Luckenbaugh DA, Niciu MJ, *et al.* A single infusion of ketamine improves depression scores in patients with anxious bipolar depression. *Bipolar Disord* 2015;17:438–43.
- Salloum NC, Fava M, Freeman MP, *et al.* Efficacy of intravenous ketamine treatment in anxious versus nonanxious unipolar treatment-resistant depression. *Depress Anxiety* 2019;36:235–43.
- Wang S, Tang S, Huang J, *et al.* Rapid-acting antidepressants targeting modulation of the glutamatergic system: clinical and Preclinical evidence and mechanisms. *Gen Psychiatr* 2022;35:e100922.
- Wang C, Zhou Y, Zheng W, *et al.* Association between depression subtypes and response to repeated-dose intravenous ketamine. *Acta Psychiatr Scand* 2019;140:446–57.
- Liu W, Zhou Y, Zheng W, *et al.* Repeated intravenous infusions of ketamine: neurocognition in patients with anxious and nonanxious treatment-resistant depression. *Journal of Affective Disorders* 2019;259:1–6.
- Dwyer JB, Landeros-Weisenberger A, Johnson JA, *et al.* Efficacy of intravenous ketamine in adolescent treatment-resistant depression: a randomized midazolam-controlled trial. *Am J Psychiatry* 2021;178:352–62.
- Cullen KR, Amatya P, Roback MG, *et al.* Intravenous ketamine for adolescents with treatment-resistant depression: an open-label study. *Journal of Child and Adolescent Psychopharmacology* 2018;28:437–44.
- Dwyer JB, Beyer C, Wilkinson ST, *et al.* Ketamine as a treatment for adolescent depression: A case report. *J Am Acad Child Adolesc Psychiatry* 2017;56:352–4.
- Zarrinpar P, Kothari J, Cheng K. Successful use of ketamine for the treatment of psychotic depression in a teenager. *J Child Adolesc Psychopharmacol* 2019;29:472–3.
- Zhou Y, Lan X, Wang C, *et al.* Three low-dose Esketamine infusions as an adjunct to routine inpatient care and treatment affected a greater Antisuicidal remission rate in MDD adolescents without anxiety compared to those with anxiety [Accepted]. *J Am Acad Child Adolesc Psychiatry* 2023.
- American Psychiatric Association. Diagnostic and statistical Manual of mental disorders. 5th edn. American Psychiatric Association, 22 May 2013.
- Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry* 1960;23:56–62.
- Xie GR, Shen QJ. Use of the Chinese version of the Hamilton Rating Scale for Depression in general population and patients with major depression (in Chinese). *Chin J Nerv Ment Dis* 1984;10:364.
- Posner K, Brown GK, Stanley B, *et al.* The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *AJP* 2011;168:1266–77.
- Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *Journal of Consulting and Clinical Psychology* 1979;47:343–52.
- Cleary P GW. Factor analysis of the Hamilton Depression Scale. *Drugs Exp Clin Res* 1977;1:115–20.
- Li HF. *Common scales for clinical research on psychotropic drugs*. Shanghai Science and Technology Education Press, 2014.
- Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.
- Zhong BL, Wang Y, Chen HH, *et al.* Reliability, validity and sensitivity of Montgomery-Åsberg Depression Rating Scale for patients with current major depressive disorder. *Chinese Journal of Behavioural Medicine and Brain Sciences* 2011;20:85–7.
- Overall JE, Beller SA. The Brief Psychiatric Rating Scale (BPRS) in Geropsychiatric research: I factor structure on an inpatient unit. *J Gerontol* 1984;39:187–93.
- Bremner JD, Krystal JH, Putnam FW, *et al.* Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress* 1998;11:125–36.
- Green MF, Nuechterlein KH, Gold JM, *et al.* Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICES conference to select cognitive domains and test criteria. *Biol Psychiatry* 2004;56:301–7.
- Shi C, Kang L, Yao S, *et al.* The MATRICS Consensus Cognitive Battery (MCCB): co-norming and standardization in China. *Schizophrenia Research* 2015;169:109–15.
- Short B, Fong J, Galvez V, *et al.* Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry* 2018;5:65–78.
- Lyssenko L, Schmahl C, Bockhacker L, *et al.* Dissociation in psychiatric disorders: a meta-analysis of studies using the Dissociative Experiences Scale. *Am J Psychiatry* 2018;175:37–46.

- 36 Černis E, Evans R, Ehlers A, *et al.* Dissociation in relation to other mental health conditions: an exploration using network analysis. *J Psychiatr Res* 2021;136:460–7.
- 37 Kadak MT, Nasıroğlu S, Boysan M, *et al.* Risk factors predicting posttraumatic stress reactions in adolescents after 2011 Van earthquake. *Comprehensive Psychiatry* 2013;54:982–90.
- 38 Uğur K, Kartal F, Mete B, *et al.* The relationship between peritraumatic dissociation and anxiety level, perceived stress, anxiety sensitivity and coping with earthquake stress in post-earthquake acute stress disorder patients. *Türk Psikiyatri Derg* 2021;32:253–60.
- 39 Glue P, Medlicott NJ, Harland S, *et al.* Ketamine's dose-related effects on anxiety symptoms in patients with treatment refractory anxiety disorders. *J Psychopharmacol* 2017;31:1302–5.
- 40 Glue P, Neehoff S, Sabadel A, *et al.* Effects of ketamine in patients with treatment-refractory generalized anxiety and social anxiety disorders: exploratory double-blind psychoactive-controlled replication study. *J Psychopharmacol* 2020;34:267–72.
- 41 Swainson J, McGirr A, Blier P, *et al.* The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the use of racemic ketamine in adults with major depressive disorder: Recommendations Du Groupe de Travail Du Réseau Canadien pour LES Traitements de L'Humeur et de L'Anxiété (Canmat) Concernant L'Utilisation de la Kétamine Racémique Chez LES Adultes Souffrant de trouble Dépressif Majeur. *Can J Psychiatry* 2021;66:113–25.
- 42 Albott CS, Shiroma PR, Cullen KR, *et al.* The antidepressant effect of repeat dose intravenous ketamine is delayed by concurrent benzodiazepine use. *J Clin Psychiatry* 2017;78:e308–9.



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