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ARTICLE

Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: a double-blind randomized placebo–control study

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Increasing evidence supports a rapid antidepressant and antisuicidal effect of a single subanesthetic dose of ketamine infusion for treatment-resistant depression (TRD). Maintaining the initial clinical response after ketamine infusion in TRD is a crucial next-step challenge. D-cycloserine (DCS), a partial agonist of the glycine co-agonist of the N-methyl-D-aspartate (NMDA) glutamate receptor, is potentially effective as a depression augmentation treatment. However, whether DCS maintains the antidepressant and antisuicidal effects of ketamine infusion remains unknown. In all, 32 patients with TRD (17 with major depression and 15 with bipolar depression) who responded to ketamine infusion with an average 17-item Hamilton Depression Rating Scale (HAMD) score of 9.47 ± 4.11 at baseline were randomly divided to 6-week DCS treatment (250 mg for 2 days, 500 mg for 2 days, 750 mg for 3 days, and 1000 mg for 5 weeks) and placebo groups. Depression symptoms were rated at timepoints of dose titration and weekly. During the 6-week treatment, the total scores of HAMD did not differ between the DCS and placebo groups. The results remained consistent when stratified by disorder. A mixed model analysis indicated that the DCS group exhibited lower scores of HAMD item 3 (suicide) compared with the placebo group throughout the follow-up period ($p = 0.01$). A superior maintenance of the antisuicidal effect of ketamine was observed in the DCS group than in the placebo group. DCS may be therapeutically beneficial for patients with TRD who responded to ketamine infusion but have a residual suicidal risk.

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INTRODUCTION

The Sequenced Treatment Alternatives to Relieve Depression study reported that up to 40% of the patients with major depressive disorders did not achieve symptomatic remission after two trials of traditional antidepressants, which is defined as treatment-resistant major depression [1]. In comparison with treatment-resistant major depression, treatment-resistant bipolar depression has been less studied, although depressive and dysthymic episodes contribute to the majority of the clinical course of bipolar disorder [2–4]. Treatment resistance in major depression and bipolar depression has been commonly coupled with functional impairment, poor quality of life, suicide ideation and attempts, self-injurious behaviors, and a high relapse rate [2, 4, 5].

Increasing evidence suggests a rapid antidepressant effect of a single subanesthetic dose of ketamine infusion for treatment-resistant major depression and bipolar depression [6–8]. Beyond the rapid antidepressant effect of ketamine infusion, a recent meta-analysis supports a rapid antisuicidal effect of a single low-dose ketamine infusion in patients with treatment-resistant major depression and bipolar depression [9]. Wilkinson et al. indicated that ketamine rapidly reduced suicidal thoughts within 1 day and for up to 1 week in depressed patients with suicidal ideation and further determined that ketamine's effects on suicidal ideation were partially independent of its effects on depression [9]. Thus, the underlying mechanisms of ketamine effects on depression and suicidality mitigation may differ.

However, maintaining the initial response of ketamine infusion is an important therapeutic challenge in the psychiatric clinical practice [10]. The benefits of ketamine may be extended by repeated dosing, but ketamine infusion is resource intensive and is associated with risks, including addiction liability, dissociative symptoms, and nausea [11]. Finding an optimal drug that can maintain the antidepressant effects of ketamine infusion may be clinically beneficial for patients with treatment-resistant major depression and bipolar depression [10].

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D-cycloserine (DCS), a partial agonist of the glycine site of NMDA glutamate receptors, has been reported to be potentially effective for depression augmentation treatment [12, 13]. Heresco-Levy et al. reported that only high doses (1000 mg/day) of DCS, which act as a functional NMDAR antagonist, but not low doses (250 mg/day), are significantly effective for treatment-resistant depression (TRD) [12, 14]. A small sample size ($n = 7$) open-label study suggested a potential role of DCS in the maintenance of the antidepressant effect of a single dose of ketamine infusion among patients with treatment-resistant bipolar depression [15]. However, whether DCS can really maintain the antidepressant effect of ketamine infusion in a randomized placebo–control study design setting remains unknown.

In this study, we conducted a two-phase clinical trial composed of a ketamine infusion open-label trial (phase 1 study) and a double-blind randomized DCS–placebo control trial (phase 2 study). Patients with treatment-resistant major depression or bipolar depression who responded to ketamine infusion in the phase 1 study were enrolled in the phase 2 study for the investigation of the role of DCS in the maintenance of the initial response of ketamine. We hypothesized that DCS may be superior to a placebo in maintaining the antidepressant effect of ketamine infusion.

METHODS

Inclusion criteria of patients

We enrolled 49 patients aged between 21 and 65 years with a *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, Text Revision diagnosis of major depressive disorder or bipolar disorder or major depressive episode. In addition, they met the criteria of TRD (treatment-resistant major depression and bipolar depression). Treatment-resistant major depression was defined as the failure of treatment response for at least two different antidepressants with adequate dosage and treatment duration [7]. Treatment-resistant bipolar depression was defined as a lack of response to at least two trials with antidepressants or mood stabilizers with documented efficacy in bipolar depression (lithium, lamotrigine, quetiapine, or olanzapine) in adequate doses and treatment duration [16]. Mini-International Neuropsychiatric Interview (MINI) for depression and suicidality and Maudsley staging method (MSM) for level of treatment resistance were also assessed [17, 18]. Patients were excluded if they had a history of any major medical or neurological illness (i.e., stroke or seizure), alcohol or substance abuse, and mild symptoms (17-item Hamilton Depression Rating Scale (HAMD) score < 16 before study entry) [19]. This clinical trial was registered in the UMIN Clinical Trials Registry (R000027142-UMIN000023581). This study was performed in accordance with the Declaration of Helsinki, and was approved by the Taipei Veterans General Hospital Institutional Review Board. Informed consent was provided by all participants.

Study procedures

This study was composed of phase 1 open-label ketamine infusion study and phase 2 double-blind randomized DCS–placebo control study (Fig. 1). In the phase 1 study, patients with TRD received the add-on 40-min intravenous ketamine (0.5 mg/kg) infusions at day 1 and day 4 of the phase 1 study. Depressive symptoms were rated using the HAMD on day 1 (first ketamine infusion: 0, 40, 80, 120, and 240 min), day 2, day 4 (second ketamine infusion: 0, 40, 80, 120, and 240 min), day 5, and day 7. The purpose of two ketamine infusions is to improve the response rate in the phase 1 study, because our previous clinical trial study found only ~50% of the response rate after a single dose (0.5 mg/kg) of ketamine infusion in Taiwanese patients with TRD [7]. Responder status was defined by the response

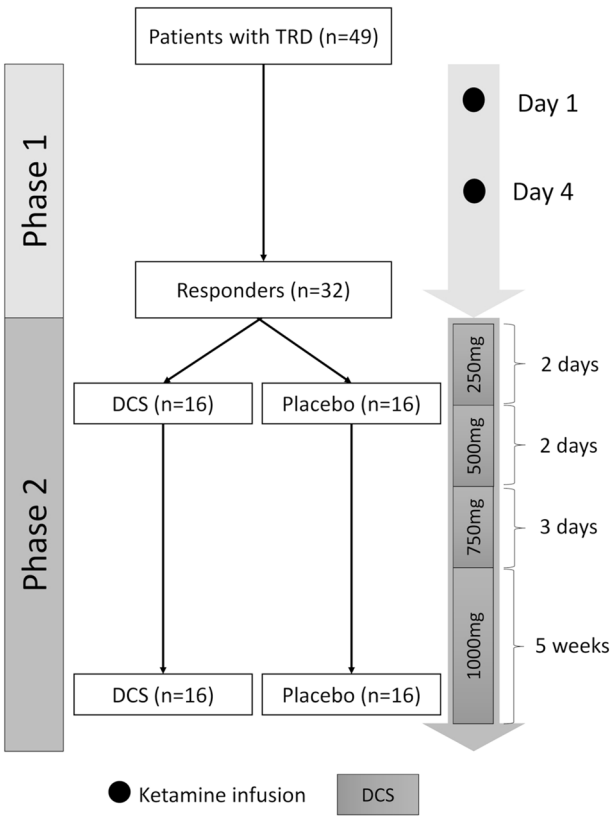

Fig. 1 Study design flow chart. TRD treatment-resistant depression (major depression, bipolar depression), DCS D-cycloserine

Table 1. Demographic and clinical characteristic among patients with treatment-resistant depression in phase 1 open-label study

	All patients ($n = 49$)	Bipolar ($n = 19$)	MDD ($n = 30$)	*p*-value
Age (years, SD)	47.35 (10.66)	45.47 (11.33)	48.53 (10.23)	0.33
Male (*n*, %)	13 (26.5%)	5 (26.3%)	8 (26.7%)	>0.99
Education (years, SD)	13.47 (2.79)	13.68 (2.63)	13.33 (2.93)	0.67
Duration of illness (years, SD)	13.69 (8.43)	14.74 (6.94)	13.03 (9.30)	0.50
Psychiatric comorbidities				
PD	16 (32.7%)	7 (36.8%)	9 (30.0)	0.62
PTSD	2 (4.1%)	0 (0.0%)	2 (6.7%)	0.52
GAD	21 (42.9%)	6 (31.6%)	15 (50.0%)	0.25
Suicide history (*n*, %)	24 (49.0%)	11 (57.9%)	13 (43.3%)	0.39
HAMD score (SD)				
Baseline (day 1)	22.08 (3.54)	22.42 (3.25)	21.87 (3.75)	0.60
First injection (day 1)				
40 min	14.67 (5.61)	14.47 (4.98)	14.80 (6.05)	0.85
80 min	13.90 (5.59)	13.63 (5.42)	14.07 (5.78)	0.79
120 min	13.27 (5.40)	13.16 (5.74)	13.33 (5.64)	0.91
240 min	13.06 (5.40)	13.16 (5.74)	13.00 (5.28)	0.92
Day 2	12.90 (6.21)	12.79 (6.92)	12.97 (5.85)	0.92
Second injection (day 4)	13.96 (6.60)	14.53 (7.91)	13.60 (5.73)	0.64
40 min	11.98 (6.41)	12.37 (7.02)	11.73 (6.10)	0.74
80 min	11.84 (6.54)	12.63 (7.51)	11.33 (5.93)	0.50
120 min	11.80 (6.60)	12.53 (7.73)	11.33 (5.88)	0.54
240 min	11.78 (6.53)	12.16 (7.37)	11.53 (6.05)	0.75
Day 5	12.33 (6.93)	12.63 (8.49)	12.13 (5.89)	0.81
Day 7	13.20 (7.02)	13.63 (8.25)	12.93 (6.25)	0.74
Response rate (*n*, %)	32 (65%)	13 (68.4%)	19 (63.3%)	0.77

HAMD Hamilton Depression Rating Scale, *PD* panic disorder, *PTSD* posttraumatic stress disorder, *GAD* generalized anxiety disorder, *SD* standard deviation

(≥ 50% reduction of mood ratings) at any two daily HAMD measures during the period of day 1 to day 7 post-ketamine administration. Only those who responded to ketamine infusion ($n = 32$) were enrolled in the phase 2 double-blind randomized DCS–placebo control study. In the phase 2 study, patients with TRD were randomly divided into 6-week DCS (Seromycin, Eli Lilly) treatment and placebo groups. For the DCS group, the dose titration procedure was applied from 250 mg/day for 2 days, 500 mg/day for 2 days, and 750 mg/day for 3 days to 1000 mg/day for 5 weeks. The final dose was adjusted in the range of 500–1000 mg/day based on the patients' tolerability. Depression symptoms were rated at timepoints of dose titration and weekly.

Statistical analysis

The data were checked for normality prior to analysis. There were no missing data in our study. Independent *t* tests for continuous variables and Fisher's chi-square tests for nominal variables were used to assess between-group differences in baseline demographic and clinical data. In the phase 1 study, a mixed model analysis with an autoregressive correlation structure for the repeated measures on the same individual over time was used to assess the effects of ketamine on depression symptoms during the treatment period with group (major depression vs. bipolar depression) as a between-patient factor, time (day 1 to day 7) as a within-patient factor, and baseline depression symptoms as a between-patient predictor, as well as all possible interactions. In the phase 2 study, mixed model analyses with autoregressive correlation structure of the repeated measures for the same individual over time was used to assess the effects of DCS on the total HAMD scores and on item 3 (suicide) HAMD scores during the treatment period with group (DCS vs. placebo) as a between-patient factor, time (week 1 to week 6) as a within-patient factor, and baseline depression (after ketamine infusion) scores as a between-patient predictor, as well as all possible interactions. Furthermore, separate analyses for patients with major depression and with bipolar depression were also conducted to investigate the potential role of disorder type in DCS treatment efficacy. A two-tailed p-value < 0.05 was considered statistically significant. All data processing and statistical analyses were performed using the SPSS version 21 software (SPSS Inc.).

RESULTS

Phase 1 open-label ketamine infusion study

In the phase 1 study, 30 patients with treatment-resistant major depression and 19 with treatment-resistant bipolar depression were enrolled, with an average age of 47.35 (SD = 10.66) years and predominantly female (73.5%; Table 1). Average HAMD scores were 22.08 (SD = 3.54) at baseline before ketamine infusion. The response rate was 65% ($n = 32$) after two ketamine infusions, and did not differ between major depression and bipolar depression (63.3% vs. 68.4%, $p = 0.77$). The mixed model analyses demonstrated that the repeated ketamine infusions were effective for treatment-resistant major depression ($F(1,65) = 17.58$, $p < 0.001$) and bipolar depression ($F(1,27) = 10.24$, $p = 0.003$) (Fig. 2).

Phase 2 double-blind randomized DCS–placebo control study

In phase 2 double-blind randomized placebo control study, 32 patients with TRD who responded to ketamine infusions in the

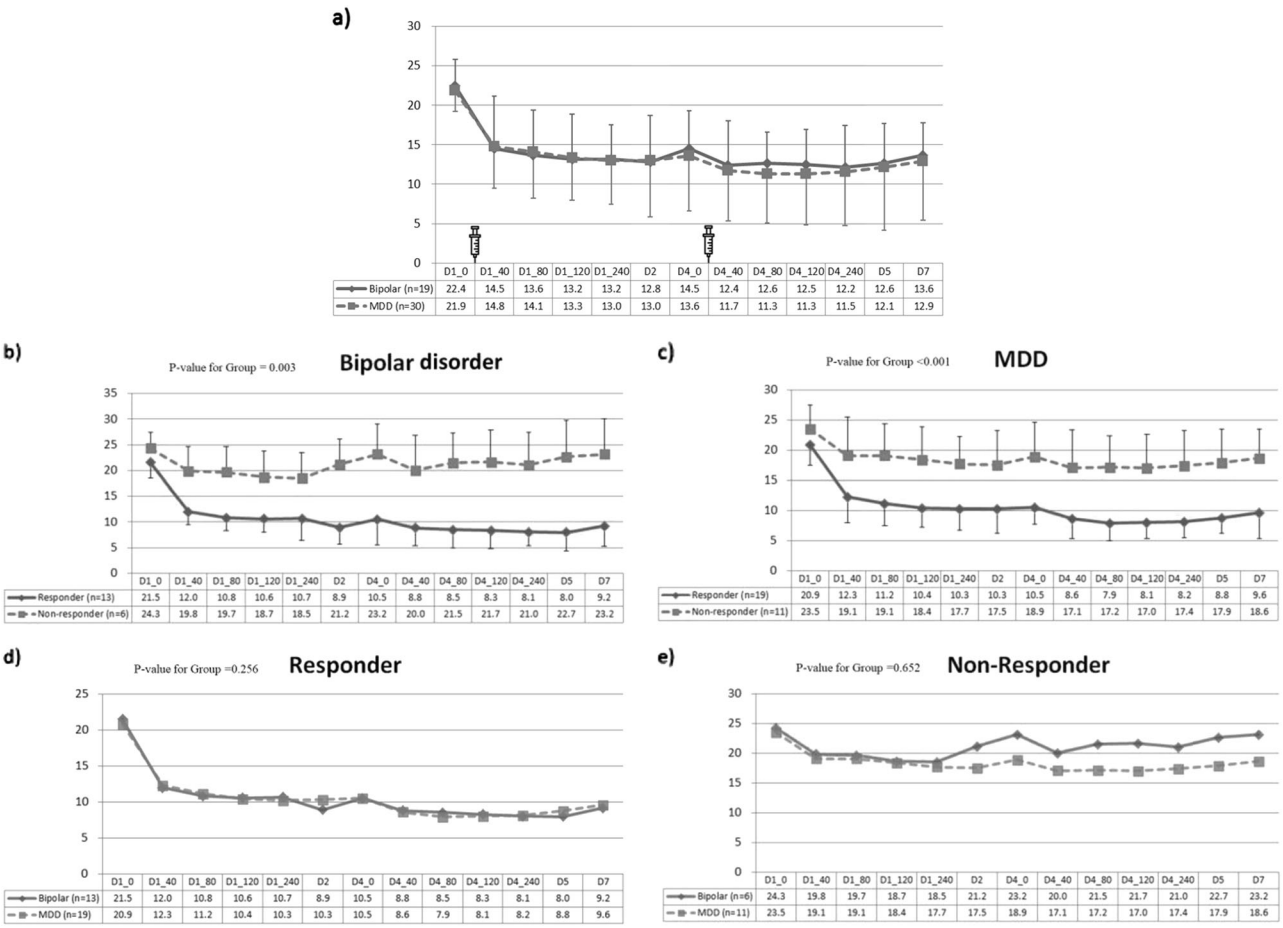

Fig. 2 Trajectory of depression in phase 1 open-label study (the mixed model with adjustment of baseline score, age and sex). **a** Total patients, **b** bipolar disorder patients, **c** major depressive disorder (MDD) patients, **d** responders, and **e** non-responders

phase 1 study were enrolled. With the 6-week DCS or placebo treatment, the total HAMD scores did not differ throughout the follow-up period between the DCS and placebo groups ($F(1,27) = 1.11$, $p = 0.30$; Table 2 and Fig. 3). The interaction between disorder type and treatment was nonsignificant ($F(1,24) = 1.93$, $p = 0.18$). Separate analyses for individuals with major depression ($F(1,31) = 0.09$, $p = 0.77$) and with bipolar depression ($F(1,33) = 2.26$, $p = 0.14$) demonstrated that the maintenance of the antidepressant effect of ketamine infusion was similar between the DCS and placebo groups (Fig. 3).

Specifically analyzing the role of DCS in the maintenance of antisuicidal effect, measured by item 3 (suicide) of HAMD, of ketamine infusion, we found that the DCS group exhibited lower scores of HAMD item 3 than the placebo group throughout the follow-up period ($F(1,26) = 7.91$, $p = 0.01$; Fig. 4).

Adverse effects, including dizziness (18.8% vs. 6.3%, $p = 0.600$), sedation (18.8% vs. 0%, $p = 0.226$), hand tremor (12.5% vs. 0%, $p = 0.484$), and itching (6.3% vs. 0%, $p > 0.999$), were rare and did not differ between DCS and placebo groups (Supplementary Table 1).

Table 2. Demographic and clinical characteristic among patients with treatment-resistant depression in phase 2 double-blind randomized placebo–control study

	DCS group ($n = 16$)	Control group ($n = 16$)	*p*-value
Age (years, SD)	43.50 (11.00)	48.81 (9.70)	0.16
Male (*n*, %)	5 (31.3%)	5 (31.3%)	>0.99
Diagnosis (*n, %)*			>0.99
Major depression	10 (62.5%)	7 (43.8%)	
Bipolar depression	6 (37.5%)	9 (56.3%)	
Education (years, SD)	13.94 (2.79)	13.88 (3.12)	0.95
Duration of illness (years, SD)	13.56 (10.53)	12.69 (5.63)	0.77
Psychiatric comorbidities			
PD	4 (25.0%)	6 (37.5%)	0.70
PTSD	1 (6.3%)	0 (0.0%)	>0.99
GAD	5 (31.3%)	7 (43.8%)	0.72
Suicide history (*n*, %)	7 (43.8%)	8 (50.0%)	>0.99
HAMD score (SD)			
Baseline (day 1)	9.75 (3.26)	9.19 (4.92)	0.71
Day 4	9.06 (3.11)	8.75 (5.08)	0.84
Day 7	11.06 (5.09)	9.25 (5.41)	0.34
Day 14	11.19 (5.34)	10.13 (4.92)	0.56
Day 21	11.31 (5.77)	11.50 (6.21)	0.93
Day 28	11.56 (4.24)	9.81 (5.60)	0.33
Day 35	11.13 (4.77)	10.06 (6.46)	0.60
Day 42	10.94 (4.68)	10.31 (6.58)	0.76
HAMD item 3 score (SD)			
Baseline (day 1)	0.31 (0.48)	0.19 (0.54)	0.495
Day 4	0.25 (0.45)	0.25 (0.58)	0.183
Day 7	0.50 (0.73)	0.38 (0.62)	0.239
Day 14	0.44 (0.73)	0.38 (0.62)	0.239
Day 21	0.50 (0.73)	0.56 (0.73)	0.258
Day 28	0.44 (0.51)	0.31 (0.60)	0.198
Day 35	0.38 (0.62)	0.38 (0.62)	0.219
Day 42	0.44 (0.63)	0.38 (0.62)	0.221

HAMD Hamilton Depression Rating Scale, *PD* panic disorder, *PTSD* post-traumatic stress disorder, *GAD* generalized anxiety disorder, *SD* standard deviation

DISCUSSION

Our phase 2 randomized double-blind placebo control study findings did not support the study hypothesis that DCS augmentation treatment was superior to placebo in maintaining the initial antidepressant response to ketamine infusion. However, DCS did appear to maintain the antisuicidal effect of ketamine infusion during the 6-week follow-up period compared with the placebo. In addition, our phase 1 study findings revealed that the two infusions of ketamine per week improved the overall treatment response, up to 65%, among Taiwanese patients with TRD.

One question raised by the current findings is whether DCS may play a role in depression treatment by enhancing or inhibiting NMDA receptor function. Ketamine is an NMDA receptor antagonist, but it enhances neuroplasticity with intermittent administration [20]. DCS is a weak partial agonist at GluN2A- and GluN2B-containing NMDA receptors, with greater agonist efficacy at GluN2C and GluN2D-containing receptors [21, 22]. Thus DCS may preferentially facilitate or inhibit some NMDA receptor subtypes. The failure of DCS to attenuate depression in this study may suggest that DCS is not having beneficial effects in patients by blocking NMDA receptors, i.e., it is not simply a "weaker ketamine." Instead, DCS may work by enhancing NMDA receptor function. Animal studies showed that DCS facilitated hippocampal long-term synaptic plasticity via the enhanced magnitude of NMDA receptor-dependent long-term depression and the decreased neurotransmission mediated by alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate subtypes of glutamate receptors [23, 24]. Gupta et al. facilitated fear extinction via the increased activation of the MAPK signaling pathway in the orbitofrontal cortex and the increased pERK levels in the infralimbic prefrontal cortex, prelimbic prefrontal cortex intercalated cells, and lateral nucleus of the central amygdala [25, 26]. Furthermore, as mentioned in the Introduction section, only the high-dose, but not low-dose, administration of DCS was effective for depression [12, 14]. Previous studies also revealed that low-dose DCS failed to enhance executive cognitive function in neurologically intact adults or in adults with stroke [27, 28]. In this way, we suggested that high-dose DCS might attenuate executive cognitive deficits associated with suicide risk [29] or promoting the impact of anti-suicide psychosocial treatments [30, 31]. However, executive cognitive function was not assessed in this study. Further studies would be necessary to clarify the association between DCS, cognitive function, and suicidality.

Differences between the current study sample and the earlier study may have contributed to the failure to replicate the antidepressant efficacy of DCS. The earlier study excluded patients with significant suicide risk [12], while in this study nearly half of the patients had attempted suicide and approximately one-quarter of patients had moderate-to-high risk based on the MINI. It is also possible that patients in this study had more severely treatment-resistant symptoms, with over two-thirds of patients meeting criteria for moderate-to-high treatment resistance based on MSM [17, 18].

A second problem may have been the confounding effect of persisting antidepressant effects of ketamine during the trial. The findings from the mixed samples of previous ketamine infusion studies for TRD patients with and without concomitant medications showed that ~ 80% of patients with TRD may relapse within 18 days or so after a single ketamine infusion [6, 32]. However, the duration of relapse between add-on and drug-free studies remained unknown. Increasing evidence reported that repeated injections may prolong the antidepressant effect of ketamine infusion [33–35]. Our previous studies demonstrated that the

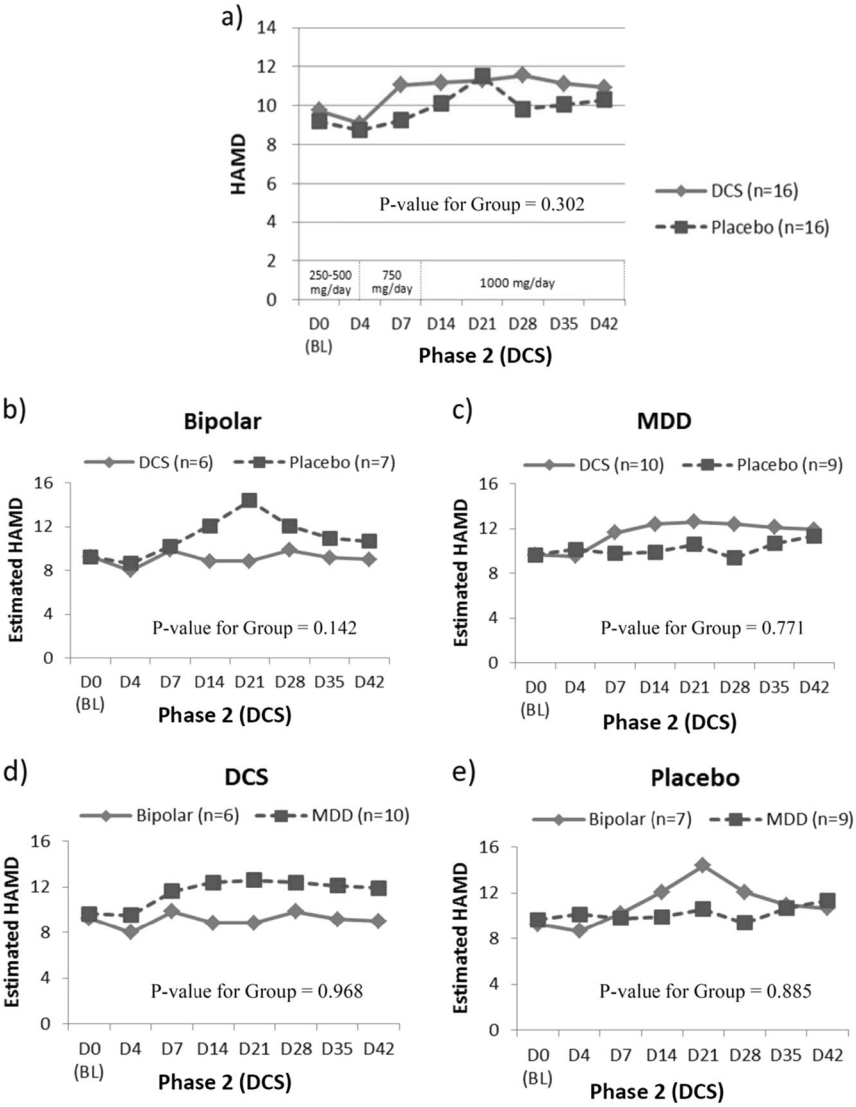

Fig. 3 Trajectory of depression in phase 2 double-blind randomized placebo control study (the mixed model with adjustment of baseline score, age, and sex). **a** Total patients, **b** bipolar disorder patients, **c** major depressive disorder (MDD) patients, **d** D-cycloserine group, and **e** placebo group

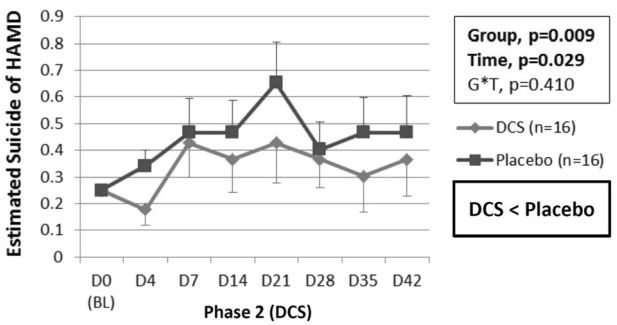

Fig. 4 Trajectory of suicide (item 3 of HAMD) in phase 2 double-blind randomized placebo control study. HAMD Hamilton Depression Rating Scale, DCS D-cycloserine

antidepressant effect of a single ketamine infusion may last for ~4 weeks in Taiwanese patients with TRD at average baseline depression severity (baseline HAMD score = 23) [7]. Murrough et al. reported that the median and 75th percentiles time to depression relapse were 18 and 27 days, respectively, after six infusions of ketamine [33]. Thus, the antidepressant effect of two ketamine infusions may last for as long as 1 month. Longer studies may be needed to unconfound the antidepressant effects of repeated ketamine exposure and DCS maintenance. Besides, the duration of treatment response to repeated ketamine infusions would still need further investigation among Caucasian and Taiwanese patients with TRD.

Another study finding was that two ketamine infusions may improve the overall treatment response (up to 65%) in Taiwanese patients with TRD, although this inference is based on open-label data. In an open-label study of 12 patients with TRD receiving repeated ketamine infusions, Shiroma et al. reported that the cumulative response rate increased from 25% after the first ketamine infusion to ~91% after six infusions [36]. Murrough et al. also demonstrated a response rate of 62.5% after the first ketamine infusion with 70.8% response after a series of six thrice weekly infusions [33].

Our study had several limitations. First, our study was an add-on DCS study because the medications normally used by patients with TRD were not discontinued during the DCS augmentation treatment (Supplementary Table 2). Therefore, the potential maintaining effects of DCS could have resulted from a

combinatory or regulatory effect of DCS with the medications that the patients were already using. However, the medications were not changed during the study period; therefore, the findings can be appropriately explained as the add-on effect of DCS. Furthermore, the add-on study design was ethically appropriate for such severely depressed patients and provided naturalistic data. Second, only 2 patients reported no suicide ideation at baseline, but 22 patients scored equal to 1 at HAMD item 3, and 25 patients scored ≥ 2 at HAMD item 3 in this study. However, item 3 of the HAMD rather than a rating scale specific to suicide ideation, such as the Scale for Suicide Ideation, was used as the clinical suicide covariate in the mixed model analysis; hence, we could not comprehensively investigate the potential role of DCS in the various dimensions of suicidality. Third, in addition, our current study only suggested that add-on DCS may maintain the antisuicidal effect of low-dose ketamine infusion after patients with TRD achieved the treatment response. Use of DCS may not generalize to patients with more severe symptoms of suicide. Furthermore, it appeared that the difference of HAMD item 3 may be due to a worsening in the placebo group rather than a significant improvement in the DCS group. Whether DCS may be effective for acute or severe suicide ideation would need further investigation. Fourth, there was a lack of a biomarker obtained to indicate whether DCS was having the antidepressant and antisuicidal effects in our study.

In conclusion, two ketamine infusions increase the treatment response rate, up to 65%, in Taiwanese patients with treatment-resistant major depression and bipolar depression compared with a single ketamine dose. DCS augmentation may maintain the antisuicidal effect of ketamine, although it cannot maintain the overall antidepressant effect of ketamine. Repeated ketamine infusion followed by DCS augmentation treatment may be beneficial for patients with TRD who had a high treatment resistance and a suicide risk. The mechanisms underlying the potentially beneficial effect of DCS in depression and suicidality are not well understood, and need further investigation.

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ADDITIONAL INFORMATION

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