Effects of Adjunctive Ketamine Intravenous Infusion in Taiwanese Patients with Treatment-Resistant Depression: Antidepression, Antisuicidality, BDNF Val66Met, and Brain Imaging

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Abstract About 21% of Taiwanese patients with major depression developed treatment-resistant depression (TRD) during 1-year follow-up in Taiwan. TRD was commonly coupled with functional impairment, poor quality of life, suicide ideation and attempts, self-injurious behaviors, and a high relapse rate. From 2012 and 2015, we had conducted the first randomized, double-blind, placebo control trial in Asian countries to examine the therapeutic efficacy of a single low-dose ketamine infusion in Taiwanese patients with TRD. Seventy one subjects were evenly distributed in three dose groups with 0.5 mg/kg, 0.2 mg/kg, and placebo, respectively. Responder was identified by response (≥50% reduction of mood ratings) at any two daily HAMD measures during the period of 24–96 h (day 2–5) post-ketamine infusion. There was a significant difference in the response rate across the three groups (0.5 mg/kg: 45.8%; 0.2 mg/kg: 39.1%; placebo: 12.5%; $p = 0.03$), which is much lower than that in the Caucasians (70%). Two factors might be related: lower serum ketamine levels and lower Val/Val allele percentage in BDNF Val66Met genotyping found in the Taiwanese patients. In addition to the rapid antidepressant effect of ketamine, a greater antisuicidal effect (59%) was also identified. The former may only account for 52.7% of the latter, indicating that the antisuicidality may be independent from antidepressiveness. Single dose of ketamine only resulted in short-lived

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psychedelic/dissociation adverse effect, which was resolved within 2 h post-infusion. Up to present, no long-term side effects were identified, given a single-dose administration. Using ^{18}F-FDG-PET scanning and 24 h post-ketamine infusion, glucose metabolism of the prefrontal cortex (PFC), supplementary motor area (SMA), and dorsal anterior cingulate cortex (dACC) were activated immediately (40 min post-infusion), and activation of SMA and dACC could sustain for 1 day, which may contribute to the persistent antidepressant effect of ketamine beyond its half-life, suggesting that a short activation in the PFC engendered by ketamine infusion may be a kindler, facilitating the persistent increase in glucose metabolism in the SMA and dACC; therefore, the PFC may be still considered to play a key role in improving TRD. These findings were also supported by a simple wearable forehead EEG monitoring from baseline to 40 min post-infusion, revealing that ketamine may increase the theta and low alpha power and decrease asymmetry in the PFC. Finally, a maintenance trial in a double-blind, randomized fashion using a partial NMDA agonist, D-cycloserine (DCS) vs. placebo, was conducted in the ketamine responders. This DCS augmentation treatment was not superior to placebo in maintaining the initial antidepressant response to ketamine infusion, but DCS did appear to maintain the antisuicidal effect during the 6-week follow-up study.

Keywords Ketamine · Depression · Suicide · BDNF · Brain imaging

1 Introduction

Major depressive disorder (MDD) is a severe chronic mental disorder that was predicted to be the leading cause of the disease burden by 2015 (WHO 2008). The Sequenced Treatment Alternatives to Relieve Depression (STAR∗D) study determined that up to 40% of MDD patients did not reach symptomatic remission after at least two trials of antidepressants (Howland 2008). Such patients were then defined as having treatment-resistant depression (TRD), and approximately 30% of MDD patients were found to continue to suffer from depression and related symptoms, such as insomnia, psychomotor retardation, and suicidal ideation, after four trials of different antidepressant treatments, including combination therapy and augmentation therapy (Howland 2008).

In Taiwan, the prevalence of common mental disorders doubled from 11.5% in 1990 to 23.8% in 2010 in parallel with the increase in national rates of unemployment, divorce, and suicide (Fu et al. 2013). Based on a cohort of 704,265 adults randomly sampled from Taiwan National Health Insurance Research database, among 2751 patients with MDD who were treated with antidepressants, approximately 21% ($n = 576$) developed TRD, which was defined as the failure to respond to more than two adequate antidepressant trials, during the 1-year follow-up (Fife et al. 2017). TRD was commonly coupled with functional impairment, poor quality

of life, suicide ideation and attempts, self-injurious behaviors, and a high relapse rate (Al-Harbi 2012).

Between 2012 and 2015, we had conducted the first randomized, double-blind, placebo control trial, approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHTPE) and the Department of Health of Taiwan in Asian countries and in Taiwan to examine the therapeutic efficacy of a single low-dose ketamine infusion in Taiwanese patients with TRD. Here, we summarized our study findings and proposed our personal clinical experiences for the application of ketamine infusion in TRD treatment in Asian and Taiwanese population.

2 Clinical Response of a Single Low-Dose Ketamine Infusion in Taiwanese Patients with TRD

Based on the hypothesis that Asian patients with MDD may respond fairly to the lower dose of antidepressants compared with Caucasian patients (Hong Ng et al. 2006; Lin and Shen 1991), Taiwanese patients with TRD were randomized to receive an infusion of saline (placebo group) or R/S-ketamine hydrochloride (Ketalar, Pfizer Pharmacueticals) at doses of 0.2 mg/kg (lower dose group) or 0.5 mg/kg (standard dose group) in our study (UMIN Clinical Trials Registry: UMIN000016985) (Su et al. 2017a). Hamilton Depression Rating Scale (HAMD) and Montgomery-Asberg Depression Rating Scale (MADRS) were administered in person prior to the initiation of test infusions and 40, 80, 120, and 240 min later, and telephone ratings were conducted 24, 48, 72, 96, 120, 144, and 288 h post-infusion.

2.1 Treatment Response and Ketamine Infusion in Taiwanese Patients with TRD

TRD patients treated with 0.5 mg/kg ketamine infusion exhibited more HAMD score reduction than those with 0.2 mg/kg ketamine infusion and normal saline (Fig. 1). Responder status was identified by response (≥50% reduction of mood ratings) at any two daily HAMD measures during the period of 24–96 h (day 2 to 5) post-infusion. There was a significant difference in the response rate across the three groups (0.5 mg/kg: 45.8%; 0.2 mg/kg: 39.1%; placebo: 12.5%; $p = 0.03$) with a significant linear trend test for the dose effect ($p = 0.01$). Post hoc test analyses indicated that responder rate was greater in the 0.5 mg/kg than placebo ($p = 0.01$) and in the 0.2 mg/kg than placebo ($p = 0.05$) but not between the two ketamine groups ($p = 0.77$). However, several studies with a similar study design investigating the therapeutic efficacy of 0.5 mg/kg ketamine in Caucasian patients with TRD have demonstrated that the response rate in patients is as high as 70% (Murrough et al.

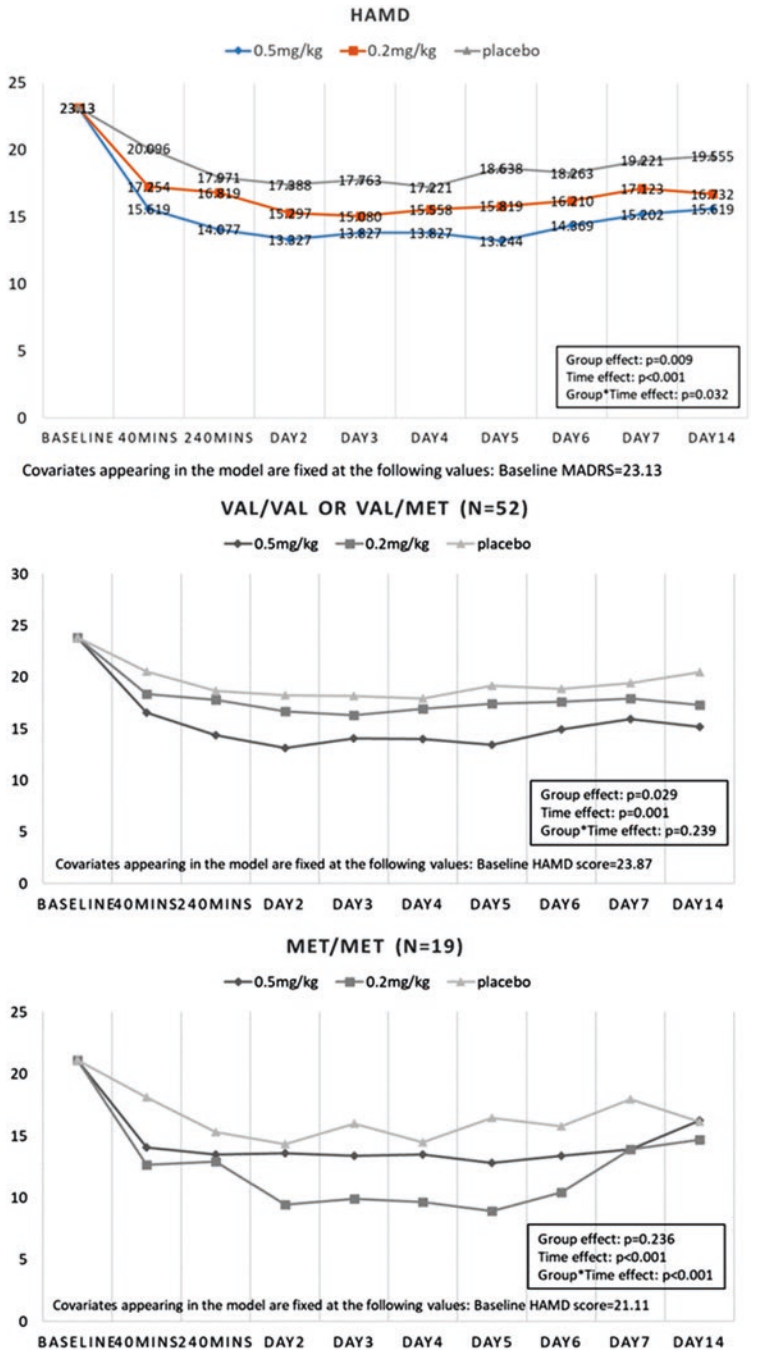

Fig. 1 Trajectory of HAMD after ketamine infusion. *HAMD* Hamilton depression rating scale

2013; Wan et al. 2015; Zarate et al. 2012). However, we only found approximately 50% response rate in Taiwanese patients receiving 0.5 mg/kg ketamine infusion, which was much lower compared with response rate in Caucasian patients (Su et al. 2017a). The lower responsiveness was attributed to the following factors: lower serum ketamine/norketamine levels and different distribution of genotypes of the BDNF Val66Met polymorphism observed in the Taiwanese subjects.

2.2 *Serum Levels of Ketamine and Norketamine After Ketamine Infusion in Taiwanese Patients with TRD*

Ketamine and norketamine levels were dose related (0.5 mg/kg group >0.2 mg/kg group) in our study. They varied by time point, but there were no significant differences by responder status. However, we found that both ketamine (115.86 ng/mL vs. 204.13 ng/mg) and norketamine (33.39 ng/mL vs. 55.52 ng/mL) levels at 40 min after ketamine infusion were much lower in Taiwanese patients than in Caucasian patients, which may confound the treatment efficacy of ketamine in Taiwanese patients (Fig. 2) (Su et al. 2017a; Zarate et al. 2012). However, the mechanisms of the lower ketamine and norketamine levels at post-infusion remained unknown in Taiwanese patients with TRD. The pharmacokinetics and pharmacodynamics of ketamine infusion need further investigation between Asian and Caucasian population.

2.3 *BDNF and Treatment Response of Ketamine Infusion in Taiwanese Patients with TRD*

The allele distribution of Val66Met BDNF polymorphism significantly varies across ethnicities, with the derived Met allele of Val66Met ranging in frequency from 0 to 72% across populations (Petryshen et al. 2010). Estimation of the Pooled Prevalence

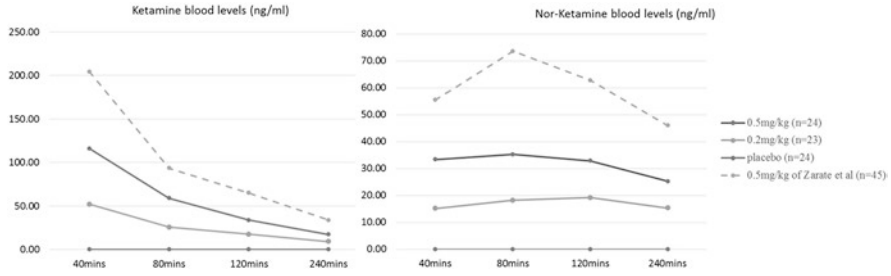

Fig. 2 Levels of ketamine and norketamine across time points

of the BDNF Val66Met Allele found that the frequency of Val allele was approximately 80% in Caucasians, but was much lower (<50%) in Asians, which may partially explain the difference of prevalence and susceptibility of mental disorders between Caucasians and Asians (Gratacos et al. 2007).

In our study, the distribution of genotypes of the Val66Met BDNF polymorphism was Val/Val (17%), Val/Met (56.3%), and Met/Met (26.8%) (Su et al. 2017a). There were no significant differences in ketamine treatment response between carriers of the Met allele and Val/Val patients (responder rate: 33.9% vs. 25.0%, $p = 0.55$). Despite Val66Met BDNF is not a biomarker of treatment response to ketamine infusion, we found that low-dose ketamine infusion was only effective for TRD patients with Val/Val or Val/Met in our study. As for those with Met/Met, the treatment efficacy of low-dose ketamine infusion did not differ between groups. However, the non-effectiveness of ketamine infusion may be due to limited cases with Met/Met (Fig. 1). A higher dose (i.e., 0.8–1 mg/kg) of ketamine infusion may be necessary for patients with TRD carrying Met/Met.

2.4 BDNF and Antisuicidal Effect of Ketamine Infusion in Taiwanese Patients with TRD

Traditional antidepressants, such as selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, require 2–3 weeks to achieve antidepressant efficacy. The period between the initiation of antidepressant use and their optimal efficacy is a crucial period for treatment as well as depression-related consequences, such as suicide. During this period, the risk of suicide remains high; therefore, choosing antidepressants with rapid efficacy that reduce suicide risk is crucial in clinical practice and the mental health domain.

A meta-analysis of 10 randomized placebo control trials involving 167 patients with MDD, bipolar depression, or posttraumatic stress disorder reported that ketamine rapidly (within 1 day) and significantly reduced suicidal ideation in terms of both clinician-administered and self-report outcome measures (Wilkinson et al. 2018). However, the duration of the antisuicidal effects of a single low-dose ketamine infusion may not be longer than a week based on previous western studies (Murrough et al. 2015).

In our study, patients with TRD that received 0.5 mg/kg ketamine infusion exhibited a significantly lower score in item 3 of the HAMD and in item 10 of MADRS than the groups that received 0.2 mg/kg ketamine or placebo infusion (Chen et al. 2019). Based on item 10 score of MADRS, among those carrying any Val allele of BDNF, both 0.5 and 0.2 mg/kg ketamine infusions were effective in the reduction in suicidal thoughts, but among those with Met/Met of BDNF, only 0.5 mg/kg ketamine infusion was effective in the reduction in suicidal thoughts (Chen et al. 2019). Furthermore, for the higher severity of suicidal thought (item 3 of the HAMD ≥ 2 [wishes he or she were dead or any thoughts of possible death to self] or item 10 of

the MADRS ≥4 [suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention]), we found that 0.5 mg/kg ketamine infusion was more effective in reducing suicidal symptoms than 0.2 mg/kg and placebo infusion (Chen et al. 2019). Our findings may suggest a higher dose of ketamine infusion for Taiwanese patients with TRD carrying Met/Met BDNF polymorphism and those having the higher severity of suicidal thought.

2.5 Greater Antisuicidal Than Antidepressant Effect of Ketamine Infusion in Taiwanese Patients with TRD

Reanalysis of our study data (Su et al. 2017a) showed a robust and fast antidepressant and antisuicidal effect with significant reduction of ratings by high dose (0.5 mg/kg) vs. placebo from 40-min to day 7 after ketamine infusion. Symptom attenuation in HAMD_17 rating within 1 week post-infusion was not only seen in depression (43%) but even greater in suicidal ideation (59%) (Su et al. 2017b). Although there were correlations for these two symptom changes ($r = 0.76$, $p < 0.05$), regression analysis elicited decrease percentage at 240 min accounted only for 52.7% of reduction in suicidal ideation, suggesting that improvements of suicidal ideation after ketamine infusion are related to, but not completely driven by, improvement in depression. There might have other neural substrate influenced by ketamine to account for decreasing suicidal ideation.

2.6 Adverse Effects of Low-Dose Ketamine Infusion in Taiwanese Patients with TRD

Psychotomimetic and dissociative symptoms and hypertension were the common, but temporary, adverse effects during ketamine infusion in Taiwanese patients with TRD (Su et al. 2017a; Zarate et al. 2012). They always resolved completely within 80–120 min post-infusion. Nausea was another adverse effect (approximately 10%) that clinicians should pay attention.

3 Cognitive Effect of a Single Low-Dose Ketamine Infusion in Taiwanese Patients with TRD

Cognitive impairment may be an important concern in the clinical practice when TRD is treated with low-dose ketamine infusion because animal studies have demonstrated that a single anesthetic dose and repeated subanesthetic doses of ketamine infusion can impair cognitive function and increase impulsive behaviors (Ding et al.

2016; Melo et al. 2016; Wang et al. 2014). A Taiwanese study demonstrated that the ketamine-dependent patients had significantly poorer performance than did the controls in many cognitive tasks, including verbal memory, motor speed, verbal fluency, and attention and processing speed (Wang et al. 2018).

In our clinical trial, working memory task and a go/no-go task were performed at baseline and at Day 3 and Day 14 post-ketamine infusion (Chen et al. 2018a). We found no group effect, no time effect, and no group × time interaction effect for cognitive function among baseline, Day 3, and Day 14 among the three groups, which may indicate that a low dose of ketamine infusion did not impair cognitive function in patients with TRD (Chen et al. 2018a). Subanalyses additionally demonstrated that specific cognitive improvement measured using the go/no-go task was observed only among the responders in the 0.5-mg/kg ketamine infusion group (Chen et al. 2018a). Furthermore, increasing evidence suggested that the repeated low-dose ketamine infusion may be more beneficial for the improved treatment response and the longer antidepressant effect (Singh et al. 2016). In the future, cognitive function changes after repeated ketamine infusion should be investigated for patients with TRD.

4 Central Mechanisms of the Low-Dose Ketamine Infusion in Taiwanese Patients with TRD

At low doses, ketamine is believed to preferentially bind to and inhibit NMDARs on GABA-ergic interneurons (Ide and Ikeda 2018; Zanos and Gould 2018). The process, initiated by ketamine, in GABA interneurons leading to the subsequent increase in synaptogenesis and BDNF levels has been considered a major biological mechanism of the rapid antidepressant effect of ketamine (Ide and Ikeda 2018; Zanos and Gould 2018).

Hypofrontality and hyperactivity of limbic system structures, such as the amygdala, measured according to prefrontal cortex (PFC) glucose metabolism or functional MRI have been reported to be significantly correlated with depression severity in patients with MDD and were the biosignature of TRD (Drevets et al. 2008; Li et al. 2015; Phillips et al. 2015). The anterior cingulate cortex (ACC) dysfunction is another notable biosignature of MDD and TRD. The dorsal ACC (dACC) is a critical hub that integrates the emotional and cognitive domains of emotional and behavioral regulation, thereby connecting the PFC, supplementary motor area (SMA), and limbic system (Bush et al. 2000). The dACC synergically works with the dorsolateral PFC (DLPFC) in attentional and cognitive control and in emotional regulation through the inhibition of the hyperactive limbic system and subgenual ACC (De Raedt et al. 2015; Ressler and Mayberg 2007). Furthermore, SMA plays a critical role in human volition, executive function, and integration of affective, behavioral, and cognitive functions, which were severely impaired in patients with TRD (Haggard 2008; Leisman et al. 2016; Nachev et al. 2008). Impairment in attention

regulation and cognitive control function was correlated with hypoactivation in the SMA and ACC (Halari et al. 2009).

In our randomized placebo control clinical trial, all patients with TRD were assessed with ^{18}F-FDG-PET scan at baseline and 48 with PET scan immediately at 40 min post-infusion for the evaluation of the rapid onset antidepressant effect of ketamine and the other 24 with PET at 24-h post-infusion for the persistent antidepressant effect of ketamine because the half-life values of ketamine and its active metabolites, norketamine and dehydronorketamine, are approximately 3, 5, and 7 h, respectively (Chen et al. 2018b; Li et al. 2016). We found that the glucose metabolism of the PFC, SMA, and dACC in patients with TRD provided with the low-dose ketamine infusion were higher than those in the control group at 40 min post-infusion (Li et al. 2016). Interestingly, two other PET studies have not observed increased glucose metabolism in the PFC 2 h after ketamine infusion, but they also reported that the rapid antidepressant effect of ketamine infusion was mediated by activation in the dACC (Carlson et al. 2013; Lally et al. 2015). Lastly, we found that the activation in the SMA and dACC could persist 1 day after a single-dose ketamine infusion and may contribute to the persistent antidepressant effect of ketamine considerably beyond its half-life (Chen et al. 2018b). Taking the preceding pieces of evidence together, we hypothesize that the effect of ketamine infusion on PFC activation rapidly occurred within 1 h and then rapidly disappeared approximately 2 h later. A short activation in the PFC engendered by ketamine infusion may be a kindler, facilitating the persistent increase in glucose metabolism in the SMA and dACC; therefore, the PFC may still be considered to play a key role in improving TRD (Fig. 3) (Chen et al. 2018b; Li et al. 2016).

5 Identifying Ketamine Responses in Taiwanese Patients with TRD Using a Wearable Forehead EEG

Electroencephalography (EEG) has been widely used to study antidepressant treatment responses due to its broad availability and cost-effectiveness. Prefrontal EEG power at baseline was reported to predict the SSRI antidepressant response with 63% (Iosifescu et al. 2009) and 88% accuracy (Khodayari-Rostamabad et al. 2013), suggesting that the use of forehead EEG patterns might be a potential for building a baseline predictor for responses to ketamine treatment. With the development of sensor technology, an alternative to conventional EEG devices with wet electrodes and cables has emerged. Wearable wireless EEG device with dry sensors have led to a reduction in the amount of preparatory work required for a long-term monitoring and daily use (Lin et al. 2008). Since ketamine has a rapid and robust antidepressant effect in treatment-resistant depression (TRD), which is paralleling with increased glucose metabolism in the frontal area by PET-FDG, our study aim is to investigate the role of frontal EEG as predictor for clinical response to ketamine in TRD via a wireless EEG device. In our double-blind, randomized trial and placebo control

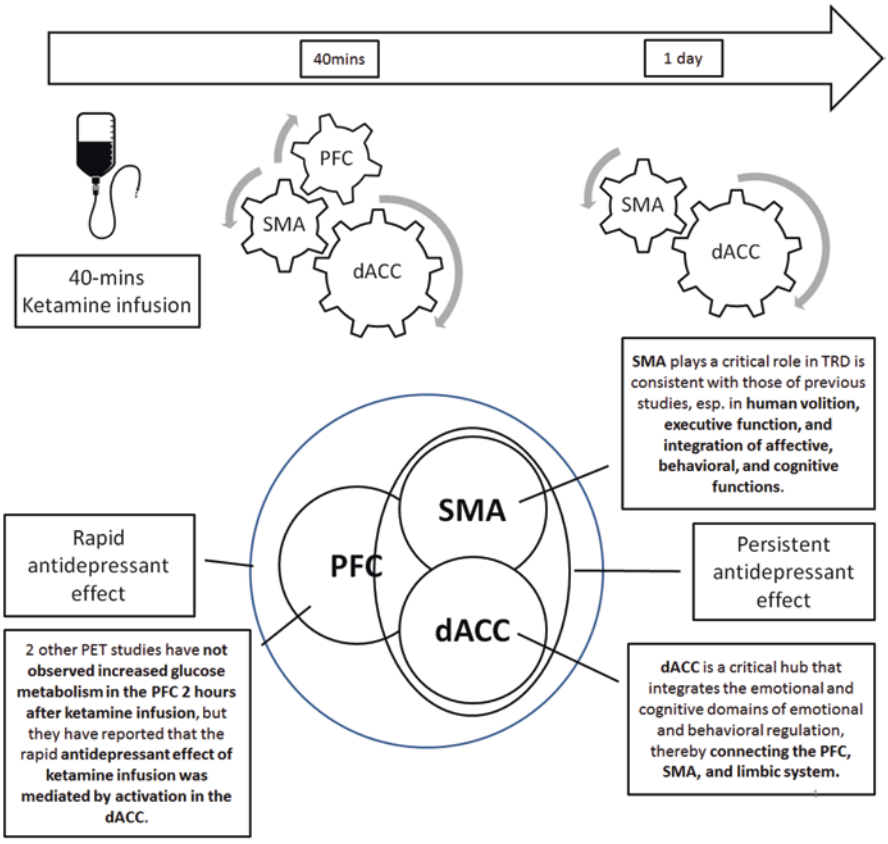

Fig. 3 Hypothesis of central mechanisms of antidepressant effect of low-dose ketamine infusion. *PFC* prefrontal cortex, *SMA* supplementary motor area, *dACC* dorsal anterior cingulate cortex

study (Cao et al. 2018), 36 patients on active ketamine dose (0.2–0.5 mg/kg) vs. 18 patients on placebo received 5-min electroencephalography (EEG) recording via a wireless EEG device with four prefrontal dry-contact sensors at baseline (0 min) and posttreatment (240 min), respectively. The ketamine responses were measured by EEG signals and Hamilton depression rating scale (HDRS) scores. Responder was identified (≥50% reduction of baseline depression symptoms at 240 min post-infusion). EEG power and hemispheric asymmetry were calculated in the delta, theta, low alpha, and high alpha bands. Our results showed that, at baseline, responders had a significantly weaker EEG theta and lower level of low alpha power than did nonresponders ($p < 0.05$). Further, in the responders, we found that ketamine increased the low relative alpha power ($p < 0.01$) and decreased its hemispheric (Fp2-Fp1) asymmetry over bilateral frontals ($p < 0.05$), which was observed in neither nonresponders nor placebo controls. The result is consistent with the pre-

vious studies that decreased frontal EEG asymmetry may be positively correlated with response to behavioral therapy in depression (Gollan et al. 2014; Jesulola et al. 2015) and is also required for the ketamine-specific fast antidepressant effect. Moreover, our baseline EEG predictor classified responders and nonresponders with 81.3 ± 9.5% accuracy, 82.1 ± 8.6% sensitivity, and 91.9 ± 7.4% specificity. In conclusion, this study provided the evidence of immediate changes of frontal activity, which may account for rapid clinical response of ketamine, and the pretreatment frontal brain activity measured by simple EEG device might be a biosignature for better outcome prediction.

6 The Maintenance of Antidepressant and Antisuicidal Effect of Low-Dose Ketamine Infusion with D-Cycloserine in Taiwanese Patients with TRD

Maintaining the initial response of ketamine infusion is the next step in therapeutic challenge in the psychiatric clinical practice (Iosifescu 2015). The safety and tolerability of repeated or long-term ketamine infusion have not been established until now; particularly, long-term ketamine misuse has been reported to cause various psychiatric and physical complications and adversities, including cognitive impairment, psychosis, and interstitial cystitis (Wang et al. 2018; Cheng et al. 2018; Chu et al. 2008).

D-Cycloserine (DCS), a partial NMDA agonist, has been reported to be potentially effective for depression augmentation treatment (Heresco-Levy et al. 2013; Henter et al. 2018). In our recent clinical trial (UMIN Clinical Trials Registry: UMIN000023581), patients with TRD (N = 32) who responded to the add-on 40-min intravenous ketamine (0.5 mg/kg) infusions at Day 1 and Day 4 in the phase 1 study were enrolled in the phase 2 double-blind randomized DCS–placebo control study (Chen, et al, 2019, accepted in Neuropsychopharmacology). In the phase 2 study, patients with TRD were randomly divided into 6-week DCS (Seromycin, Eli Lilly) treatment (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) and placebo groups.

Unfortunately, DCS augmentation treatment was not superior to placebo in maintaining the initial antidepressant response to ketamine infusion in Taiwanese patients with TRD. But, interestingly, DCS did appear to maintain the antisuicidal effect, measured by item 3 of HAMD, of ketamine infusion during the 6-week follow-up period compared with the placebo (Fig. 4). This finding may imply that DCS augmentation was helpful for patients with TRD who responded to ketamine infusion but still had residual suicidal thought. However, the mechanisms underlying the potentially beneficial effect of DCS in depression and suicidality are not well understood and need further investigation.

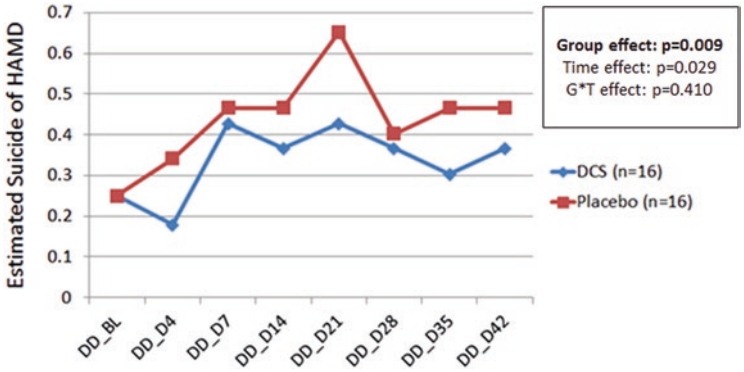

Fig. 4 Trajectory of suicide (item 3 of HAMD) in phase 2 double-blind randomized placebo control study. *HAMD* Hamilton depression rating scale, *DCS* D-cycloserine

7 Conclusion

Our clinical trials and clinical experience supported that the low-dose ketamine infusion (0.5 and 0.2 mg/kg) was a safe, tolerable, and effective treatment for Taiwanese patients with TRD although the Met allele of BDNF polymorphism is predominant in Taiwanese and Asian population. However, the higher dose (i.e., 0.8–1.0 mg/kg) of ketamine infusion may be necessary for those who carry Met/Met BDNF polymorphism or have higher severity of suicidality. We also found the potential maintenance effect for suicidality of DCS after ketamine infusions. Furthermore, the modulation of PFC-related circuits and increased activation of PFC, SMA, and dACC may play a crucial role in the antidepressant and antisuicidal effects of ketamine infusion. Further clinical trial will be required to elucidate the optimal dose (i.e., 0.5–1.0 mg/kg) and infusion frequency (once or twice per week for 2–4 weeks) of ketamine infusion for the maximized treatment outcome among Taiwanese patients with TRD. The therapeutic strategy that may maintain the initial response of ketamine infusion also needs further investigation.

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