Serum BDNF levels and the antidepressant effects of electroconvulsive therapy with ketamine anaesthesia: a preliminary study

Wei Zheng Equal first author, 1, Qiaomei Cen Equal first author, 1, Sha Nie 1, Minyi Li 1, Rong Zeng 1, Sumiao Zhou 1, Dong-Bin Cai 2, Miaoling Jiang Corresp. 1, Xiong Huang Corresp. 1

1 the Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, China
2 Shenzhen Traditional Chinese Medicine Hospital, Shenzhen, China

Corresponding Authors: Miaoling Jiang, Xiong Huang
Email address: miaoling2011_0318@163.com, 1195768576@qq.com

Objective: To first examine the relationship between serum brain-derived neurotrophic factor (BDNF) levels and antidepressant response to ketamine as an anaesthesia in electroconvulsive therapy (ECT) in Chinese patients with treatment-refractory depression (TRD). Methods: Thirty patients with TRD were enrolled and underwent eight ECT sessions with ketamine (0.8 mg/kg) alone anaesthesia. Depression severity, response and remission were evaluated using the 17-item Hamilton Depression Rating Scale (HAMD-17). Enzyme-linked immunosorbent assay (ELISA) was applied to examine serum BDNF levels in patients with TRD at baseline and after the second, fourth, and eighth ECT sessions. Baseline serum samples were also collected for 30 healthy controls. Results: No significant differences were observed in serum BDNF levels between patients with TRD and healthy controls at baseline ($p>0.05$). The remission rate was 76.7% (23/30) after the last ECT treatment, although all patients with TRD obtained antidepressant response criteria. Serum BDNF levels were not altered compared to baseline, even between remitters and nonremitters, despite the significant reduction in HAMD-17 and Brief Psychiatric Rating Scale (BPRS) scores after ECT with ketamine anaesthesia (all $p>0.05$). The antidepressant effects of ECT with ketamine anaesthesia were not correlated with changes in serum BDNF levels (all $p>0.05$). Conclusion: This preliminary study indicated that serum BDNF levels do not appear to be a reliable biomarker to determine the antidepressant effects of ketamine as an anaesthesia in ECT for patients with TRD. Further studies with larger sample sizes are warranted to confirm these findings.
Serum BDNF levels and the antidepressant effects of electroconvulsive therapy with ketamine anaesthesia: a preliminary study

Running head: BDNF and ketamine

1#Wei Zheng, MD, PhD;
1#Qiao-Mei Cen, MD;
1Sha Nie, MD;
1Min-Yi Li, MD;
1Rong Zeng, MD;
1Su-Miao Zhou, MD;
2Dong-Bin Cai, MD;
1*Miao-Ling Jiang, MD;
1*Xiong Huang, MD;

1. The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China;
2. Shenzhen Traditional Chinese Medicine Hospital, Shenzhen, China;

#These authors contributed equally to this work.

*Address correspondence to Dr. Xiong Huang, the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China; Fax: +86-20-81778484. Telephone: +86-18922165303. E-mail: 1195768576@qq.com; or Dr. Miao-Ling Jiang, the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China; Fax: +86-20-81891425. Telephone: +86-18922165301. E-mail: miaoling2011_0318@163.com.
Abstract

Objective: To first examine the relationship between serum brain-derived neurotrophic factor (BDNF) levels and antidepressant response to ketamine as an anaesthesia in electroconvulsive therapy (ECT) in Chinese patients with treatment-refractory depression (TRD).

Methods: Thirty patients with TRD were enrolled and underwent eight ECT sessions with ketamine (0.8 mg/kg) alone anaesthesia. Depression severity, response and remission were evaluated using the 17-item Hamilton Depression Rating Scale (HAMD-17). Enzyme-linked immunosorbent assay (ELISA) was applied to examine serum BDNF levels in patients with TRD at baseline and after the second, fourth, and eighth ECT sessions. Baseline serum samples were also collected for 30 healthy controls.

Results: No significant differences were observed in serum BDNF levels between patients with TRD and healthy controls at baseline ($p>0.05$). The remission rate was 76.7% (23/30) after the last ECT treatment, although all patients with TRD obtained antidepressant response criteria. Serum BDNF levels were not altered compared to baseline, even between remitters and nonremitters, despite the significant reduction in HAMD-17 and Brief Psychiatric Rating Scale (BPRS) scores after ECT with ketamine anaesthesia (all $p>0.05$). The antidepressant effects of ECT with ketamine anaesthesia
were not correlated with changes in serum BDNF levels (all $p>0.05$).

**Conclusion:** This preliminary study indicated that serum BDNF levels do not appear to be a reliable biomarker to determine the antidepressant effects of ketamine as an anaesthesia in ECT for patients with TRD. Further studies with larger sample sizes are warranted to confirm these findings.

**Keywords:** Electroconvulsive therapy; ketamine; depression; brain-derived neurotrophic factor
Introduction

Electroconvulsive therapy (ECT) is widely considered to be the most effective nonpharmacological therapy for mental disorders (Grover et al. 2018; Zong et al. 2020), especially for major depressive disorder (MDD), despite negative public perceptions (Dean & Keshavan 2017; Gajaria & Ravindran 2018; Sackeim et al. 2007). For example, Petrides et al. reported that the remission rate was 87% for both psychotic and nonpsychotic patients with MDD after an acute ECT course (Petrides et al. 2001). To minimize the clinical risks and subjective unpleasantness during ECT, patients are administered an intravenous anaesthetic, such as thiopental, methohexital, propofol, ketamine or even a combination of ketamine and propofol (ketofol) (Huang et al. 2020; Zheng et al. 2019a). A recent meta-analysis of 16 trials (n=928) found that ketamine used in ECT accelerated the improvement of depressive symptoms in patients with MDD, with a short-term advantage in antidepressive effect at the early stages of ECT (Ren et al. 2018).

Ketamine, an N-methyl-d-aspartate receptor (NMDAR) antagonist, has been widely used as an analgesic, anaesthetic and antihyperalgesic agent (Radvansky et al. 2015). Interestingly, a single ketamine infusion at sub-anaesthesia doses elicited a rapid but time-limited antidepressant effect in treatment-refractory depression (TRD) (Hu et al. 2016; Zarate et al. 2006). Repeated ketamine infusions at sub-anaesthesia doses have a cumulative
and sustained antidepressant effect on TRD (Phillips et al. 2019; Zheng et al. 2018; Zheng et al. 2019b). Thus, ketamine used as an anaesthesia in ECT may enhance the antidepressant effects of ECT, while also having rapid independent antidepressant properties itself (Erdil et al. 2015; Kranaster et al. 2011; Okamoto et al. 2010; Ren et al. 2018; Zheng et al. 2019a). Zhong et al. found that ketamine anaesthesia achieved earlier antidepressant efficacy and a higher rate of remission than propofol anaesthesia and ketofol anaesthesia in TRD treated with ECT, suggesting that ketamine alone in ECT may represent an optimized therapy for TRD (Zhong et al. 2016).

When compared to healthy controls, patients with TRD have low serum BDNF levels (Molendijk et al. 2014; Polyakova et al. 2015b). Many, but not all studies (Brunoni et al. 2008; Groves 2007; Polyakova et al. 2015b) found that low serum BDNF levels in patients with TRD were normalized after obtaining an antidepressant response. A few studies have examined the correlation of blood BDNF levels and the antidepressant response to ECT with ketamine anaesthesia or ketofol anaesthesia, but with inconsistent findings. For instance, a recent study reported that ECT treatment with ketamine anaesthesia, but not with methohexital anaesthesia, significantly increased plasma BDNF levels (Carspecken et al. 2018). However, another study found that ECT with ketofol anaesthesia was not correlated with enhanced serum BDNF levels (Huang et al. 2020). Moreover, baseline serum
BDNF levels did not appear to be an eligible biomarker for predicting the antidepressant response to ECT with ketofol anaesthesia, as measured using the 17-item Hamilton Depression Rating Scale (HAMD-17) (Huang et al. 2020).

To date, no study has been conducted to examine whether serum BDNF levels predict a rapid antidepressant response to ketamine used alone as an anaesthesia during ECT in Chinese patients with TRD. In this study, thirty Chinese patients with TRD were administered ketamine alone as an anaesthesia in ECT. We hypothesized that (1) patients with TRD would exhibit lower serum BDNF levels than healthy controls and (2) the antidepressant response to ketamine anaesthesia in ECT would be correlated with serum BDNF levels.

Methods

The protocol for this study was approved by the ethics review board of the Affiliated Brain Hospital of Guangzhou Medical University (Ethics Number: [2013]020). This study was conducted following the Declaration of Helsinki and was performed between February 2013 and December 2013.

Participants
All patients were recruited from the wards of the Affiliated Brain Hospital of Guangzhou Medical University based on the following criteria: (1) age from 18 to 65 years; (2) diagnosed with major depression according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) with a current major depressive episode; (3) having severe depressive symptoms (HAMD-17 scores ≥20) at screening; (4) did not respond adequately to appropriate courses of at least two antidepressants in the current episode (Huang et al. 2020; Zheng et al. 2020); (5) had no a history of severe physical illness (i.e., Parkinson disease) and no drug or alcohol abuse; (6) had no a history of seizures; (7) was not breastfeeding or pregnant; and (8) had no any contraindication for ketamine anaesthesia and ECT. All patients with TRD provided written informed consent at the beginning of participation.

Thirty age and sex-matched apparently healthy volunteers were recruited from the local community during the same phase with no alcohol or other substance abuse/dependence or serious physical diseases. All healthy volunteers provided written informed consent at the beginning of participation.

Treatment
All patients with TRD received eight ECT treatments with ketamine anaesthesia alone (0.8 mg/kg). ECT treatment was performed three times per week for three consecutive weeks for a total of eight treatments. During the courses of ECT, no psychiatric medications were prescribed to the subjects. The seizure threshold of each patient was determined based on the half-age method (% energy=half the age) (Petrides & Fink 1996; Yasuda et al. 2015), and bitemporal ECT for each case was conducted by using Thymatron ® IV device (Somatics LLC, Lake Bluff, Illinois, USA). Vital signs, such as temperature and heart rate, were regularly recorded.

**Clinical Assessment**

The HAMD-17 (Hamilton 1960) and the Brief Psychiatric Rating Scale (BPRS) were used to assess the severity of depressive and psychotic symptoms, respectively, at baseline, after the second, fourth, and eighth sessions of ECT. Antidepressant response was defined as a 50% or greater reduction in HAMD-17 scores (Lin & Lin 2019) and antidepressant remission as HAMD-17 scores ≤6 (Riedel et al. 2010). Riedel et al. found that a HAMD-17 cut-of ≤6 (area under the curve=0.90) was correlated with a maximum sensitivity and specificity for defining remission criteria (Riedel et al. 2010).

**Serum BDNF levels**
Blood samples were collected from healthy controls at baseline. Blood samples from patients with TRD were collected at baseline and after the second, fourth, and eighth treatments of ECT. Before analysis of serum BDNF levels, blood samples were stored at −80 °C. In line with the manufacturer’s instructions, an enzyme-linked immunosorbent assay (ELISA) kit (BDNF Emax Immunoassay System, Promega, USA) was used to examine serum BDNF levels. Absorbance at 450 nm wavelength was used to analyse BDNF concentrations based on a standard curve.

**Data analyses**

Comparison of demographics and clinical characteristics between healthy controls and patients with TRD, and between remitters and nonremitters defined as HAMD-17 scores ≤6 (Riedel et al. 2010), was examined using the Student’s t-test, Mann–Whitney U-test, chi-square test, or Fisher’s exact test, as appropriate. A linear mixed model was used to compare serum BDNF levels and the severity of depressive and psychotic symptoms between remitters and nonremitters following eight ECT treatments. The correlation between changes in illness severity and changes in serum BDNF levels was analysed using Pearson’s bivariate correlation analysis. All outcomes were analysed using IBM SPSS statistics version 25.0, and \( p<0.05 \) was considered significant.
Results

Participant characteristics

As shown in Table 1 and Supplemental Figure 1, no significant differences were observed in baseline serum BDNF levels between healthy controls and patients with TRD ($p>0.05$). Similarly, no significant differences in terms of baseline serum BDNF levels, HAMD-17 scores or BPRS scores were found between remitters and nonremitters (all $p>0.05$, Table 2).

Treatment remission and serum BDNF levels

After the last ECT treatment, the remission rate was 76.7% (23/30), while the response rate was 100% (30/30) (Table 1). Significant reduction in illness severity as measured by HAMD-17 (Figure 1) and BPRS (Supplemental Figure 2) was observed following eight ECT treatments. No significant difference in serum BDNF levels was found at any of the indicated times between remitters and nonremitters, even when compared to baseline across the total sample (all $p>0.05$, Figure 2). In the linear mixed model, serum BDNF levels showed no significant main effects for group, time, or group-by-time interactions (all $p>0.05$, Table 3). Changes in HAMD-17 and BPRS scores following ECT treatment between remitters and nonremitters was also analysed using a linear mixed model (Table 3).
Association between serum BDNF levels and illness severity

As reported in Supplemental Table 1, there were no significant correlations between serum BDNF levels and illness severity as measured by HAMD-17 and BPRS.

Discussion

This study was, to our knowledge, the first to examine the relationship of serum BDNF levels and the rapid antidepressant effects of ECT with ketamine anaesthesia in Chinese patients with TRD. The main findings of the current study included the following: 1) there was no significant difference in baseline serum BDNF levels between healthy controls and patients with TRD; 2) following eight sessions of ECT with ketamine anaesthesia, all patients with TRD met the response criteria, and 76.7% remitted based on the criteria reported by Riedel et al.’s study (Riedel et al. 2010); 3) ketamine used in ECT did not alter serum BDNF levels compared to baseline, and serum BDNF levels between remitters and nonremitters was not significantly different; 4) there was no significant correlation between serum BDNF levels and improvement of depressive symptoms following eight sessions of ECT with ketamine anaesthesia.

In line with findings from early studies (Fernandes et al. 2009; Huang et
al. 2020; Maffioletti et al. 2019; Polyakova et al. 2015a; Ryan et al. 2018), no significant difference was observed in serum BDNF levels between patients with TRD and healthy controls. However, other studies have reported that patients with depression exhibit reduced serum BDNF levels compared to healthy controls (Allen et al. 2015; Karege et al. 2002; Kishi et al. 2017; Matrisciano et al. 2009; Nase et al. 2016; Rapinesi et al. 2015; Wolkowitz et al. 2011; Zheng et al. 2020), suggesting that serum BDNF deficit might represent a potential biomarker in patients with TRD. However, low serum BDNF levels were not specific to patients with TRD, but were also observed in patients with schizophrenia and mania, and even in patients with acne vulgaris (Karamustafalioglu et al. 2015; Li et al. 2016; Mikhael et al. 2019; Mora et al. 2019). Taken together, blood BDNF level appears to have no value for diagnosis of depression in clinical practice.

After completing eight ECT treatments with ketamine as an anesthesia, 100% of patients with TRD responded in this study, and 76.7% met remission criteria, similar with the prior findings (Huang et al. 2020). Huang et al. found that thirty patients with TRD underwent eight ECT treatments with ketofol as anesthesia where 100% responded and 53.3% remitted (Huang et al. 2020). Zhong et al. reported higher remission rates for patients with TRD receiving ECT with ketamine alone than propofol alone and ketofol, indicating that ketamine used alone as an anesthesia in ECT may
be considered an optimal treatment in Chinese patients with TRD (Zhong et al. 2016). Importantly, the findings of the current study also support the results of a meta-analysis of randomized controlled trials that ketamine used in ECT accelerates the antidepressive response and remission in depressed patients (Ren et al. 2018).

Consistent with findings of previous studies (Allen et al. 2015; Huang et al. 2020), serum BDNF levels did not significantly change during ECT with ketamine anaesthesia in this study. For example, Huang et al. found that ECT with ketofol anaesthesia did not alter serum BDNF levels, despite its rapidly decreasing depressive symptoms (Huang et al. 2020). However, findings on the effect of ECT with other anaesthesia types, such as methohexital or thiopental sodium, on serum BDNF levels are inconsistent (Maffioletti et al. 2019; Vanicek et al. 2019b). For example, Vanicek et al. found a significant increase in serum BDNF levels after continuation ECT treatments with methohexital (Vanicek et al. 2019b), while another study found that ECT with thiopental sodium did not alter serum BDNF levels (Maffioletti et al. 2019).

The current study also confirmed the findings of previous studies that the antidepressant effects of ECT with ketamine anaesthesia were not correlated with serum BDNF levels (Allen et al. 2015; Huang et al. 2020; Kishi et al. 2017). Similar to nonconvulsive electrotherapy (NET) using
standard ECT technique but below seizure threshold, the change in serum BDNF levels in patients with TRD was not correlated with the antidepressant effects of NET (Zheng et al. 2020). A recent study concluded that serum BDNF levels in patients with late-life unipolar depression cannot be considered an eligible biomarker for the antidepressant effects of ECT (van Zutphen et al. 2019).

It is important to mention the following limitations of this study. The primary limitation of this study is the small sample size, partly accounting for the negative findings. Another limitation of the current study was the open-label design, limiting the interpretation of efficacy. For instance, Carspecken et al. found that ketamine used in ECT does not significantly improve depressive symptoms compared to methohexital used in ECT (Carspecken et al. 2018). Finally, the absence of follow-up visits after the entire treatment for this study limited our capacity to further examine how long the antidepressant effects of ECT with ketamine persists and whether increased BDNF concentrations require a longer time to manifest. For instance, Vanicek et al. found that peak serum BDNF levels were achieved one month after the final ECT treatment (Vanicek et al. 2019a).

In conclusion, this preliminary study indicated that serum BDNF levels do not appear to be a reliable biomarker to determine the antidepressant
effects of ketamine as an anaesthesia in ECT for patients with TRD. Further
studies with larger sample sizes are warranted to confirm these findings.

Acknowledgements

This study was funded by the Science and Technology Planning Project of
Guangdong Province (B2016109), Science and Technology Planning Project
of Liwan District of Guangzhou (202004034), and Guangzhou Clinical
Characteristic Technology Project (2019TS67).

Conflict of Interest

The authors have no conflicts of interest concerning this article.

References

Allen AP, Naughton M, Dowling J, Walsh A, Ismail F, Shorten G, Scott L, McLoughlin DM, Cryan JF, Dinan TG, Clarke
G. 2015. Serum BDNF as a peripheral biomarker of treatment-resistant depression and the rapid
antidepressant response: A comparison of ketamine and ECT. J Affect Disord 186:306-311.
Brunoni AR, Lopes M, and Fregni F. 2008. A systematic review and meta-analysis of clinical studies on major
depression and BDNF levels: implications for the role of neuroplasticity in depression. Int J
Neuropsychopharmacol 11:1169-1180.
Carspecken CW, Borisovskaya A, Lan ST, Heller K, Buchholz J, Ruskin D, and Rozet I. 2018. Ketamine anesthesia
does not improve depression scores in electroconvulsive therapy: a randomized clinical trial. J Neurosurg
Anesthesiol 30:305-313.
Dean J, and Keshavan M. 2017. The neurobiology of depression: An integrated view. Asian J Psychiatr 27:101-111.
Erdil F, Ozgul U, Çolak C, Cumurcu B, and Durmus M. 2015. Effect of the addition of ketamine to sevoflurane
anesthesia on seizure duration in electroconvulsive therapy. J Ect 31:182-185.
Fernandes B, Gama CS, Massuda R, Torres M, Camargo D, Kunz M, Belmonte-de-Abreu PS, Kapczinski F, de Almeida
Fleck MP, and Inês Lobato M. 2009. Serum brain-derived neurotrophic factor (BDNF) is not associated
with response to electroconvulsive therapy (ECT): a pilot study in drug resistant depressed patients.
Neurosci Lett 453:195-198.

Gajaria A, and Ravindran AV. 2018. Interventions for perinatal depression in low and middle-income countries: A systematic review. Asian J Psychiatr 37:112-120.

Grover S, Satapathy A, Chakrabarti S, and Avasthi A. 2018. Electroconvulsive therapy among elderly patients: a study from tertiary care centre in north India. Asian J Psychiatr 31:43-48.

Groves JO. 2007. Is it time to reassess the BDNF hypothesis of depression? Mol Psychiatry 12:1079-1088.

Hamilton M. 1960. A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56-62.

Hu YD, Xiang YT, Fang JX, Zu S, Sha S, Shi H, Ungvari GS, Correll CU, Chiu HF, Xue Y, Tian TF, Wu AS, Ma X, Wang G. 2016. Single i.v. ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. Psychol Med 46:623-635.

Huang XB, Huang X, He HB, Mei F, Sun B, Zhou SM, Yan S, Zheng W, and Ning YP. 2020. BDNF and the antidepressant effects of ketamine and propofol in electroconvulsive therapy: a preliminary study. Neuropsychiatr Dis Treat 16:901-908.

Karamustafalioglu N, Genc A, Kalelioglu T, Tasdemir A, Umut G, Incir S, Akkuş M, and Emul M. 2015. Plasma BDNFs level initially and post treatment in acute mania: comparison between ECT and atypical antipsychotic treatment and healthy controls. J Psychopharmacol 29:898-902.

Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, and Aubry JM. 2002. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res 109:143-148.

Kishi T, Yoshimura R, Ikuta T, and Iwata N. 2017. Brain-derived neurotrophic factor and major depressive disorder: evidence from meta-analyses. Front Psychiatry 8:308.

Kranaster L, Kammerer-Ciernioch J, Hoyer C, and Sartorius A. 2011. Clinically favourable effects of ketamine as an anaesthetic for electroconvulsive therapy: a retrospective study. Eur Arch Psychiatry Clin Neurosci 261:575-582.

Li J, Ye F, Xiao W, Tang X, Sha W, Zhang X, and Wang J. 2016. Increased serum brain-derived neurotrophic factor levels following electroconvulsive therapy or antipsychotic treatment in patients with schizophrenia. Eur Psychiatry 36:23-28.

Lin HS, and Lin CH. 2019. Early improvement in HAMD-17 and HAMD-6 scores predicts ultimate response and remission for depressed patients treated with fluoxetine or ECT. J Affect Disord 245:91-97.

Maffioletti E, Gennarelli M, Gainelli G, Bocchio-Chiavetto L, Bortolomasi M, and Minelli A. 2019. BDNF genotype and baseline serum levels in relation to electroconvulsive therapy effectiveness in treatment-resistant depressed patients. J ECT 35:189-194.

Matrisciano F, Bonaccorso S, Ricciardi A, Scaccianoce S, Panaccione I, Wang L, Ruberto A, Tatarelli R, Nicoletti F, Girardi P, Shelton R. 2009. Changes in BDNF serum levels in patients with major depression disorder (MDD) after 6 months treatment with sertraline, escitalopram, or venlafaxine. J Psychiatr Res 43:247-254.

Mikhael NW, Hamed AM, Mansour AI, and Abdelrahman ES. 2019. Serum levels of brain-derived neurotrophic factor in patients with acne vulgaris. J Cosmet Dermatol 18:1998-2003.

Molendijk ML, Spinholven P, Polak M, Bus BA, Penninx BW, and Elzinga BM. 2014. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N=9484). Mol Psychiatry 19:791-800.

Mora E, Portella MJ, Piñol-Ripoll G, López R, Cuadras D, Forcada I, Teres M, Vieta E, and Mur M. 2019. High BDNF serum levels are associated to good cognitive functioning in bipolar disorder. Eur Psychiatry 60:97-107.
Nase S, Köhler S, Jennebach J, Eckert A, Schweinfurth N, Gallinat J, Lang UE, and Kühn S. 2016. Role of serum brain derived neurotrophic factor and central n-acetylaspartate for clinical response under antidepressive pharmacotherapy. Neurosignals 24:1-14.

Okamoto N, Nakai T, Sakamoto K, Nagafusa Y, Higuchi T, and Nishikawa T. 2010. Rapid antidepressant effect of ketamine anesthesia during electroconvulsive therapy of treatment-resistant depression: comparing ketamine and propofol anesthesia. J ECT 26:223-227.

Petrides G, and Fink M. 1996. The "half-age" stimulation strategy for ECT dosing. Convuls Ther 12:138-146.

Petrides G, Fink M, Husain MM, Knapp RG, Rush AJ, Mueller M, Rummans TA, O'Connor KM, Rasmussen KG, Jr, Bernstein HJ, Biggs M, Bailine S H, Kellner C H. 2001. ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. J ECT 17:244-253.

Phillips JL, Norris S, Talbot J, Birmingham M, Hatchard T, Ortiz A, Owoeye O, Batten LA, and Blier P. 2019. Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. Am J Psychiatry 176:401-409.

Polyakova M, Schroeter ML, Elzinga BM, Holiga S, Schoenknecht P, de Kloet ER, and Molendijk ML. 2015a. Brain-derived neurotrophic factor and antidepressive effect of electroconvulsive therapy: systematic review and meta-analyses of the preclinical and clinical literature. PLoS One 10:e0141564.

Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenknecht P, and Schroeter ML. 2015b. BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis. J Affect Disord 174:432-440.

Radvansky BM, Shah K, Parikh A, Sifonios AN, Le V, and Eloy JD. 2015. Role of ketamine in acute postoperative pain management: a narrative review. Biomed Res Int 2015:749837.

Rapinesi C, Kotzalidis GD, Curto M, Serata D, Ferri VR, Scatena P, Carbonetti P, Napoletano F, Miele J, Scaccianoce S, Del Casale A, Nicoletti F, Angeletti G, Girardi P. 2015. Electroconvulsive therapy improves clinical manifestations of treatment-resistant depression without changing serum BDNF levels. Psychiatry Res 227:171-178.

Ren L, Deng J, Min S, Peng L, and Chen Q. 2018. Ketamine in electroconvulsive therapy for depressive disorder: A systematic review and meta-analysis. J Psychiatr Res 104:144-156.

Riedel M, Möller HJ, Obermeier M, Schennach-Wolff R, Bauer M, Adli M, Kronmüller K, Nickel T, Brieger P, Laux G, Bender W, Heuser I, Zeiler J, Gaebel W, Seemüller F. 2010. Response and remission criteria in major depression--a validation of current practice. J Psychiatr Res 44:1063-1068.

Ryan KM, Dunne R, and McLoughlin DM. 2018. BDNF plasma levels and genotype in depression and the response to electroconvulsive therapy. Brain Stimul 11:1123-1131.

Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, and Olfson M. 2007. The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology 32:244-254.

van Zutphen EM, Rhebergen D, van Exel E, Oudega ML, Bouckaert F, Sienaert P, Vandenbulcke M, Stek M, and Dols A. 2019. Brain-derived neurotrophic factor as a possible predictor of electroconvulsive therapy outcome. Transl Psychiatry 9:155.

Vanicek T, Kranz GS, Vyssoki B, Fugger G, Komorowski A, Höflich A, Saumer G, Milovic S, Lanzenberger R, Eckert A, Kasper S, Frey R. 2019a. Acute and subsequent continuation electroconvulsive therapy elevates serum BDNF levels in patients with major depression. Brain Stimul 12:1041-1050.

Vanicek T, Kranz GS, Vyssoki B, Komorowski A, Fugger G, Höflich A, Micskei Z, Milovic S, Lanzenberger R, Eckert
A, Kasper S, Frey R. 2019b. Repetitive enhancement of serum BDNF subsequent to continuation ECT. Acta Psychiatr Scand 140:426-434.

Wolkowitz OM, Wolf J, Shelly W, Rosser R, Burke HM, Lerner GK, Reus VI, Nelson JC, Epel ES, and Mellon SH. 2011. Serum BDNF levels before treatment predict SSRI response in depression. Prog Neuropsychopharmacol Biol Psychiatry 35:1623-1630.

Yasuda K, Kobayashi K, Yamaguchi M, Tanaka K, Fujii T, Kitahara Y, Tamaoki T, Matsushita Y, Nunomura A, and Motohashi N. 2015. Seizure threshold and the half-age method in bilateral electroconvulsive therapy in Japanese patients. Psychiatry Clin Neurosci 69:49-54.

Zarate CA, Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, and Manji HK. 2006. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63:856-864.

Zheng W, Jiang ML, He HB, Li RP, Li QL, Zhang CP, Zhou SM, Yan S, Ning YP, and Huang X. 2020. Serum BDNF levels are not associated with the antidepressant effects of nonconvulsive electrotherapy. Neuropsychiatr Dis Treat 16:1555-1560.

Zheng W, Li XH, Zhu XM, Cai DB, Yang XH, Ungvari GS, Ng CH, Ning YP, Hu YD, He SH, Wang G, Xiang YT. 2019a. Adjunctive ketamine and electroconvulsive therapy for major depressive disorder: A meta-analysis of randomized controlled trials. J Affect Disord 250:123-131.

Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, Chen LJ, Li MD, and Ning YP. 2018. Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. J Psychiatr Res 106:61-68.

Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, Chen LJ, Li MD, and Ning YP. 2019b. Investigation of medical effect of multiple ketamine infusions on patients with major depressive disorder. J Psychopharmacol 33:494-501.

Zhong X, He H, Zhang C, Wang Z, Jiang M, Li Q, Zhang M, and Huang X. 2016. Mood and neuropsychological effects of different doses of ketamine in electroconvulsive therapy for treatment-resistant depression. J Affect Disord 201:124-130.

Zong QQ, Qi H, Wang YY, Zhang C, Balbuena L, Ungvari GS, An FR, and Xiang YT. 2020. Knowledge and attitudes of adolescents with psychiatric disorders and their caregivers towards electroconvulsive therapy in China. Asian J Psychiatr 49:101968.
Table 1 (on next page)

Comparison of demographic and clinical characteristics between patients with TRD and healthy controls

\(^a\) Antidepressant response was defined as a 50% or greater reduction in HAMD-17 scores.

\(^b\) Antidepressant remission was defined as HAMD-17 scores ≤6 as recommended by Riedel et al.’s study. Abbreviations: BDNF=brain-derived neurotrophic factor; df=degrees of freedom; ECT=electroconvulsive therapy; SD=standard deviation; TRD=treatment-refractory depression.
**Table 1.** Comparison of demographic and clinical characteristics between patients with TRD and healthy controls

| Variables                                           | Patients with TRD (n=30) | Healthy controls (n=30) | Statistics |
|-----------------------------------------------------|--------------------------|-------------------------|------------|
|                                                     | n | % | n | % | χ² | df | P |
| Male                                                | 14 | 46.7 | 13 | 43.3 | 0.07 | 1 | 0.795 |
| Employed                                            | 24 | 80.0 | - | - | - | - | - |
| Married                                             | 20 | 66.7 | - | - | - | - | - |
| Antidepressant response after the last ECT<sup>a</sup> | 30 | 100.0 | - | - | - | - | - |
| Antidepressant remission after the last ECT<sup>b</sup> | 23 | 76.7 | - | - | - | - | - |
| Mean Age (years)                                    | 32.1 | 9.9 | 30.8 | 8.2 | 0.58 | 58 | 0.561 |
| Baseline serum BDNF levels (ng/ml)                  | 23.7 | 8.9 | 24.2 | 6.1 | -0.24 | 58 | 0.810 |

<sup>a</sup>Antidepressant response was defined as a 50% or greater reduction in HAMD-17 scores.

<sup>b</sup>Antidepressant remission was defined as HAMD-17 scores ≤6 as recommended by Riedel et al.’s study.

Abbreviations: BDNF=brain-derived neurotrophic factor; df=degrees of freedom; ECT=electroconvulsive therapy; SD=standard deviation; TRD=treatment-refractory depression.
Table 2 (on next page)

Comparison of demographic and clinical characteristics between remitters and nonremitters after ECT

*Fisher’s exact test. Abbreviations: BDNF=brain-derived neurotrophic factor; BPRS=the Brief Psychiatric Rating Scale; df=degrees of freedom; ECT=electroconvulsive therapy; HAMD-17=the 17-item Hamilton Depression Rating Scale; SD=standard deviation.
Table 2. Comparison of demographic and clinical characteristics between remitters and nonremitters after ECT

| Variables                        | Total samples (n=30) | Remitters (n=23) | Nonremitters (n=7) | Statistics |
|----------------------------------|----------------------|------------------|-------------------|------------|
|                                  | n        | %   | n   | %   | n   | %   | χ² | df | P   |
| Male                             | 14       | 46.6 | 10  | 43.4 | 4   | 57.1 | 0.4 | 1  | 0.526 |
| Employed                         | 24       | 80.0 | 19  | 82.6 | 5   | 71.4 | ---a | ---a | 0.603 |
| Married                          | 20       | 66.7 | 14  | 60.8 | 6   | 85.7 | ---a | ---a | 0.372 |
| Mean SD                          |           |      | Mean SD |      | Mean SD |       | t/z | df | P   |
| Age (years)                      | 32.1     | 9.9  | 31.2 | 10.5 | 35.3 | 7.5  | 0.9 | 28 | 0.344 |
| Baseline serum BDNF levels (ng/ml)| 23.7     | 8.9  | 24.3 | 9.8  | 21.8 | 5.8  | -0.6 | 28 | 0.543 |
| Baseline HAMD-17 scores          | 26.7     | 1.6  | 26.7 | 1.7  | 26.8 | 1.1  | 0.3  | 28 | 0.769 |
| Baseline BPRS scores             | 35.5     | 4.2  | 35.6 | 4.5  | 35.0 | 3.1  | -0.3 | 28 | 0.741 |

*A Fisher's exact test.

Abbreviations: BDNF=brain-derived neurotrophic factor; BPRS=the Brief Psychiatric Rating Scale; df=degrees of freedom; ECT=electroconvulsive therapy; HAMD-17=the 17-item Hamilton Depression Rating Scale; SD=standard deviation.
Comparison of serum BDNF levels, HAMD-17 scores, and BPRS scores between remitters and nonremitters using linear mixed model analysis

Bolded values are $p<0.05$. Abbreviations: BDNF=brain-derived neurotrophic factor; BPRS=the Brief Psychiatric Rating Scale; HAMD-17=the 17-item Hamilton Depression Rating Scale.

| Table 3 (on next page) |
|------------------------|
| Comparison of serum BDNF levels, HAMD-17 scores, and BPRS scores between remitters and nonremitters using linear mixed model analysis |
| Bolded values are $p<0.05$. Abbreviations: BDNF=brain-derived neurotrophic factor; BPRS=the Brief Psychiatric Rating Scale; HAMD-17=the 17-item Hamilton Depression Rating Scale. |
| Variables                | Group-by-time interaction | Time main effect | Group main effect |
|--------------------------|---------------------------|------------------|-------------------|
|                          | F  | P    | F  | P    | F  | P    |
| Serum BDNF levels        | 1.2| 0.321| 1.6| 0.214| 0.9| 0.355|
| HAMD-17 scores           | 3.7| **0.019**| 2095.5| **<0.001**| 5.0| **0.028**|
| BPRS scores              | 1.2| 0.309| 332.1| **<0.001**| 1.6| 0.208|

Bolded values are \( p < 0.05 \).

Abbreviations: BDNF=brain-derived neurotrophic factor; BPRS=the Brief Psychiatric Rating Scale; HAMD-17=the 17-item Hamilton Depression Rating Scale.
Figure 1

Changes in depressive symptoms following eight ECT treatments

'Significant difference was found at any of the indicated times when compared baseline (p<0.05). *Significant difference was found between remitters and nonremitters at indicated times (p<0.05). Abbreviations: ECT=electroconvulsive therapy; HAMD-17=the 17-item Hamilton Depression Rating Scale.'
Significant difference was found at any of the indicated times when compared baseline ($p<0.05$).

Significant difference was found between remitters and nonremitters at indicated times ($p<0.05$).

Abbreviations: ECT=electroconvulsive therapy; HAMD-17=the 17-item Hamilton Depression Rating Scale.
Figure 2

Changes in serum BDNF levels following eight ECT treatments

Notes: no significant difference was found at any of the indicated times when compared to baseline across the total sample, even among remitters and nonremitters ($p>0.05$); no significant difference was found between remitters and nonremitters at any of the indicated times ($p>0.05$). Abbreviations: BDNF=brain-derived neurotrophic factor; ECT=electroconvulsive therapy; TRD=treatment-refractory depression.
Notes: no significant difference was found at any of the indicated times when compared to baseline across the total sample, even among remitters and nonremitters ($p>0.05$); no significant difference was found between remitters and nonremitters at any of the indicated times ($p>0.05$).

Abbreviations: BDNF=brain-derived neurotrophic factor; ECT=electroconvulsive therapy; TRD=treatment-refractory depression.