Plasma BDNF concentrations and the antidepressant effects of six ketamine infusions in unipolar and bipolar depression

Wei Zheng Corresp., 1, Yan-Ling Zhou 1, Cheng-Yu Wang 1, Xiao-Feng Lan 1, Bin Zhang 1, Su-Miao Zhou 1, Su Yan 1, Yu-Ping Ning Corresp. 1, 2

1 Psychiatry, The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China
2 Psychiatry, The first School of Clinical Medicine, Southern Medical University, Guangzhou, China

Corresponding Authors: Wei Zheng, Yu-Ping Ning
Email address: zhengwei0702@163.com, ningjeny@126.com

Objectives: Accumulating evidence has implicated that brain derived neurotrophic factor (BDNF) is thought to be involved in the pathophysiology of depression, but its correlation with ketamine’s antidepressant efficacy focusing on Chinese individuals with depression is not known. This study was aimed to determine the correlation of plasma BDNF (pBDNF) concentrations and ketamine’s antidepressant efficacy. Methods: Ninety-four individuals with depression received six intravenous infusions ketamine (0.5 mg/kg). Remission and response were defined as Montgomery-Asberg Depression Rating Scale (MADRS) scores less than 10 and a reduction of 50% or more in MADRS scores, respectively. Plasma was collected at baseline and at 24 h and 2 weeks after completing six ketamine infusions (baseline, 13 d and 26 d). Results: A significant improvement in MADRS scores and pBDNF concentrations was found after completing six ketamine infusions compared to baseline (all \( p<0.05 \)). Higher baseline pBDNF concentrations were found in ketamine responders/remitters (11.0±6.2/10.1±5.8 ng/ml) than nonresponders/nonremitters (8.0±5.5/9.2±6.4 ng/ml) (all \( p<0.05 \)). Baseline pBDNF concentrations were correlated with MADRS scores at 13 d (t=−2.011, p=0.047) or 26 d (t=−2.398, p=0.019) in depressed patients (all \( p<0.05 \)). Subgroup analyses found similar results in individuals suffering from treatment refractory depression. Conclusion: This preliminary study suggests that baseline pBDNF concentrations appeared to be correlated with ketamine’s antidepressant efficacy in Chinese patients with depression.
Plasma BDNF concentrations and the antidepressant effects of six ketamine infusions in unipolar and bipolar depression

Running title: BDNF and ketamine

1. Wei Zheng, MD, PhD;
2. Yan-Ling Zhou, MD, PhD;
3. Cheng-Yu Wang, MD, PhD;
4. Xiao-Feng Lan, MD;
5. Bin Zhang, MD, PhD;
6. Su-Miao Zhou, MD;
7. Su Yan, MD;
8. 1,2* Yu-Ping Ning, MD, PhD

1. The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China;
2. The first School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, China

*Address correspondence to Dr. Yu-Ping Ning, the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China; Email address: ningjeny@126.com.
Disclosure/Conflicts of Interest

The authors declare no conflicts of interest in conducting this study or preparing the manuscript.

Financial support

This work was supported by the National Natural Science Foundation of China (81801343, 81801345), Guangdong Basic and Applied Basic Research Foundation (2019A1515011366), the National Key Research and Development Program of China (2016YFC0906300), Science and Technology Department of Guangdong Province major science and technology (2016B010108003) and Guangzhou Municipal Psychiatric Disease Clinical Transformation Laboratory (201805010009). The funding source had no role in the study design, analysis or interpretation of data or in the preparation of the report or decision to publish.

Acknowledgements

None.
Abstract

Objectives: Accumulating evidence has implicated that brain derived neurotrophic factor (BDNF) is thought to be involved in the pathophysiology of depression, but its correlation with ketamine’s antidepressant efficacy focusing on Chinese individuals with depression is not known. This study was aim to determine the correlation of plasma BDNF (pBDNF) concentrations and ketamine’s antidepressant efficacy.

Methods: Ninety-four individuals with depression received six intravenous infusions ketamine (0.5 mg/kg). Remission and response were defined as Montgomery-Asberg Depression Rating Scale (MADRS) scores less than 10 and a reduction of 50% or more in MADRS scores, respectively. Plasma was collected at baseline and at 24 h and 2 weeks after completing six ketamine infusions (baseline, 13 d and 26 d).

Results: A significant improvement in MADRS scores and pBDNF concentrations was found after completing six ketamine infusions compared to baseline (all \( p < 0.05 \)). Higher baseline pBDNF concentrations were found in ketamine responders/remitters (11.0±6.2/10.1±5.8 ng/ml) than nonresponders/nonremitters (8.0±5.5/9.2±6.4 ng/ml) (all \( p < 0.05 \)). Baseline pBDNF concentrations were correlated with MADRS scores at 13 d (\( t = -2.011, p = 0.047 \)) or 26 d (\( t = -2.398, p = 0.019 \)) in depressed patients (all \( p < 0.05 \)). Subgroup analyses found similar results in individuals
suffering from treatment refractory depression.

**Conclusion:** This preliminary study suggests that baseline pBDNF concentrations appeared to be correlated with ketamine’s antidepressant efficacy in Chinese patients with depression.

**Key words:** Brain-derived neurotrophic factor; ketamine; depression; response
**Introduction**

Accumulating evidence suggests that glutamatergic abnormalities are associated with the pathophysiology of mood disorders (Yüksel & Öngür 2010). Numerous early studies had consistently reported that an antagonist of glutamatergic N-methyl-D-aspartate (NMDA) receptors ketamine at subanesthetic doses could result in fast-acting and sustained antidepressant effects in individuals suffering from unipolar and bipolar depression (Na & Kim 2021; Phillips et al. 2020). For example, ketamine’s repeated administration had quick and enduring antidepressant and antisuicidal effects in depressed patients (Kryst et al. 2020).

The precise mechanisms underlying subanesthetic intravenous ketamine’s antidepressant actions are still incompletely understood (Rong et al. 2018). A recent animal study found that blockade of NMDA receptors increased the induction of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor expression in models of depression, and subsequent activation of the mammalian target of rapamycin (mTOR) pathway was needed for the rapid and robust antidepressant action of ketamine (Li et al. 2010). Growing evidence implicated neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), played an important in the pathophysiology of mood disorders (Duman 2004; Duman & Monteggia 2006). BDNF is a key protein in facilitating and supporting memory growth.
and neuronal survival (Leal et al. 2017). Rapid and transient upregulation of
BDNF reversed or blocked atrophy and cell loss in patients with depression,
and it may be a critical component in subanesthetic intravenous ketamine’s
antidepressant actions (Haile et al. 2014).

In general, BDNF plays a role in the pathophysiology of schizophrenia
(Singh et al. 2020) and mood disorders (Molendijk et al. 2014; Sagud et al.
2016). For example, several studies found that individuals suffering from
depression had lower serum BDNF concentrations and pBDNF concentrations
than that of healthy subjects (Molendijk et al. 2014; Sagud et al. 2016) and
recovered after successful antidepressant therapy (Brunoni et al. 2008;
Polyakova et al. 2015). Central and peripheral BDNF is positively correlated
with the response and remission of antidepressant treatment (Lee & Kim
2010). Notably, Kurita et al. reported that remitted than nonremitted
depressed patients appeared to have higher pBDNF concentrations, and
these concentrations were associated with the Montgomery-Asberg
Depression Rating Scale (MADRS) scores (Kurita et al. 2012).

BDNF as a predictor of ketamine’s antidepressant efficacy in individuals
suffering from treatment-refractory depression (TRD) has been investigated,
but with inconsistent findings. For example, several open-label studies on
ketamine and BDNF found a negative association of the increase in BDNF
following a single ketamine infusion with the severity of depression (Cornwell
et al. 2012; Duncan et al. 2013). Another study found that BDNF did not mediate single subanesthetic intravenous ketamine’s antidepressant efficacy (Machado-Vieira et al. 2009). However, no studies had been published to examine the relationship of pBDNF concentrations and serial subanesthetic intravenous ketamine infusions’ antidepressant efficacy in Chinese individuals suffering from depression.

The present study was performed to examine the correlation of pBDNF concentrations and six subanesthetic intravenous ketamine’s antidepressant efficacy (0.5 mg/kg) administered thrice weekly over two weeks in Chinese individuals suffering from unipolar and bipolar depression. In this study, we hypothesized that serial intravenous subanesthetic ketamine would increase pBDNF concentrations, and baseline pBDNF concentrations would be associated with ketamine’s antidepressant efficacy in individuals suffering from depression.

Methods

Study sample

Data of the current study were collected from an open-label clinical study, which examined serial intravenous subanesthetic ketamine’s antidepressant and antisuicidal efficacy in individuals suffering from depression and was performed between November 2016 to December 2017 (registration number:
ChicCTR-OOC-17012239) (Zheng et al. 2018). The Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University approved the current trial’s protocol (Ethical Application Ref: 2016-030) and written informed consent was obtained from all participants.

All subjects were recruited based on the following inclusion criteria: (1) aged between 18 and 65 years, without psychotic symptoms; (2) diagnosis of unipolar or bipolar depression by a certified psychiatrist according to the Structured Clinical Interview for DSM-V (SCID-5) criteria, with a score of 17 or more for the Hamilton Depression Rating Scale (HAMD-17) (Hamilton 1960); (3) suffering from TRD, which was defined as nonresponse to 2 or more antidepressant treatments, or experiencing suicidal ideation as measured with the Scale for Suicidal Ideations (Beck et al. 1979); (4) had no a history of neurological diseases (e.g., dementia), drug or alcohol abuse; (5) negative urine toxicology; (6) were not pregnant or breast feeding; and (7) had no any unstable medical illness (e.g., cerebrovascular diseases).

**Treatment**

All patients received a thrice-weekly ketamine treatment regimen for 2 weeks, with a follow-up period of two weeks. The method for repeated ketamine infusions was described in detail in our early trial (Zheng et al. 2018). Briefly, vital signs and clinical status of participants were
routinely monitored, and each subject received six intravenous infusions of 0.5 mg/kg ketamine over 40 min. During the study period, all subjects continued taking psychotropic agents.

**Response and remission**

The MADRS (Montgomery & Asberg 1979; Zhong et al. 2011) was used to assess depressive symptoms at baseline, 1 d after the sixth infusion (13 d), and 2 weeks after the last ketamine treatments (26 d). Remission and response were defined as MADRS scores less than 10 (Zimmerman et al. 2004) and a reduction of 50% or more in MADRS scores, respectively.

**Measurement of pBDNF concentrations**

Plasma was collected at baseline, 13 d and 26 d, which were stored at −80 °C until further use. In accordance with the manufacturer's instructions, in this study a commercially available enzyme-linked immunosorbent assay (ELISA) kit (EMD Millipore Corporation, MA, USA) was used to measure pBDNF concentrations.

**Statistical analysis**

The Mann–Whitney U test was conducted to analyze nonnormally distributed continuous data, and independent t tests were applied for normally
distributed continuous data. For categorical variables, the Fisher’s exact test
or Chi-squared test were applied for comparisons between groups
(responders versus nonresponders and remitters versus nonremitters).
Changes in pBDNF concentrations and MADRS scores over time and
subgroup differences (responders/nonresponders and remitters/nonremitters)
were examined using linear mixed models. Bivariate correlation analysis was
applied in order to determine the correlation of baseline pBDNF
concentrations and MADRS scores at 13 d and 26 d in individuals suffering
from unipolar or bipolar depression. Multiple linear regression were also used
to examine the independent association of baseline pBDNF concentrations
and MADRS scores at 13 d and 26 d. MADRS scores were entered as the
dependent variable, while Baseline pBDNF concentrations were entered as
independent variables and other variables including age, gender, body
weight, body mass index, psychiatric family history, previous hospitalization,
psychiatric comorbidity, and age of onset were entered as covariate
variables. Furthermore, an additional analysis was also performed on a
subsample of patients with TRD in this study. IBM SPSS version 23 software
(IBM Corporation, Armonk, NY, USA) was used in this study, and significance
was set as p-value less than 0.05.

Results
Ninety-four individuals (aged 18 to 62 years) with unipolar or bipolar depression who provided a baseline blood sample were enrolled. Of these patients, 81.9% (77/94) fulfilled the diagnostic criteria of TRD. Baseline pBDNF concentrations with a mean value of 10.1 ng/ml, ranged from 0.9 to 27.2 ng/ml.

**Treatment outcome and BDNF**

After the last ketamine treatments, the rates of response and remission were 65.3% (64/94) and 51.1% (48/94), respectively. The rates of response and remission for patients with TRD were 68.8% (53/77) and 51.9% (40/77), respectively, after completion of six ketamine infusions. Higher baseline pBDNF concentrations were found in ketamine responders/remitters (11.0±6.2/10.1±5.8 ng/ml) than nonresponders/nonremitters (8.0±5.5/9.2±6.4 ng/ml) (all ps<0.05, Table 1).

Linear mixed models showed that MADRS scores and pBDNF concentrations exhibited significant time main effects between responders and nonresponders and remitters and nonremitters (Table 2). Ketamine produced a significant change in MADRS scores and pBDNF concentrations at 13 d and 26 d when compared to baseline (Figure 1 and Figure 2). Similar results were found in patients with TRD (Supplemental Table 1, Supplemental Figure 1 and 2).
Correlation of BDNF and MADRS scores

Correlation analyses showed significant associations between pBDNF concentrations at baseline and MADRS scores at 13 d and 26 d in depressed patients (all \(p\)s< 0.05; Table 3). The significant association of pBDNF concentrations at baseline and MADRS scores at 13 d (\(t=-2.011, p=0.047\)) and 26 d (\(t=-2.398, p=0.019\)) remained in multiple regression analysis. Similar results were found in patients with TRD (Supplemental Table 2).

Discussion

This is the first study to determine pBDNF concentrations after six subanesthetic intravenous ketamine in Chinese individuals suffering from unipolar and bipolar depression and to investigate the correlation of pBDNF concentrations at baseline and six subanesthetic intravenous ketamine’s antidepressant efficacy. The following main findings included: 1) ketamine increased pBDNF at 13 d and 26 d compared to baseline; 2) responders/remitters had significantly higher baseline pBDNF concentrations than nonresponders/nonremitters; 3) MADRS scores showed significant improvement at both time points across the total sample in responders/remitters and nonresponders/nonremitters compared to baseline; 4) baseline pBDNF concentrations were related with MADRS scores; and 5)
additional analysis of patients with TRD also found that pBDNF concentrations were related with the antidepressant outcome of ketamine in patients with TRD.

Consistent with an animal study after single ketamine infusion (Pytka et al. 2018), our study demonstrated that ketamine increased pBDNF concentrations after six ketamine infusions. Although nonresponders/nonremitters had significantly lower pBDNF concentrations at baseline than responders/remitters, repeated ketamine infusions failed to significantly increase pBDNF concentrations in responders/remitters when compared to nonresponders/nonremitters. Similarly, a previous study found no changes in pBDNF concentrations in individuals suffering from TRD after completion of an intravenous infusion of ketamine compared to baseline (Machado-Vieira et al. 2009). However, Haile et al. found that pBDNF concentrations were significantly increased following a single ketamine infusion in responders compared to nonresponders (Haile et al. 2014). Therefore, these findings should be confirmed by randomized controlled trials.

The observed rapid reduction in MADRS scores lasted up to 2 weeks, replicating the previous findings (Rasmussen et al. 2013; Shiroma et al. 2014). However, the primary objective of this study is to examine the association of baseline pBDNF concentrations and six subanesthetic
intravenous ketamine’s antidepressant efficacy. Several studies examined
the association of pBDNF concentrations with the antidepressant response of
a single infusion of ketamine, but these findings are inconsistent (Haile et al.
2014; Lee & Kim 2010). For instance, one study reported that pBDNF
concentrations were related with the severity of depression (Haile et al.
2014). However, Machado-Vieira et al.’s study reported a negative finding on
the association of pBDNF concentrations and ketamine’s antidepressant
efficacy (Machado-Vieira et al. 2009).

   Notably, several animal studies reported that increased hippocampal and
cortical BDNF expression can partly accounting for ketamine’s
antidepressant-like efficacy (Autry et al. 2011; Réus et al. 2011). pBDNF
concentrations were lower in individuals suffering from depression compared
to healthy controls (Kishi et al. 2017; Munno et al. 2013) and increased after
receiving antidepressants (Munno et al. 2013; Polyakova et al. 2015),
electroconvulsive therapy (Luan et al. 2020; Piccinni et al. 2009), and
repeated transcranial magnetic stimulation (Yukimasa et al. 2006).
Therefore, neurotrophic factors, such as BDNF, might be involved in
ketamine’s antidepressant mechanism. Notably, BDNF is implicated in the
regulation of synaptic plasticity, including the synaptic recruitment of AMPA
receptors. Growing studies indicate that synaptic plasticity is altered in
individuals with depression (Machado-Vieira et al. 2006; Schloesser et al.
2008; Zarate et al. 2006), and ketamine’s antidepressant efficacy may be attributed to the synaptic potentiation of neural circuits mediated by increased AMPA-to-NMDA glutamate receptors (Maeng & Zarate 2007).

The following limitations should be acknowledged. First, the participants continued receiving previous medications and lacked a washout period during the study, which may have affected pBDNF concentrations. However, the combination of ketamine and other antidepressants for individuals with depression is increasingly being used in the real-world clinical setting (Shiroma et al. 2014). Second, the sample size was small in the current study. Third, the possible impact of subjective evaluation was inevitable due to lack of a control group. Fourth, some comprehensive analyses, such as the mediating and moderating effect analysis, were not conducted in this study. Finally, brain BDNF concentrations and other key neurobiological mediators, such as mTOR, were not directly measured. However, BDNF crosses the blood-brain barrier, and pBDNF concentrations are closely correlated with cortical BDNF concentrations, and likely reflect brain BDNF concentrations (Pillai et al. 2010; Poduslo & Curran 1996).

In conclusion, this preliminary study suggests that baseline pBDNF concentrations appeared to be correlated with ketamine’s antidepressant efficacy in Chinese patients with depression.
References

Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, and Monteggia LM. 2011. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475:91-95.

Beck AT, Kovacs M, and Weissman A. 1979. Assessment of suicidal intention: the Scale for Suicide Ideation. J Consult Clin Psychol 47:343-352.

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.

Cornwell BR, Salvadore G, Furey M, Marquardt CA, Brutsche NE, Grillon C, and Zarate CA, Jr. 2012. Synaptic potentiation is critical for rapid antidepressant response to ketamine in treatment-resistant major depression. Biol Psychiatry 72:555-561.

Duman RS. 2004. Role of neurotrophic factors in the etiology and treatment of mood disorders. Neuromolecular Med 5:11-25.

Duman RS, and Monteggia LM. 2006. A neurotrophic model for stress-related mood disorders. Biol Psychiatry 59:1116-1127.

Duncan WC, Sarasso S, Ferrarelli F, Selter J, Riedner BA, Hejazi NS, Yuan P, Brutsche N, Manji HK, Tononi G, Zarate CA. 2013. Concomitant BDNF and sleep slow wave changes indicate ketamine-induced plasticity in major depressive disorder. Int J Neuropsychopharmacol 16:301-311.

Haile CN, Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Foulkes A, Iqbal S, Mahoney JJ, 3rd, De La Garza R, 2nd, Charney DS, Newton TF, Mathew SJ. 2014. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. Int J Neuropsychopharmacol 17:331-336.

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

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

Kryst J, Kawalec P, Mitoraj AM, Pile A, Lasoń W, and Brzostek T. 2020. Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials. Pharmacol Rep 72:543-562.

Kurita M, Nishino S, Kato M, Numata Y, and Sato T. 2012. Plasma brain-derived neurotrophic factor levels predict the clinical outcome of depression treatment in a naturalistic study. PLoS ONE 7:e39212.

Leal G, Bramham CR, and Duarte CB. 2017. BDNF and hippocampal synaptic plasticity. Vitam Horm 104:153-195.

Lee BH, and Kim YK. 2010. The roles of BDNF in the pathophysiology of major depression and in antidepressant treatment. Psychiatry Invest 7:231-235.

Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, and Duman RS. 2010. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329:959-964.

Luan S, Zhou B, Wu Q, Wan H, and Li H. 2020. Brain-derived neurotrophic factor blood levels after electroconvulsive therapy in patients with major depressive disorder: A systematic review and meta-analysis. Asian J Psychiatr 51:101983.

Machado-Vieira R, Yuan P, Brutsche N, DíazGranados N, Luckenbaugh D, Manji HK, and Zarate CA, Jr. 2009. Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist.
Machado-Vieira R, Zarate CA, Jr., and Manji HK. 2006. Emerging novel treatments for severe mood disorders involving cellular plasticity cascades. Curr Psychos Ther Rep 4:181-190.

Maeng S, and Zarate CA, Jr. 2007. The role of glutamate in mood disorders: results from the ketamine in major depression study and the presumed cellular mechanism underlying its antidepressant effects. Curr Psychiatry Rep 9:467-474.

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.

Montgomery SA, and Asberg M. 1979. A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382-389.

Munno D, Sterpone S, Fania S, Cappellin F, Mengozzi G, Saroldi M, Bechon E, and Zullo G. 2013. Plasma brain derived neurotrophic factor levels and neuropsychological aspects of depressed patients treated with paroxetine. Panminerva Med 55:377-384.

Na KS, and Kim YK. 2021. Increased use of ketamine for the treatment of depression: Benefits and concerns. Prog Neuropsychopharmacol Biol Psychiatry 104:110060.

Phillips JL, Norris S, Talbot J, Hatchard T, Ortiz A, Birmingham M, Owoeye O, Batten LA, and Blier P. 2020. Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. Neuropsychopharmacology 45:606-612.

Piccinni A, Del Debbio A, Medda P, Bianchi C, Roncaglia I, Velti A, Zanello S, Massimetti E, Origlia N, Domenici L et al. Marazziti D, Dell’Osso L. 2009. Plasma Brain-Derived Neurotrophic Factor in treatment-resistant depressed patients receiving electroconvulsive therapy. Eur Neuropsychopharmacol 19:349-355.

Pillai A, Kale A, Joshi S, Naphade N, Raju MS, Nasrallah H, and Mahadik SP. 2010. Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology. Int J Neuropsychopharmacol 13:535-539.

Poduslo JF, and Curran GL. 1996. Permeability at the blood-brain and blood-nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. Brain Res Mol Brain Res 36:280-286.

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

Pytka K, Gluch-Lutwin M, Kotasinska M, Waszkielewicz A, Kij A, and Walczak M. 2018. Single administration of HBK-15-a Triple 5-HT(1A), 5-HT(7), and 5-HT(3) receptor antagonist-reverses depressive-like behaviors in mouse model of depression induced by corticosterone. Mol Neurobiol 55:3931-3945.

Réus GZ, Stringari RB, Ribeiro KF, Ferraro AK, Vitto MF, Cesconetto P, Souza CT, and Quevedo J. 2011. Ketamine plus imipramine treatment induces antidepressant-like behavior and increases CREB and BDNF protein levels and PKA and PKC phosphorylation in rat brain. Behav Brain Res 221:166-171.

Rasmussen KG, Lineberry TW, Galardy CW, Kung S, Lapid MI, Palmer BA, Ritter MJ, Schak KM, Sola CL, Hanson AJ, Frye MA. 2013. Serial infusions of low-dose ketamine for major depression. J Psychopharmacol 27:444-450.

Rong C, Park C, Rosenblat JD, Subramaniapillai M, Zuckerman H, Fus D, Lee YL, Pan Z, Brietzke E, Mansur RB, Cha DS, Lui LMW, McIntyre RS. 2018. Predictors of response to ketamine in treatment resistant major depression. Mol Psychiatry 23:722-731.
depressive disorder and bipolar disorder. *Int J Environ Res Public Health* 15.

Sagud M, Nikolac Perkovic M, Vuksan-Cusa B, Maravic A, Svob Strac D, Mihaljevic Peles A, Zivkovic M, Kusevic Z, and Pivac N. 2016. A prospective, longitudinal study of platelet serotonin and plasma brain-derived neurotrophic factor concentrations in major depression: effects of vortioxetine treatment. *Psychopharmacology (Berl)* 233:3259-3267.

Schloesser RJ, Huang J, Klein PS, and Manji HK. 2008. Cellular plasticity cascades in the pathophysiology and treatment of bipolar disorder. *Neuropsychopharmacology* 33:110-133.

Shiroma PR, Johns B, Kuskowski M, Wels J, Thuras P, Albott CS, and Lim KO. 2014. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *J Affect Disord* 155:123-129.

Singh J, Verma R, Raghav R, Sarkar S, Sood M, and Jain R. 2020. Brain-derived neurotrophic factor (BDNF) levels in first-episode schizophrenia and healthy controls: A comparative study. *Asian J Psychiatr* 54:102370.

Yüksel C, and Öngür D. 2010. Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biol Psychiatry* 68:785-794.

Yukimasa T, Yoshimura R, Tamagawa A, Uozumi T, Shinkai K, Ueda N, Tsuji S, and Nakamura J. 2006. High-frequency repetitive transcranial magnetic stimulation improves refractory depression by influencing catecholamine and brain-derived neurotrophic factors. *Pharmacopsychiatry* 39:52-59.

Zarate CA, Jr., Singh J, and Manji HK. 2006. Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. *Biol Psychiatry* 59:1006-1020.

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.

Zhong BL, Wang Y, Chen HH, and Wang XH. 2011. Reliability, validity and sensitivity of Montgomery-Åsberg Depression Rating Scale for patients with current major depressive disorder [in Chinese]. *Chinese Journal of Behavioural Medicine and Brain Sciences* 20:85-87.

Zimmerman M, Posternak MA, and Chelminski I. 2004. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. *J Psychiatr Res* 38:577-582.
Table 1 (on next page)

Comparison of baseline sample characteristics between responders and nonresponders and between remitters and nonremitters
Table 1. Comparison of baseline sample characteristics between responders and nonresponders and between remitters and nonremitters.

| Variables                  | Total (n=94) | Response after six ketamine infusions | Remission after six ketamine infusions |
|----------------------------|--------------|---------------------------------------|----------------------------------------|
|                            |              | Responders (n=64) | Nonresponders (n=30) | Statistics | Remitters (n=48) | Nonremitters (n=46) | Statistics |
|                            | N (%)        | N (%)          | N (%)          | X² | p           | N (%)          | N (%)          | X² | p           |
| Female                     | 50 (53.2)    | 35 (54.7)      | 15 (50.0)      | 0.2 | 0.67       | 22 (45.8)      | 28 (60.9)      | 2.1 | 0.14       |
| Employment                 | 38 (40.4)    | 29 (45.3)      | 9 (30.0)       | 2.0 | 0.16       | 22 (45.8)      | 16 (34.8)      | 1.2 | 0.28       |
| Married                    | 50 (53.2)    | 35 (54.7)      | 15 (50.0)      | 0.2 | 0.67       | 27 (56.3)      | 23 (50.0)      | 0.4 | 0.54       |
| Age (years)                | 34.6 (11.6)  | 35.1 (11.2)    | 33.4 (12.5)    | -0.7 | 0.50       | 34.8 (10.9)    | 34.3 (12.4)    | -0.2 | 0.83       |
| Education (years)          | 12.4 (3.3)   | 12.8 (3.2)     | 11.4 (3.4)     | -2.0 | **0.049**  | 12.6 (3.2)     | 12.1 (3.4)     | -0.6 | 0.53       |
| BMI (kg/m²)                | 22.4 (3.6)   | 22.5 (3.5)     | 22.2 (3.8)     | -0.4 | 0.66       | 22.7 (3.9)     | 22.1 (3.2)     | 0.8  | 0.43       |
| Duration of illness (months) | 102.5 (98.3) | 106.3 (101.7)  | 94.5 (91.9)    | ---a | 0.51       | 107.3 (101.4)  | 97.6 (95.9)    | ---a | 0.58       |
| Baseline MADRS scores      | 31.9 (7.6)   | 31.8 (7.6)     | 32.2 (7.6)     | 0.3  | 0.80       | 30.6 (7.3)     | 33.3 (7.7)     | -1.8 | 0.08       |
| Baseline plasma BDNF levels (ng/ml) | 10.1 (6.2) | 11.0 (6.2) | 8.0 (5.5) | ---a | **0.01** | 10.1 (5.8) | 9.2 (6.4) | ---a | **0.045** |

*aMann-Whitney U test. Bolded values are p<0.05.

Abbreviations: BDNF=brain-derived neurotrophic factor; BMI=Body Mass Index; MADRS=the Montgomery-Asberg Depression Rating Scale; SD=standard deviation.
Table 2 (on next page)

Comparison of MADRS scores and plasma BDNF levels between responders and non-responders and between remitters and non-remitters in patients with unipolar and bipolar depression using linear mixed model analysis
Table 2. Comparison of MADRS scores and plasma BDNF levels between responders and nonresponders and between remitters and nonremitters in patients with unipolar and bipolar depression using linear mixed model analysis.

| Outcomes                     | Variables                        | Group-by-time interaction | Time main effect | Group main effect |
|------------------------------|----------------------------------|----------------------------|------------------|------------------|
|                              | MADRS scores                     | F  | p     | F  | p     | F  | p     |
| Responders vs. nonresponders | 59.79                            | <0.001                    | 223.39           | <0.001           | 59.32 | <0.001 |
| Plasma BDNF levels (ng/ml)   | 0.04                             | 0.837                      | 8.55             | <0.001           | 3.90  | 0.024  |
| Remitters vs. nonremitters   | 74.95                            | <0.001                    | 263.13           | <0.001           | 29.52 | <0.001 |
| Plasma BDNF levels (ng/ml)   | 0.02                             | 0.888                      | 6.40             | 0.003            | 2.61  | 0.079  |

Bolded values are $p<0.05$.

Abbreviations: BDNF=brain-derived neurotrophic factor; MADRS=the Montgomery-Asberg Depression Rating Scale.
Table 3 (on next page)

Correlation of baseline plasma BDNF levels and MADRS scores at 13 d or 26 d in patients with unipolar and bipolar depression
Table 3. Correlation of baseline plasma BDNF levels and MADRS scores at 13 d or 26 d in patients with unipolar and bipolar depression.

| Variables                      | MADRS scores at 13 d | MADRS scores at 26 d |
|--------------------------------|----------------------|----------------------|
| Baseline plasma BDNF levels (ng/ml) | $r = -0.220$    | $r = -0.278$      |
|                                 | $p = 0.033$         | $p = 0.007$         |

Bolded values are $p<0.05$.

Abbreviations: BDNF=brain-derived neurotrophic factor; MADRS=the Montgomery-Asberg Depression Rating Scale; $r$=Pearson coefficient of correlation.
Figure 1

Figure 1. Change in depressive symptoms in patients with unipolar and bipolar depression.

*Significant difference was found when comparing baseline to the indicated times (p<0.05).

*Significant difference was found between responders and nonresponders and between remitters and nonremitters at the indicated times (p<0.05). Abbreviations: MADRS=the Montgomery-Asberg Depression Rating Scale.
Figure 2

Figure 2. Change in plasma BDNF levels in patients with unipolar and bipolar depression.

*Significant difference was found when comparing baseline to the indicated times ($p<0.05$).

*Significant difference was found between responders and nonresponders and between remitters and nonremitters at the indicated times ($p<0.05$). Abbreviations: BDNF = brain-derived neurotrophic factor.
