ORIGINAL ARTICLE

Altered serum levels of glial cell line-derived neurotrophic factor in male chronic schizophrenia patients with tardive dyskinesia

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Abstract

Objectives: Many research indicate that the tardive dyskinesia (TD) is generally linked with long-term antipsychotic therapy for schizophrenia. Glial cell line-derived neurotrophic factor (GDNF) is a critical role in the protection of catecholaminergic, dopaminergic, and cholinergic neurons. Thus, we examined the serum GDNF levels in schizophrenia patients with TD (WTD) and without TD (NTD) and compared with healthy controls (HC), respectively.

Methods: Totally 75 males with schizophrenia were recruited into this study. All were measured by the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, the Positive and Negative Syndrome Scale, and the Abnormal Involuntary Movement Scale (AIMS). The patient group was divided into two subgroups: WTD ($n = 32$) and NTD ($n = 43$) according to the AIMS score. Fifty-three healthy controls matching in age and gender were also enlisted from the region. GDNF levels were examined with sandwich enzyme-linked immunosorbent assay.

Results: Analysis of variance indicated significant differences between the three groups ($P = 0.012$); GDNF levels in the WTD group were significantly different from those in the NTD ($P = 0.030$) and HC ($P = 0.003$) groups.

Conclusion: Decreased GDNF levels in TD patients indicated that alterations in neurotrophic factors may be involved in the pathophysiology of TD, but the exact mechanisms need further investigation.

KEYWORDS

glial cell line-derived neurotrophic factor, schizophrenia, tardive dyskinesia

1 | INTRODUCTION

Schizophrenia is a severe mental disorder characterized by acute or chronic psychotic symptoms that affects not only those afflicted with the disease but also the individuals' families, as well as society as a whole (Owen, Sawa, & Mortensen, 2016). Yet to date, the causes and pathogenesis of the disease remain relatively unknown. Those with schizophrenia have a large probability for recrudescence psychiatric problems and disabilities in social and professional situations and have a reduced life expectancy and an increased likelihood of health

care spending (Akisulore et al., 2015; Atun, 2015; Carmona, Gómez-Benito, Huedo-Medina, & Rojo, 2017; Chesney, Goodwin, & Fazel, 2014; Mayer-Amberg, Woltmann, & Walther, 2016). The emergence of antipsychotic drugs in the 1950s, following the finding that chlorpromazine could reduce psychotic episodes, gave those afflicted with psychiatric diseases the first real chance to live normal lives (Abbott, Jaramillo, Wilcox, & Hamilton, 2013; Adams et al., 2005; Haan & Liu, 2009; Shohamy et al., 2010). As the symptoms of schizophrenia were intermittent, long-term drug therapy was needed to successfully combat the disease (Heilbronner, Samara, Leucht, Falkai,

& Schulze, 2016; Novick, Montgomery, Treuer, Moneta, & Haro, 2016). However, long-term use of antipsychotic drugs was found to have a variety of negative effects on patients, including weight gain, movement disorders, drowsiness, and a sedated physical state (Leucht et al., 2009; Leucht et al., 2012). For example, movement disorders related to antipsychotic medication included acute extrapyramidal side effects (dystonia, drug-induced parkinsonism, akathisia, and catatonia) and tardive dyskinesia (TD), a potentially irreversible disorder (Carof, Hurford, Lybrand, & Campbell, 2011; Miller et al., 2005; Remington, 2007). TD was characterized by involuntary, repetitive, and stereotyped choreiform movements that were related to extremities, orofacial muscles, paraspinal muscles, and various other body parts (American Psychiatric Association, 2013). The emergence of TD was nearly always associated with uninterrupted psychotic medication, and symptoms rapidly decreased when treatment was interrupted, altered, or lessened (Carof et al., 2011). Therefore, detection of the earliest symptoms of TD and possible treatment options have proved challenging (Remington, 2007).

Although the function of both the first-generation antipsychotics (FGA) and the second-generation antipsychotics (SGA) involves balancing the ratio of activity of dopamine D2/serotonin 5-HT (2A) receptors and glutamate, SGA have gradually replaced FGA in clinical practice due to their superior outcomes in relieving psychotic symptoms and in eliciting fewer side effects as they emerged (Correll & Schenk, 2008; Leucht et al., 2009; Parker, 2009). However, some research showed that chronic use of many SGA was still associated with onset of TD (Bonham & Abbott, 2008; Divac, Prostran, Jakovcevski, & Cerovac, 2014; Rummel-Kluge et al., 2010; Rummel-Kluge et al., 2012; Woods et al., 2010), and therefore, uninterrupted use of these medications by schizophrenic patients remains questionable (Correll & Schenk, 2008; Remington, 2007). Moreover, other mental disorders such as affective disorder and disruptive behavior disorders are also treated with both FGA and SGA (Olfson, Blanco, Liu, Wang, & Correll, 2012). Hence, it is imperative that clinical research should be done to elucidate effective strategies to reduce antipsychotic-related TD. However, a more basic understanding of how TD develops in response to chronic antipsychotic drug treatment is first needed before clinical research can begin.

Although there have been numerous theories regarding the etiology and pathophysiology of TD, to date, no definitive mechanisms have been identified. Although not proven, it is theorized that the mechanisms of TD involve postsynaptic dopamine hypersensitivity resulting from blockade of dopaminergic receptors on a variety of neurons, including gamma-aminobutyric acid (GABA) and striatal cholinergic neurons, resulting in structural changes in the brain (Margolese, Chouinard, Kolivakis, Beauclair, & Miller, 2005; Sachdev, 2000; Sarro et al., 2013). In addition, evidence has been found that oxidative stress (OS) and increased free radical formation may contribute to the onset and progression of TD (Cho & Lee, 2013; Elkashef & Wyatt, 1999; Margolese et al., 2005; Sachdev, 2000). Interestingly, OS has also been linked with abnormal changes in both dopaminergic and GABAergic neurons, as well as brain structure (Cho & Lee, 2013; Olfson et al., 2012; Sachdev, 2000). Although, these findings regarding the mechanisms involved in the onset and progression of TD remain controversial, and most researchers believe that a combination of

factors are responsible (Margolese et al., 2005). To date, several risk factors associated with the onset of TD have been found, including gender, age, long-term antipsychotic treatment, sex, alcohol or drug abuse, diabetes mellitus, cognitive impairment, and organic brain injuries (Cho & Lee, 2013; Miller et al., 2005; Sachdev, 2000). In addition, elevated OS is thought to be associated with several risk factors for TD, including advanced age diabetes and drug abuse (Sachdev, 2000; West, 2000; Yamamoto & Raudensky, 2008).

It is well established that a variety of neurotrophic factors are required to promote the growth, differentiation, and maintenance of neurons (Santos, Gonzalez-Perez, Navarro, & Valle, 2016; Xiao & Le, 2016). In recent years, neurotrophic treatments have become promising drug candidates for patients suffering from several degenerative diseases (Bezdjian et al., 2016), and as a result, an increasing number of studies have been performed to identify the role of neurotrophic factors in mental illness. Among these factors, brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor (GDNF), and nerve growth factor have attracted the most interest among the research community (Airaksinen & Saarma, 2002; Allen, Watson, Shoemark, Barua, & Patel, 2013; Angelucci, Brenè, & Mathé, 2005; Buckley, Pillai, & Howell, 2011; Favalli, Li, Belmonte-de-Abreu, Wong, & Daskalakis, 2012; Ghitza et al., 2010; Green, Matheson, Shepherd, Weickert, & Carr, 2011; Lai et al., 2016; Niitsu et al., 2014; Tunca, Akdede, et al., 2015). GDNF was first identified as a neurotrophic factor involved in the survival and function of embryonic dopamine neurons *in vitro* and later *in vivo* and was subsequently shown to affect other neuronal subpopulations (Airaksinen & Saarma, 2002). And unlike the neurotrophin family (nerve growth factor, brain-derived neurotrophic factor, etc.), GDNF belongs to the transforming growth factor β superfamily. GDNF interacts with the receptor tyrosine kinase similar to other neurotrophic factors, but it must associate with the GDNF family receptor α for Ret receptors to function *in vivo* (Allen et al., 2013; Skaper, 2012). A number of studies have revealed a potential role for GDNF in neurodegenerative disorders as well as neuropsychiatric diseases, such as Alzheimer's disease (AD; Sopova, Gatsiou, Stellos, & Laske, 2014), Parkinson's disease (Esther & Gonzalo, 2011; Mickiewicz & Kordower, 2011), drug addiction (Esther & Gonzalo, 2011; Ghitza et al., 2010), stress vulnerability (Uchida et al., 2011), and mood disorders (Ma, Chen, Zhu, Jia, & Gao, 2013; Takebayashi et al., 2006; Zhang et al., 2010). To date though, there have been conflicting data regarding GDNF and schizophrenia, with several studies indicating altered serum GDNF levels and others finding no significant changes in levels in schizophrenic patients (Niitsu et al., 2014; Skibinska et al., 2017; Tunca, Akdede, et al., 2015; Xiao & Le, 2016). Furthermore, no significant associations have been found between genes encoding for GDNF and schizophrenia (Ma et al., 2013; Williams et al., 2007). Interestingly though, a positive correlation was found between schizophrenia and GDNF family receptor genes (Souza et al., 2010). Taken together, these findings suggest that altered GDNF levels may be associated the pathophysiology of schizophrenia.

However, to the best of our knowledge, peripheral GDNF levels have not been measured in schizophrenia accompanied with TD or without TD. Therefore, this study was designed to investigate serum levels of GDNF in chronic schizophrenic patients with and without

TD and compare them between the groups, as well as with healthy controls, to find a possible relationship between GDNF and TD in chronic schizophrenia.

2 | METHODS

2.1 | Subjects

Seventy-five males with schizophrenia inpatients from Affiliated WuTaiShan Hospital of Medical College of Yangzhou University, China, were enrolled in the current study. The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, was used as diagnostic criteria for chronic schizophrenia. TD was diagnosed based on the criteria of Schooler and Kane (1982). Chronic patients were assessed by four separate and skilled clinical psychiatrists. Patients with mental retardation, dementia, affective disorders, substance abuse/dependence, neurological disease (including epilepsy), and diabetes mellitus, as well as heart, liver, and kidney diseases, were excluded. All patients were receiving regular oral antipsychotic drug treatment at the time of the study. Treatment was composed primarily of monotherapy with clozapine ($n = 17$), risperidone ($n = 8$), perphenazine ($n = 20$), sulpiride ($n = 11$), chlorpromazine ($n = 12$), and haloperidol ($n = 7$). Mean antipsychotic doses were taken as chlorpromazine equivalents of 534.67 ± 257.75 mg/day. All patients had been medicated continually for 13.65 ± 6.99 years at the time of the investigation. The average duration of illness was 25.03 ± 7.07 years, and all patients were between 32 and 65 years old. Subjects taking part in this study did not have a history of drug or alcohol abuse or dependence abuse.

In parallel, 53 healthy subjects were recruited from the community in Yangzhou. Healthy volunteers were all in good physical health and had no personal or familial psychiatric history as assessed by *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition Axis I psychiatric diagnosis.

This study has obtained the approval of the Ethics Committee of Yangzhou WuTaiShan Hospital before starting. Each subject gave an informed consent on paper after a complete clarification of the study's aim and procedures.

2.2 | Serum GDNF level measurements

Venous blood taken from subjects who fasted overnight between 07:30 and 08:30 was collected in tubes without anticoagulant and centrifuged at 3,000 g for 15 min after sampling. Serum was then separated, aliquoted, and stored at -70°C prior to use. GDNF levels in serum were measured using a sandwich enzyme-linked immunosorbent assay according to the manufacturer's instructions (Promega, Madison, WI, USA), and the optical density of each well was scaled using an automated microplate reader (Epoch; BioTek Instruments, Winooski, VT, USA). To determine total GDNF, we first acid-treated and then neutralized the samples according to the manufacturer's instructions before proceeding with the enzyme-linked immunosorbent assay protocol. All samples were analyzed in the same time. And the patient's and control's samples have been detected altogether on the same plates. All samples were performed in duplicate by researchers who were blinded to the experimental groups. GDNF

serum concentrations were depicted as picogram/milliliter. The intra-assay and interassay coefficients of variation were $<4\%$ and $<5\%$, respectively.

2.3 | Clinical measures

A questionnaire method was used to gather basic data, demographic features, psychological status, and medical history of each subject. Other information was acquired from their case history. Four skilled trained psychiatrists who did not know the clinical situation of the patients evaluated the severity of TD using the Abnormal Involuntary Movement Scale. Thirty-two subjects who scored ≥ 2 were placed in the patients group with TD (WTD). The remaining 43 patients were included in the patients group without TD (NTD). At the beginning of this study, the same four clinicians conducted the psychiatric assessment of all participants using the Positive and Negative Syndrome Scale (PANSS). The four evaluators simultaneously received relevant training ahead of the assessment. Finally, all assessments were recorded before laboratory measurements were taken.

2.4 | Statistical analysis

Data were analyzed with SPSS 19.0 (IBM, Armonk, NY, USA). Calculations on categorical data were carried out using chi-squared analysis. The data of continuous variables were normally distributed and homogeneity of variance. Means $\pm$ standard deviations (SD) of continuous variables of data were presented and analyzed using one-way analysis of variance, analysis of covariance (ANCOVA), and independent sample t tests. In addition, a power calculation and effect size determination were performed using the G*Power 3.1.9.2 program. The relationship between the two variables was examined using Spearman's correlation coefficient. Differences of $P < 0.05$ were regarded as significant.

3 | RESULTS

3.1 | Demographic data

The major findings of the study are presented in Table 1. There was a significant difference between the two patient groups with regard to PANSS negative subscale score ($t = 2.522$, $df = 73$, 140 , $P = 0.014$), but not in age, education, smoking status, and duration of illness. There were no differences in demographic data (education, body mass index, age, and smoking status) among the three groups ($P > 0.05$).

3.2 | Serum GDNF levels

One-way analysis of variance showed that there was a significant difference among the three groups ($F = 4.571$, $df = 2$, 125 , $P = 0.012$) and an effect size of 0.23 with power of 0.71. GDNF levels in TD patients were significantly decreased compared with those in the NTD group as well as healthy controls ($P = 0.030$ and $P = 0.003$, respectively), as assessed by least significant difference post hoc (Figure 1). Following univariate analysis of ANCOVA and controlling for PANSS negative subscale scores as a covariate, GDNF levels

TABLE 1 Demographics, clinical characteristics, and GDNF of the sample cohort

	WTD (n = 32)	NTD (n = 43)	HC (n = 53)	P value
Age (years)	53.13 ± 5.701	52.58 ± 7.19	52.47 ± 5.70	0.890 ^a
Education (years)	9.25 ± 2.92	8.30 ± 3.23	9.45 ± 3.08	0.175 ^a
Smoker/Nonsmokers	20/12	27/16	29/24	0.666 ^b
BMI (kg/m ²)	24.34 ± 2.40	25.03 ± 3.48	25.13 ± 2.91	0.474 ^a
Age of onset (years)	28.09 ± 7.96	27.56 ± 8.89		0.788 ^a
Duration of illness (years)	25.03 ± 6.99	25.02 ± 7.22		0.625 ^c
chlorpromazine equivalents	573.59 ± 276.17	505.70 ± 242.39		0.262 ^c
PANSS positive subscale	11.66 ± 4.24	13.23 ± 5.65		0.190 ^c
PANSS negative subscale	17.94 ± 5.34	15.16 ± 4.19		0.014^c
PANSS general subscale	27.78 ± 5.03	27.63 ± 6.02		0.907 ^c
PANSS total score	57.38 ± 10.11	56.02 ± 11.11		0.590 ^c
GDNF (pg/ml)	641.71 ± 151.57	709.99 ± 133.21	730.54 ± 120.92	0.012^a

Note. Data expressed as mean ± SD. Significant differences ($P < 0.05$) were marked in bold. HC: healthy controls; WTD: male chronic schizophrenic patients with TD; NTD: male chronic schizophrenic patients without TD; BMI: body mass index; PANSS: Positive and Negative Syndrome Scale; GDNF: glial cell line-derived neurotrophic factor.

^aOne-way analysis of variance with least significant difference posttest.

^bChi-squared analysis.

^cIndependent sample t test.

remained significantly lower in the WTD group compared with the NTD group ($F = 4.092$, $df = 2, 75$, $P = 0.047$). Interestingly, no significant decreases in GDNF levels were observed in NTD patients compared with healthy controls ($P = 0.454$). Lastly, no correlations were found between clinical variances and serum GDNF levels in schizophrenia ($P > 0.05$).

4 | DISCUSSION

In this study, decreased GDNF levels were found in chronic schizophrenia (including WTD and NTD) compared with healthy controls. These decreased GDNF levels were not in agreement with a recently published report in which unchanged levels were found in a Japanese cohort suffering from chronic schizophrenia (Niitsu et al., 2014). In

contrast though, Tunca et al. (2015) conducted a comparative study of four major psychiatric disorders and detected that in schizophrenia, GDNF levels were decreased compared with mania and healthy controls (Tunca, Akdede, et al., 2015). Similarly, results regarding GDNF levels have also been found to be inconsistent among studies involving affective disorders. Tunca, Bayin, et al. (2015) found increased serum GDNF levels during acute manic and lower serum GDNF levels during depressive episodes in bipolar patients, whereas Zhang et al. (2014) and Lee et al. (2015) detected lower GDNF levels in major depressive disorder patients compared with healthy controls. Several other studies found that there was a reduced density of glial cells in patients suffering from schizophrenia and mood disorders (Cotter, Pariante, & Everall, 2001; Elsayed & Magistretti, 2015; Niciu, Henter, Sanacora, & Zarate, 2013; Tobe, 2013; Vostrikov, Uranova, & Orlovskaya, 2007; Williams et al., 2013). The changes in glial cells may result from a weakening of normal trophic support usually provided by neurotrophic factors (Cotter et al., 2001). Therefore, loss or injury to glial cells may contribute to a decline in glutamate uptake in patients with mood disorders (Zarate et al., 2003). Similarly, it was found that there were impaired glutamate–glutamine cycles and glutamatergic disturbances during active episodes in schizophrenia that may have been caused by altered astrocyte activity (Kondziella, Brenner, Eyjolfsson, & Sonnewald, 2007; Marrsman et al., 2013). Interestingly, concentrations of glutamine were shown to be increased in never treated schizophrenia (Olbrich et al., 2008; Théberge et al., 2007), whereas its levels were significantly reduced in chronic patients (Ohrmann et al., 2005). Furthermore, previous data have demonstrated that GDNF provides benefit to the maturation of nerve cells (Santos et al., 2016; Xiao & Le, 2016) and affords protection to dopaminergic neurons (Airaksinen & Saarna, 2002; Granholm et al., 2000; Skaper, 2012). In astrocytes, GDNF expression is induced by dopaminergic neurons (Saavedra, Baltazar, Santos, Carvalho, & Duarte, 2006), and we therefore speculate that there is a relation between decreased GDNF levels and dopaminergic abnormality in schizophrenia. Overall,

FIGURE 1 Serum GDNF levels in WTD, NTD, and HC. WTD: male chronic schizophrenic patients with TD; NTD: male chronic schizophrenic patients without TD; HC: healthy controls; GDNF: glial cell line-derived neurotrophic factor; ANOVA: analysis of variance

neuron–glia interaction mechanisms deserve further studies to clarify their role in schizophrenia, which would give possible direction to future clinical studies.

Interestingly, we found significant deviations in GDNF levels between the WTD and NTD groups. In particular, we found that GDNF levels were significantly lower in the WTD group compared with both the NTD and healthy control groups. It is worth noting that there was a significant difference between the two patient groups with regard to PANSS negative subscale score. GDNF levels in the WTD group remained markedly lower compared with the NTD group when we controlled for PANSS negative subscale scores as a covariate; therefore, the result of the ANCOVA indicated that the difference of GDNF levels between the two patient groups was associated with the existence of TD regardless of the severity of negative symptoms. Although GDNF levels in the NTD group were lower than normal controls, the difference was not significant. These differences of GDNF levels between the three groups may be associated with the pathophysiology of TD in chronic schizophrenia. As mentioned earlier, the mechanism of TD is complicated and undefined, and numerous factors have been implicated in TD onset and progression, including postsynaptic dopamine hypersensitivity, OS, and loss of dopaminergic receptors on GABA and striatal cholinergic neurons (Cho & Lee, 2013; Elkashef & Wyatt, 1999; Margolese et al., 2005; Sachdev, 2000; Sarro et al., 2013). In particular, the dopamine TD hypothesis considers that decreasing dopamine receptor sensitivity and postsynaptic dopamine hypersensitivity are associated with the antipsychotic TD induction (Margolese et al., 2005; Sachdev, 2000). As GDNF has been shown to have positive effects on the survival and development of dopamine neurons (Airaksinen & Saarna, 2002; Skaper, 2012), alterations in GDNF thus can possibly influence dopamine neurons (Kumar et al., 2015) and TD onset. In the current study, although we found decreased GDNF levels in the WTD group compared with the NTD group, these levels were in serum GDNF and not brain-derived GDNF (Kastin, Akerstrom, & Pan, 2003). Interestingly, Straten, Eschweiler, Maetzler, Laske, and Leyhe (2009) measured GDNF in the cerebrospinal fluid (CSF) of patients with AD and normal controls, then found that there has a strong correlation between GDNF levels in the serum and CSF of normal controls; the authors postulated that movement of GDNF from the periphery into central nervous system was occurring. In contrast, no correlation between GDNF levels in the serum and CSF of AD patients was found (Straten et al., 2009). However, several other studies found no evidence that GDNF could pass through the blood–brain barrier into the central nervous system (Airaksinen & Saarna, 2002; Kastin et al., 2003; Kumar et al., 2015; Luz, Mohr, & Fibiger, 2016). Thus, we could not accurately determine if serum GDNF levels correlated with brain GDNF. Furthermore, there are many unknown factors that may contribute to the onset of schizophrenia and TD, and further research is required to elucidate them. In particular, the OS hypothesis has gained increasing attention among the scientific community (Cho & Lee, 2013; Lister, Nobrega, Fletcher, & Remington, 2014). In 2007, Smith and Cass conducted a study in patients with Parkinson's disease and then found that the effects of GDNF involved the attenuation of free radical damage and a reduction in OS. Therefore, the relation between GDNF and OS in schizophrenia with TD warrants further investigation. Moreover, GDNF was not

related to the factors (age, duration, PANSS score, etc.) in our study, which is partly inconsistent with the result of some previous research (Souza et al., 2010).

There were several limitations to this study that must be taken into account. First, every subject in both patient groups was treated with antipsychotics; thus, an influence of medicine on GDNF levels cannot be rule out. The effects of antipsychotics on GDNF levels have been demonstrated in a previous study, and this effect was related to the type and dosage of the selected drug (Shao, Dyck, Wang, & Li, 2006). Further studies are required to investigate possible discrepancy using different drug groups and medication-free subjects. Second, we measure serum GDNF levels and not brain-derived GDNF. Whether the alteration of serum GDNF reveals any change in the brain remains to be elucidated. Lastly, only male patients were recruited in the current study and as such do not represent the whole population.

In conclusion, serum GDNF levels were decreased in chronic schizophrenic patients, especially in patients with TD. Whether these results indicate a pathological mechanism of TD in schizophrenia remains to be elucidated. This finding further confirms that various factors are involved in schizophrenia with TD and that alterations in neurotrophic factors are potential mechanisms in the disease. The exact mechanisms and how mechanisms regarding neurotrophic factors influence schizophrenia with TD remain to be seen.

DECLARATION OF INTEREST STATEMENT

None to declare.

AUTHORS' CONTRIBUTIONS

Fei Ye recruited subjects and collected clinical data, performed symptoms of schizophrenia assessment, analyzed the data, and wrote the manuscript. Qiongqiong Zhan performed symptoms of schizophrenia assessment and analyzed the data. Wenhuan Xiao recruited subjects and collected clinical data. Xiaowei Tang recruited subjects and collected clinical data. Jin Li assisted in subject recruitment. Weiwei Sha trained symptoms of schizophrenia assessment and assisted in subject recruitment. Xiaobin Zhang designed the study and assisted in symptoms of schizophrenia assessment, data analysis, and manuscript preparation. All authors contributed to manuscript preparation and approved its final version.

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REFERENCES

- Abbott, C. C., Jaramillo, A., Wilcox, C. E., & Hamilton, D. A. (2013). Antipsychotic drug effects in schizophrenia: A review of longitudinal fMRI investigations and neural interpretations. *Current Medicinal Chemistry*, 20(3), 428–437.
- Adams, C. E., Rathbone, J., Thornley, B., Clarke, M., Borrell, J., Wahlbeck, K., & Awad, A. G. (2005). Chlorpromazine for schizophrenia: A Cochrane systematic review of 50 years of randomised controlled trials. *BMC Medicine*, 3, 15. <https://doi.org/10.1186/1741-7015-3-15>
- Airaksinen, M. S., & Saarna, M. (2002). The GDNF family: Signalling, biological functions and therapeutic value. *Nature Reviews. Neuroscience*, 3(5), 383–394. <https://doi.org/10.1038/nrn812>
- Akinsulore, A., Mapayi, B. M., Aloba, O. O., Oloniniyi, I., Fatoye, F. O., & Makanjuola, R. O. A. (2015). Disability assessment as an outcome measure: A comparative study of Nigerian outpatients with schizophrenia and healthy control. *Annals of General Psychiatry*, 14, 40. <https://doi.org/10.1186/s12991-015-0079-6>
- Allen, S. J., Watson, J. J., Shoemark, D. K., Barua, N. U., & Patel, N. K. (2013). GDNF, NGF and BDNF as therapeutic options for neurodegeneration. *Pharmacology & Therapeutics*, 138(2), 155–175. <https://doi.org/10.1016/j.pharmthera.2013.01.004>
- American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth ed.). Arlington, VA: Naklada Slap.
- Angelucci, F., Brenè, S., & Mathé, A. (2005). BDNF in schizophrenia, depression and corresponding animal models. *Molecular Psychiatry*, 10(4), 345–352. <https://doi.org/10.1038/sj.mp.4001637>
- Atun, R. (2015). Transitioning health systems for multimorbidity. *Lancet*, 386(9995), 721–722. [https://doi.org/10.1016/s0140-6736\(14\)62254-6](https://doi.org/10.1016/s0140-6736(14)62254-6)
- Bezdjian, A., Kraaijenga, V. r. J. C., Ramekers, D., Versnel, H., Thomeer, H. G. X. M., Klis, S. F. L., & Grolman, W. (2016). Towards clinical application of neurotrophic factors to the auditory nerve; assessment of safety and efficacy by a systematic review of neurotrophic treatments in humans. *International Journal of Molecular Sciences*, 17(12), 1981. <https://doi.org/10.3390/ijms17121981>
- Bonham, C., & Abbott, C. (2008). Are second generation antipsychotics a distinct class? *Journal of Psychiatric Practice*, 14(4), 225–231. <https://doi.org/10.1097/01.pra.0000327312.04153.da>
- Buckley, P. F., Pillai, A., & Howell, K. R. (2011). Brain-derived neurotrophic factor: Findings in schizophrenia. *Current Opinion in Psychiatry*, 24(2), 122–127. <https://doi.org/10.1097/YCO.0b013e3283436eb7>
- Carmona, V. R., Gómez-Benito, J., Huedo-Medina, T. B., & Rojo, J. E. (2017). Employment outcomes for people with schizophrenia spectrum disorder: A meta-analysis of randomized controlled trials. *International Journal of Occupational Medicine and Environmental Health*, 30(3), 345–366. <https://doi.org/10.13075/ijomeh.1896.01074>
- Carof, S. N., Hurford, I., Lybrand, J., & Campbell, E. C. (2011). Movement disorders induced by antipsychotic drugs: Implications of the CATIE schizophrenia trial. *Neurologic Clinics*, 29(1), 127–148. viii. doi: <https://doi.org/10.1016/j.ncl.2010.10.002>
- Chesney, E., Goodwin, G. M., & Fazel, S. (2014). Risks of all-cause and suicide mortality in mental disorders: A meta-review. *World Psychiatry*, 13(2), 153–160.
- Cho, C.-H., & Lee, H.-J. (2013). Oxidative stress and tardive dyskinesia: Pharmacogenetic evidence. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 46(4), 207.
- Correll, C. U., & Schenk, E. M. (2008). Tardive dyskinesia and new antipsychotics. *Current Opinion in Psychiatry*, 21(2), 151–156.
- Cotter, D. R., Pariante, C. M., & Everall, I. P. (2001). Glial cell abnormalities in major psychiatric disorders: The evidence and implications. *Brain Research Bulletin*, 55(5), 585–595.
- Divac, N., Prostran, M., Jakovcevski, I., & Cerovac, N. (2014). Second-generation antipsychotics and extrapyramidal adverse effects. *BioMed Research International*, 2014, 656370. doi: <https://doi.org/10.1155/2014/656370>, 1–6.
- Elkashef, A. M., & Wyatt, R. J. (1999). Tardive dyskinesia possible involvement of free radicals and treatment with vitamin E. *Schizophrenia Bulletin*, 25(4), 731–740.
- Elsayed, M., & Magistretti, P. J. (2015). A new outlook on mental illnesses: Glial involvement beyond the glue. *Frontiers in Cellular Neuroscience*, 9, 468. <https://doi.org/10.3389/fncel.2015.00468>
- Esther, G., & Gonzalo, H. (2011). Connecting Parkinson's disease and drug addiction: Common players reveal unexpected disease connections and novel therapeutic approaches. *Current Pharmaceutical Design*, 17(5), 449–461.
- Favalli, G., Li, J., Belmonte-de-Abreu, P., Wong, A. H. C., & Daskalakis, Z. J. (2012). The role of BDNF in the pathophysiology and treatment of schizophrenia. *Journal of Psychiatric Research*, 46(1), 1–11. <https://doi.org/10.1016/j.jpsychires.2011.09.022>
- Ghitza, U. E., Zhai, H., Wu, P., Airavaara, M., Shaham, Y., & Lu, L. (2010). Role of BDNF and GDNF in drug reward and relapse: A review. *Neuroscience and Biobehavioral Reviews*, 35(2), 157–171. <https://doi.org/10.1016/j.neubiorev.2009.11.009>
- Granhölm, A.-C., Reyland, M., Albeck, D., Sanders, L., Gerhardt, G., Hoernig, G., ... Hoffer, B. (2000). Glial cell line-derived neurotrophic factor is essential for postnatal survival of midbrain dopamine neurons. *Journal of Neuroscience the Official Journal of the Society for Neuroscience*, 20(9), 3182–3190.
- Green, M., Matheson, S., Shepherd, A., Weickert, C., & Carr, V. (2011). Brain-derived neurotrophic factor levels in schizophrenia: A systematic review with meta-analysis. *Molecular Psychiatry*, 16(9), 960–972. <https://doi.org/10.1038/mp.2010.88>
- Haan, S. D., & Liu, X. (2009). Chlorpromazine dose for people with schizophrenia. *Schizophrenia Bulletin*, 35(3), 491–492. <https://doi.org/10.1093/schbul/sbp014>
- Heilbronner, U., Samara, M., Leucht, S., Falkai, P., & Schulze, T. G. (2016). The longitudinal course of schizophrenia across the lifespan: Clinical, cognitive, and neurobiological aspects. *Harvard Review of Psychiatry*, 24(2), 118–128. <https://doi.org/10.1097/HRP.0000000000000092>
- Kastin, A. J., Akerstrom, V., & Pan, W. (2003). Glial cell line-derived neurotrophic factor does not enter normal mouse brain. *Neuroscience Letters*, 340(3), 239–241. [https://doi.org/10.1016/s0304-3940\(03\)00007-7](https://doi.org/10.1016/s0304-3940(03)00007-7)
- Kondziella, D., Brenner, E., Eyjolfsson, E. M., & Sonnewald, U. (2007). How do glial-neuronal interactions fit into current neurotransmitter hypotheses of schizophrenia? *Neurochemistry International*, 50(2), 291–301. <https://doi.org/10.1016/j.neuint.2006.09.006>
- Kumar, A., Kopra, J., Varendi, K. R., Porokukka, L. L., Panhelainen, A., Kuure, S., ... Andressoo, J.-O. (2015). GDNF overexpression from the native locus reveals its role in the nigrostriatal dopaminergic system function. *PLoS Genetics*, 11(12), e1005710. <https://doi.org/10.1371/journal.pgen.1005710>
- Lai, C.-Y., Scarr, E., Udawela, M., Everall, I., Chen, W. J., & Dean, B. (2016). Biomarkers in schizophrenia: A focus on blood based diagnostics and therapeutics. *World Journal of Psychiatry*, 6(1), 102. <https://doi.org/10.5498/wjp.v6.i1.102>
- Lee, B.-H., Hong, J.-P., Hwang, J.-A., Na, K.-S., Kim, W.-J., Trigo, J., & Kim, Y.-K. (2015). Plasma glial cell line-derived neurotrophic factor in patients with major depressive disorder: A preliminary study. *Acta Neuropsychiatrica*, 28, 45–50. <https://doi.org/10.1017/neu.2015.42>
- Leucht, S., Corves, C., Arbter, D., Engel, R. R., Li, C., & Davis, J. M. (2009). Second-generation versus first-generation antipsychotic drugs for schizophrenia: A meta-analysis. *The Lancet*, 373(9657), 31–41. [https://doi.org/10.1016/s0140-6736\(08\)61764-x](https://doi.org/10.1016/s0140-6736(08)61764-x)
- Leucht, S., Komossa, K., Rummel-Kluge, C., Corves, C., Hunger, H., Schmid, F., ... Davis, J. M. (2009). A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *American Journal of Psychiatry*, 166(2), 152–163.

- Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., & Davis, J. M. (2012). Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: A systematic review and meta-analysis. *The Lancet*, 379(9831), 2063–2071. [https://doi.org/10.1016/s0140-6736\(12\)60239-6](https://doi.org/10.1016/s0140-6736(12)60239-6)
- Lister, J., Nobrega, J. N., Fletcher, P. J., & Remington, G. (2014). Oxidative stress and the antipsychotic-induced vacuous chewing movement model of tardive dyskinesia: Evidence for antioxidant-based prevention strategies. *Psychopharmacology*, 231(11), 2237–2249. <https://doi.org/10.1007/s00213-014-3582-6>
- Luz, M., Mohr, E., & Fibiger, H. C. (2016). GDNF-induced cerebellar toxicity: A brief review. *Neurotoxicology*, 52, 46–56. <https://doi.org/10.1016/j.neuro.2015.10.011>
- Ma, X.-C., Chen, C., Zhu, F., Jia, W., & Gao, C.-G. (2013). Association of the GDNF gene with depression and heroin dependence, but not schizophrenia, in a Chinese population. *Psychiatry Research*, 210(3), 1296–1298. <https://doi.org/10.1016/j.psychres.2013.08.025>
- Margolese, H. C., Chouinard, G., Kolivakis, T. T., Beauclair, L., & Miller, R. (2005). Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 1: Pathophysiology and mechanisms of induction. *Canadian Journal of Psychiatry*, 50(9), 541–547. <https://doi.org/10.1177/070674370505000907>
- Marrsman, A., Heuvel, M. P. v. d., Klomp, D. W. J., Kahn, R. S., Luijten, P. R., & Pol, H. E. H. (2013). Glutamate in schizophrenia: A focused review and meta-analysis of ^1H -MRS studies. *Schizophrenia Bulletin*, 39(1), 120–129. <https://doi.org/10.1093/schbul/sbr069>
- Mayer-Amberg, N., Woltmann, R., & Walther, S. (2016). An integrated care initiative to improve patient outcome in schizophrenia. *Frontiers in Psychiatry*, 6, 184. <https://doi.org/10.3389/fpsy.2015.00184>
- Mickiewicz, A., & Kordower, J. (2011). GDNF family ligands: A potential future for Parkinson's disease therapy. *CNS & Neurological Disorders Drug Targets*, 10(6), 703–711.
- Miller, D. D., McEvoy, J. P., Davis, S. M., Caroff, S. N., Saltz, B. L., Chakos, M. H., ... Lieberman, J. A. (2005). Clinical correlates of tardive dyskinesia in schizophrenia: Baseline data from the CATIE schizophrenia trial. *Schizophrenia Research*, 80(1), 33–43. <https://doi.org/10.1016/j.schres.2005.07.034>
- Niciu, M. J., Henter, I. D., Sanacora, G., & Zarate, C. A. Jr. (2013). Glial abnormalities in substance use disorders and depression: Does shared glutamatergic dysfunction contribute to comorbidity? *The World Journal of Biological Psychiatry*, early online, 1–15.
- Niitsu, T., Shirayama, Y., Matsuzawa, D., Shimizu, E., Hashimoto, K., & Iyo, M. (2014). Association between serum levels of glial cell-line derived neurotrophic factor and attention deficits in schizophrenia. *Neuroscience Letters*, 575, 37–41. <https://doi.org/10.1016/j.neulet.2014.05.034>
- Novick, D., Montgomery, W., Treuer, T., Moneta, M. V., & Haro, J. M. (2016). Sex differences in the course of schizophrenia across diverse regions of the world. *Neuropsychiatric Disease and Treatment*, 12, 2927–2939. <https://doi.org/10.2147/NDT.S101151>
- Ohrmann, P., Siegmund, A., Suslow, T., Spitzberg, K., Kersting, A., Arolta, V., ... Pfeleiderer, B. (2005). Evidence for glutamatergic neuronal dysfunction in the prefrontal cortex in chronic but not in first-episode patients with schizophrenia: A proton magnetic resonance spectroscopy study. *Schizophrenia Research*, 73(2–3), 153–157. <https://doi.org/10.1016/j.schres.2004.08.021>
- Olbrich, H. M., Valerius, G., Rüsche, N., Büchert, M., Thiel, T., Hennig, J., ... Elst, L. T. V. (2008). Frontolimbic glutamate alterations in first episode schizophrenia: Evidence from a magnetic resonance spectroscopy study. *The World Journal of Biological Psychiatry*, 9(1), 59–63. <https://doi.org/10.1080/15622970701227811>
- Olfson, M., Blanco, C., Liu, S.-M., Wang, S., & Correll, C. U. (2012). National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Archives of General Psychiatry*, 69(12), 1247–1256. <https://doi.org/10.1001/archgenpsychiatry.2012.647>
- Owen, M. J., Sawa, A., & Mortensen, P. B. (2016). Schizophrenia. *Lancet*, 388(10039), 86–97. [https://doi.org/10.1016/s0140-6736\(15\)01121-6](https://doi.org/10.1016/s0140-6736(15)01121-6)
- Parker, C. (2009). Antipsychotics in the treatment of schizophrenia. *Progress in Neurology and Psychiatry*, 13, 22–29. <https://doi.org/10.1002/pnp.116>
- Remington, G. (2007). Tardive dyskinesia: Eliminated, forgotten, or overshadowed? *Current Opinion in Psychiatry*, 20(2), 131–137. <https://doi.org/10.1097/YCO.0b013e328017f6b1>
- Rummel-Kluge, C., Komossa, K., Schwarz, S., Hunger, H., Schmid, F., Kissling, W., ... Leucht, S. (2012). Second-generation antipsychotic drugs and extrapyramidal side effects: A systematic review and meta-analysis of head-to-head comparisons. *Schizophrenia Bulletin*, 38(1), 167–177. <https://doi.org/10.1093/schbul/sbq042>
- Rummel-Kluge, C., Komossa, K., Schwarza, S., Hungera, H., Schmida, F., Lobos, C. A., ... Leucht, S. (2010). Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research*, 123(2–3), 225–233. <https://doi.org/10.1016/j.schres.2010.07.012>
- Saavedra, A., Baltazar, G. A., Santos, P., Carvalho, C. M., & Duarte, E. I. P. (2006). Selective injury to dopaminergic neurons up-regulates GDNF in substantia nigra postnatal cell cultures: Role of neuron-glia crosstalk. *Neurobiology of Disease*, 23(3), 533–542. <https://doi.org/10.1016/j.nbd.2006.04.008>
- Sachdev, P. S. (2000). The current status of tardive dyskinesia. *Australian and New Zealand Journal of Psychiatry Research*, 34, 355–369.
- Santos, D., Gonzalez-Perez, F., Navarro, X., & Valle, J. D. (2016). Dose-dependent differential effect of neurotrophic factors on in vitro and in vivo regeneration of motor and sensory neurons. *Neural Plasticity*, 2016, 1–13. <https://doi.org/10.1155/2016/4969523>
- Sarro, S., Pomarol-Clotet, E., Canales-Rodríguez, E. J. C.-R., Salvador, R., Gomar, J. S. J., Ortiz-Gil, J., ... McKenna, P. J. (2013). Structural brain changes associated with tardive dyskinesia in schizophrenia. *The British Journal of Psychiatry*, 203(1), 51–57. <https://doi.org/10.1192/bjp.bp.112.114538>
- Schooler, N. R., & Kane, J. M. (1982). Research diagnoses for tardive dyskinesia (RD-TD). *Archives of General Psychiatry*, 39, 486–487. <https://doi.org/10.1001/archpsyc.1982.04290040080014>
- Shao, Z., Dyck, L. E., Wang, H., & Li, X.-M. (2006). Antipsychotic drugs cause glial cell line-derived neurotrophic factor secretion from C6 glioma cells. *Journal of Psychiatry & Neuroscience*, 31(1), 32–37.
- Shohamy, D., Mihalakos, P., Chin, R., Thomas, B., Wagner, A. D., & Tamminga, C. (2010). Learning and generalization in schizophrenia: Effects of disease and antipsychotic drug treatment. *Biological Psychiatry*, 67(10), 926–932. <https://doi.org/10.1016/j.biopsych.2009.10.025>
- Skaper, S. D. (2012). The neurotrophin family of neurotrophic factors: An overview. *Methods in Molecular Biology*, 846, 1–12. https://doi.org/10.1007/978-1-61779-536-7_1
- Skibinska, M., Kapelski, P., Pawlak, J., Rajewska-Rager, A., Dmitrzak-Weglarz, M., Szczepankiewicz, A., ... Twarowska-Hauser, J. (2017). Glial cell line-derived neurotrophic factor (GDNF) serum level in women with schizophrenia and depression, correlation with clinical and metabolic parameters. *Psychiatry Research*, 256, 396–402. <https://doi.org/10.1016/j.psychres.2017.07.014>
- Smith, M. P., & Cass, W. A. (2007). GDNF reduces oxidative stress in a 6-hydroxydopamine model of Parkinson's disease. *Neuroscience Letters*, 412(3), 259–263. <https://doi.org/10.1016/j.neulet.2006.11.017>
- Sopova, K., Gatsiou, K., Stellos, K., & Laske, C. (2014). Dysregulation of neurotrophic and haematopoietic growth factors in Alzheimer's disease: From pathophysiology to novel treatment strategies. *Current Alzheimer Research*, 11(1), 27–39. <https://doi.org/10.2174/1567205010666131120100743>
- Souza, R. P., Romano-Silva, M. A., Lieberman, J. A., Meltzer, H. Y., MacNeil, L. T., Culotti, J. G., ... Wong, A. H. C. (2010). Genetic association of the GDNF alpha-receptor genes with schizophrenia and clozapine

- response. *Journal of Psychiatric Research*, 44(11), 700–706. <https://doi.org/10.1016/j.jpsychires.2010.01.002>
- Straten, G., Eschweiler, G. W., Maetzler, W., Laske, C., & Leyhe, T. (2009). Glial cell-line derived neurotrophic factor (GDNF) concentrations in cerebrospinal fluid and serum of patients with early Alzheimer's disease and normal controls. *Journal of Alzheimer's Disease*, 18(2), 331–337. <https://doi.org/10.3233/JAD-2009-1146>
- Takebayashi, M., Hisaoka, K., Nishida, A., Tsuchioka, M., Miyoshi, I., Kozuru, T., ... Yamawaki, S. (2006). Decreased levels of whole blood glial cell line-derived neurotrophic factor (GDNF) in remitted patients with mood disorders. *The International Journal of Neuropsychopharmacology*, 9(5), 607–612. <https://doi.org/10.1017/S1461145705006085>
- Théberge, J., Williamson, K. E., Aoyama, N., Drost, D. J., Manchanda, R., Malla, A. K., ... Williamson, P. C. (2007). Longitudinal grey-matter and glutamatergic losses in first-episode schizophrenia. *The British Journal of Psychiatry*, 191(4), 325–334. <https://doi.org/10.1192/bjp.bp.106.033670>
- Tobe, E. H. (2013). Mitochondrial dysfunction, oxidative stress, and major depressive disorder. *Neuropsychiatric Disease and Treatment*, 9, 567–573. <https://doi.org/10.2147/ndt.s44282>
- Tunca, Z., Akdede, B. K., Zerdem, A. O., Alkin, T., Polat, S., Ceylan, D., ... Akan, P. (2015). Diverse glial cell line-derived neurotrophic factor (GDNF) support between mania and schizophrenia: A comparative study in four major psychiatric disorders. *European Psychiatry*, 30(2), 198–204. <https://doi.org/10.1016/j.eurpsy.2014.11.003>
- Tunca, Z., Bayin, M., Alkin, T., Özerdem, A. E. I., Resmi, H., & Akan, P. (2015). A preliminary observation of increased glial cell line-derived neurotrophic factor in manic switch due to electroconvulsive treatment in depressive patients. *Journal of ECT*, 31, 167–172. <https://doi.org/10.1097/YCT.0000000000000198>
- Uchida, S., Hara, K., Kobayashi, A., Otsuki, K., Yamagata, H., Hobara, T., ... Watanabe, Y. (2011). Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. *Neuron*, 69(2), 359–372. <https://doi.org/10.1016/j.neuron.2010.12.023>
- Vostrikov, V. M., Uranova, N. A., & Orlovskaya, D. D. (2007). Deficit of perineuronal oligodendrocytes in the prefrontal cortex in schizophrenia and mood disorders. *Schizophrenia Research*, 94(1–3), 273–280. <https://doi.org/10.1016/j.schres.2007.04.014>
- West, I. C. (2000). Radicals and oxidative stress in diabetes. *Diabetic Medicine A Journal of the British Diabetic Association*, 17(3), 171–180.
- Williams, H. J., Norton, N., Peirce, T., Dwyer, S., Williams, N. M., Moskvina, V., ... O'Donovan, M. C. (2007). Association analysis of the glial cell line-derived neurotrophic factor (GDNF) gene in schizophrenia. *Schizophrenia Research*, 97, 271–276. <https://doi.org/10.1016/j.schres.2007.09.004>
- Williams, M. R., Hampton, T., Pearce, R. K., Hirsch, S. R., Ansorge, O., Thom, M., & Maier, M. (2013). Astrocyte decrease in the subgenual cingulate and callosal genu in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, 263, 41–52. <https://doi.org/10.1007/s00406-012-0328-5>
- Woods, S. W., Morgenstern, H., Saksa, J. R., Walsh, B. C., Sullivan, M. C., Money, R., ... Glazer, W. M. (2010). Incidence of tardive dyskinesia with atypical versus conventional antipsychotic medications—A prospective cohort study. *The Journal of Clinical Psychiatry*, 71(4), 463–474.
- Xiao, N., & Le, Q.-T. (2016). Neurotrophic factors and their potential applications in tissue regeneration. *Archivum Immunologiae et Therapiae Experimentalis*, 64(2), 89–99. <https://doi.org/10.1007/s00005-015-0376-4>
- Yamamoto, B. K., & Raudensky, J. (2008). The role of oxidative stress, metabolic compromise, and inflammation in neuronal injury produced by amphetamine-related drugs of abuse. *Journal of Neuroimmune Pharmacology*, 3(4), 203–217. <https://doi.org/10.1007/s11481-008-9121-7>
- Zarate, C. A., Du, J., Quiroz, J., Gray, N. A., Denicoff, K. D., Singh, J., ... Manji, H. K. (2003). Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: Role of the glutamatergic system. *Annals of the New York Academy of Sciences*, 1003, 273–291.
- Zhang, X., Ru, B., Sha, W., Xin, W., Zhou, H., & Zhang, Y. (2014). Performance on the Wisconsin card-sorting test and serum levels of glial cell line-derived neurotrophic factor in patients with major depressive disorder. *Asia-Pacific Psychiatry*, 6, 302–307. <https://doi.org/10.1111/appy.12120>
- Zhang, X., Zhang, Z., Sha, W., Xie, C., Xi, G., Zhou, H., & Zhang, Y. (2010). Effect of treatment on serum glial cell line-derived neurotrophic factor in bipolar patients. *Journal of Affective Disorders*, 126(1–2), 326–329.

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