



ORIGINAL ARTICLE

Increase in Brain-derived Neurotrophic Factor in Patients with Schizophrenia Treated with Olanzapine: A Systemic Review and Meta-analysis

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Introduction: Studies have shown reduced levels of brain-derived neurotrophic factor (BDNF) in patients with schizophrenia, but the effects of antipsychotic agents on BDNF levels have been inconsistent. The current study aimed to examine (1) whether the levels of peripheral BDNF in patients with schizophrenia change after antipsychotic treatment, and (2) whether the effect differs among antipsychotic drugs.

Methods: Meta-analyses were performed using the random effects model. The results from 10 studies with 399 subjects were synthesized applying the random effects model.

Results: Overall, the study showed that the BDNF levels were mildly increased after antipsychotic treatment [standardized mean difference (SMD) = 0.171, 95% confidence interval (CI) = 0.008–0.334, $p = 0.040$]. When categorizing the subjects based on the antipsychotic drugs they used, BDNF levels were only significantly increased with olanzapine treatment (SMD = 0.635, 95% CI = 0.323–0.948, $p = 0.0001$), but not with risperidone (SMD = 0.005, 95% CI = –0.176 to 0.185, $p = 0.612$).

Discussion: These results suggested a differential effect of antipsychotic agents on BDNF levels in patients with schizophrenia. Peripheral BDNF may play a role in the disease process of a subset of patients, related to the use of antipsychotic agents.

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1. Introduction

Schizophrenia is a devastating brain disorder that can cause impairment of personal, social, and occupational functioning, as well as a higher risk of medical morbidity, substance abuse, and suicide. Although the pathogenesis of schizophrenia has not yet been clearly established, many lines of evidence suggested that it results from abnormalities in neural development, leading to aberrant information-processing in critical neural circuits, and finally the clinical syndrome of the disease.¹

Brain-derived neurotrophic factor (BDNF) was the second neurotrophin to be characterized after nerve growth factor. It is widely distributed in the brain and the periphery, and known to affect various functions in the processes of neurodevelopment, including neuronal survival, neuritic growth, neuronal differentiation, synaptic plasticity, and nerve repair.² Weickert et al found that BDNF expression³ and the mRNA expression of its high-affinity receptor,⁴ tyrosine kinase receptor B (trkB), were significantly reduced in the prefrontal cortex of patients with schizophrenia compared with control subjects. Later, the reduction in mRNA for

BDNF and trkB was also found in the hippocampus.⁵ Taking the evidence into account, BDNF was suggested to play an important role in the pathophysiology and treatment of schizophrenia.⁶

In addition, efforts were made to identify whether blood BDNF might be a biomarker for schizophrenia. In a recent systemic review, Green et al found a significant reduction in peripheral BDNF levels in schizophrenia.⁷ However, their meta-analysis showed considerable unexplained heterogeneity across study results, which might be explained by the use of different antipsychotics in the studies included.

Some studies have shown that serum BDNF levels were inconsistently influenced by antipsychotic drugs. For example, Rizon et al found reduced serum BDNF levels in patients with chronic schizophrenia in relapse compared with healthy controls.⁸ Moreover, the reduced levels could be recovered in the subgroup receiving olanzapine for 6 weeks, but not haloperidol, risperidone, or amisulpride.⁸ In one recent study, it was found that serum BDNF levels were raised in patients with schizophrenia after treatment with risperidone for 4 weeks, but not with clozapine.⁹ However, other studies have not found significant change in BDNF levels after antipsychotic treatment.^{10–12} This discrepancy may be related to differences in sampling procedure, the characteristics of the subjects included, methods of measurement, or usage of antipsychotic drugs.

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To clarify this uncertainty, a meta-analysis was conducted to examine (1) whether the levels of peripheral BDNF in patients with schizophrenia change after antipsychotic treatment, and (2) the effects of individual antipsychotic drugs.

2. Methods

2.1. Literature search

A computerized search, limited to literature in English and human studies, was performed for all publications available up to June 2011 through PubMed at the National Library of Medicine using the keywords: (schizophreni* OR psychotic OR antipsychotic*) AND (brain-derived neurotrophic factor OR BDNF OR neurotrophin). Reference lists from identified citations and relevant review articles were scrutinized for citations not indexed in the above electronic database. In-press articles in psychiatric journals were manually examined.

2.2. Inclusion criteria for studies in the meta-analysis

Identified citations were examined according to the following criteria for inclusion: (1) measured blood levels of BDNF in patients with schizophrenia; (2) data provided before and after antipsychotic treatment for no less than 1 month for the same group of patients; (3) studies published in peer-reviewed journals, and (4) independence from other studies. Studies that included and reanalyzed previously published data were not regarded as independent, in which case only the study with the largest number of participants was included.

2.3. Data extraction

For all studies included, the following data were extracted for each study: subject number, gender distribution, mean age, course of illness, source of BDNF sampling, and BDNF levels before and after antipsychotic treatment. The period of antipsychotic treatment was 4 weeks in most of the studies included. When the studies provided BDNF levels at multiple time points, the data at 4 weeks were used in preference, followed by those at 6 weeks or 8 weeks.

2.4. Meta-analytical methods

In the analysis, the primary outcome was comparison of blood levels of BDNF in patients with schizophrenia before and after antipsychotic treatment. The secondary outcome was examination of the effect of different antipsychotic drugs on the BDNF levels in these patients.

For each identified study, the effect size (ES) expressing the difference in BDNF levels before and after antipsychotic treatment was described as the standardized mean difference (SMD), based on Hedges' adjusted g , where a value greater than 0 indicated that the levels were higher after antipsychotic treatment. The means and standard deviations of the BDNF levels in patients at baseline and at the indicated end-point were used to derive the effect size from each included study. When these data were not available from the studies, we contacted the authors to request the data, or we derived the effect size from other statistical parameters. The effect sizes of individual studies were synthesized by the random effects model.¹³ The significance of the pooled effect sizes was determined by the z -test.

Heterogeneity was assessed by Q statistics, their related p value, and the I^2 statistic, which is the percentage of variability in the estimate of effects that is due to heterogeneity rather than random error.¹⁴ A larger value for I^2 indicates higher heterogeneity. In

addition, meta-regressions were performed to examine whether the effect sizes were associated with changes in study variables, such as age, gender distribution, duration of illness, period of antipsychotic treatment, and source of the BDNF sample (plasma or serum).

In the analysis, publication bias was assessed by both visual inspection of a funnel plot and linear regression analysis.¹⁵ In the linear regression analysis, the standard normal deviate of the ES was regressed on the precision of the effect size (the inverse of the standard error of the effect size). When there is no publication bias, the regression line should traverse the origin, and the expected value of intercept should be zero. The slope (b) of the regression line indicated the size and direction of the association. An examination of publication bias was a test of the null hypothesis that intercept (a) was equal to zero, as determined by the Student t test.

In addition, the trim-and-fill method was conducted to assess the impact of publication bias.¹⁶ Briefly, a funnel plot depicted the effect sizes vs. their precisions for all included studies. Potential missing studies were inputted into the plot. A new pooled analysis was performed in which the inputted studies were combined with the originally included studies. The results from this new pooled analysis would then show whether the presence of publication bias had influenced the result of the meta-analysis.

Meta-analyses were conducted using Comprehensive Meta-Analysis software, Version 2 (Biostat, Englewood, NJ, USA). Two-sided $p < 0.05$ were considered statistically significant. The methods and the results of the meta-analysis were reported by following the PRISMA checklist.¹⁷

3. Results

The PubMed search resulted in 319 findings for initial consideration in the meta-analysis. By examining their titles and abstracts, studies were excluded because they were review articles ($n = 76$), genetic studies not related to blood BDNF protein ($n = 83$), post-mortem human studies ($n = 16$), case reports ($n = 7$), or studies with other irrelevant topics ($n = 89$). Of the 48 studies screened to assess the inclusion criteria, most were excluded because they compared BDNF levels between patients and healthy controls, but not in patients before and after receiving antipsychotic treatment. Finally, 10 studies were included in the current meta-analysis (Figure 1),^{8–12,18–22} including 399 patients. The characteristics of these studies are described in Table 1.^{8–12,18–22}

By pooling the results of the 10 studies included, the primary outcome showed a mild but significant increase in BDNF after antipsychotic treatment in patients with schizophrenia [SMD = 0.171, 95% confidence interval (CI) = 0.008–0.334, $p = 0.040$] (Figure 2). There was no significant heterogeneity among these studies ($Q = 11.69$, $df = 9$, $I^2 = 23.0\%$, $p = 0.232$). In addition, meta-regressions showed that the effect size was not moderated by age ($p = 0.597$), gender ($p = 0.815$), duration of illness ($p = 0.509$), time of antipsychotic treatment ($p = 0.326$), or source of sample ($p = 0.759$).

Publication bias was assessed by utilizing both Egger's linear regression analysis and the funnel plot. Regression analysis showed that the intercept of the regression line was significantly deviated from zero ($t = 3.614$, $df = 8$, $p = 0.006$). In the funnel plot, it was found that some studies with a smaller sample size and negative results might be missing (Figure 3). By using the trim-and-fill analysis and adding the results of inputted studies that were regarded as missing ones, pooled analysis resulted in insignificant findings (SMD = 0.070, 95% CI = -0.122 to 0.261, $p = 0.305$) (Figure 3). Both methods consistently indicated the presence of publication bias. In addition, the significant increase in peripheral

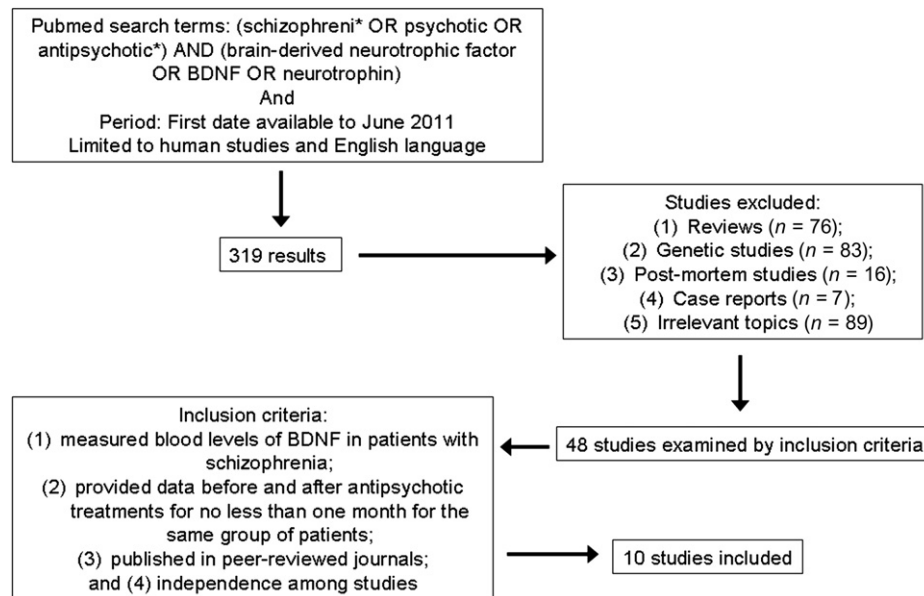


Figure 1 Flowchart describing the process for selecting papers for the current meta-analysis. BDNF = brain-derived neurotrophic factor.

BDNF with antipsychotic treatment in terms of the primary outcome may be due to the presence of publication bias.

Although primary analysis showed a mild increase in peripheral BDNF after antipsychotic treatment, the result may reflect a mixed effect of different antipsychotic drugs. In the secondary analysis, the data from the included studies were stratified by drug type, including amisulpride (1 study, 5 subjects),⁸ aripiprazole (1 study, 9 subjects),²¹ clozapine (2 studies, 24 subjects),^{9,10} haloperidol (2 studies, 20 subjects),^{8,22} olanzapine (6 studies, 91 subjects),^{8,10,11,20–22} quetiapine (1 study, 4 subjects),²² and risperidone (7 studies, 228 subjects)^{8–10,12,19,21,22} (Table 1). Compared with baseline, BDNF levels were significantly increased with olanzapine treatment (SMD = 0.635, 95% CI = 0.323–0.948, $p = 0.0001$), but not with risperidone treatment (SMD = 0.005, 95% CI = –0.176 to 0.185, $p = 0.612$) or with other antipsychotics (Figure 4). For these analyses, neither heterogeneity among included studies nor publication bias was found.

4. Discussion

Much evidence has suggested that neurodevelopmental abnormality is one of the major pathophysiological processes in schizophrenia. Data from different lines of study have converged on BDNF as it plays an important role in the process.⁶ Many studies have attempted to identify whether peripheral BDNF can be used as

a biomarker of the diagnosis or treatment process of schizophrenia. One recently published meta-analysis showed a moderate reduction in blood levels in schizophrenia, in both drug-naïve and medicated patients.⁷ In addition, this analysis showed an association between reduced BDNF in schizophrenia and increased age, but no effects of dosage of antipsychotic drugs.⁷ However, the authors did not examine whether the reduced levels could be recovered by antipsychotic drugs.

The results of current meta-analysis indicated that the baseline BDNF levels can be raised by olanzapine, but not by risperidone treatment. Although there are some limitations in interpreting the results, this is the first study providing statistical evidence of differential effects of antipsychotic drugs in changing blood BDNF levels in patients with schizophrenia.

Neurotoxicity as a side effect of using typical antipsychotic agents has long been suggested by their high risk of producing extrapyramidal syndrome and their limited effects in treating the negative symptoms of schizophrenia. On the other hand, the possibility of neuroprotective effects arising from atypical antipsychotics has stemmed from their better tolerability and efficacy in the treatment of negative and cognitive symptoms. Haloperidol, rather than risperidone, was found to induce caspase-dependent apoptosis by reducing cellular survival signaling in rat cortical neurons,²³ which possibly contributes to the differential clinical therapeutic efficacy and side effect profiles in schizophrenia.

Table 1 Summary of included studies in current meta-analysis

Studies	Country	N (M/F)	Age (y) (mean ± SD)	Illness duration (mo) (mean ± SD)	Medication use	Time point of measurement	Outcome measurement	Source of BDNF
Pirildar 2004 ¹⁰	Turkey	7/15	27.8 ± 9.5	15.2 ± 13.0	3 CLO, 3 OLA, 20 RIS	4 weeks	PANSS	Serum
Palomino 2006 ¹⁸	Spain	21 in total	NA	NA	NA	4 weeks	NA	Plasma
Hori 2007 ¹¹	Japan	18/14	35 ± 18	42 ± 15	32 OLA	8 weeks	PANSS	Plasma
Yoshimura 2007 ¹²	Japan	52/37	37 ± 13	12.8 ± 6.4	89 RIS	4 weeks	PANSS	Plasma
Lee 2009 ¹⁹	Korea	15/21	31.3 ± 7.8	56.6 ± 59.1	36 RIS	6 weeks	PANSS	Plasma
González-Pinto 2010 ²⁰	Spain	18 in total	24.4 ± 27.7	NA	18 OLA	4 weeks	PANSS	Plasma
Rizos 2010 ⁸	Greece	32/15	43.6 ± 10.9	286.1 ± 93.8	5 AMI, 18 HAL, 10 OLA, 14 RIS	6 weeks	PANSS	Serum
Yoshimura 2010 ²¹	Japan	35/24	25 ± 16	14 ± 7	9 ARI, 18 OLA, 32 RIS	8 weeks	PANSS	Plasma
Chen 2011 ⁹	Taiwan	23/30	35.4 ± 9.9	96 ± 74	21 CLO, 32 RIS	4 weeks	PANSS	Serum
Lee 2011 ²²	Germany	13/9	39.1 ± 14.0	NA	1 AMI, 2 HAL, 10 OLA, 4 QUE, 5 RIS	4 weeks	PANSS	Serum

AMI = amisulpride; ARI = aripiprazole; BDNF = brain-derived neurotrophic factor; CLO = clozapine; HAL = haloperidol; NA = not available; OLA = olanzapine; PANSS = positive and negative syndrome scale; QUE = quetiapine; RIS = risperidone; SD = standard deviation.

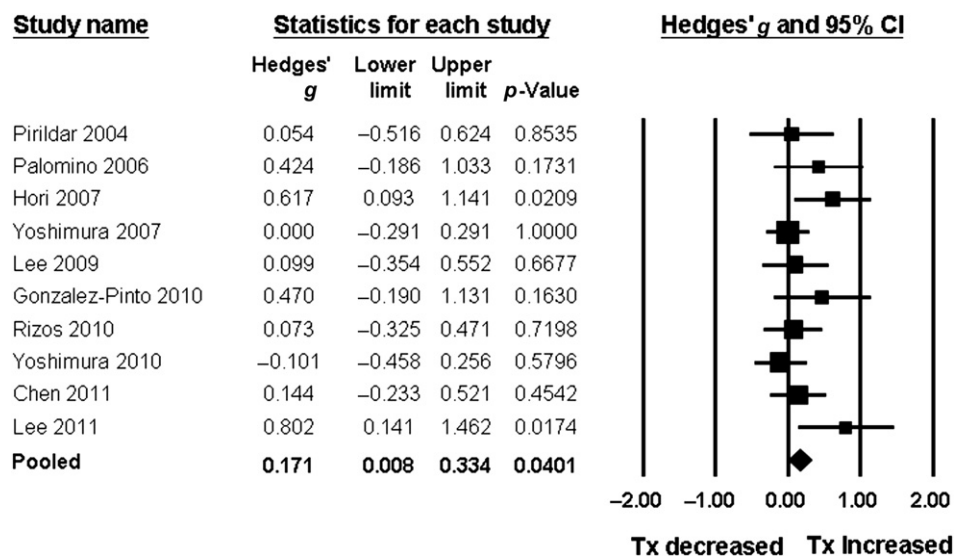


Figure 2 Forest plot showing pooled results and individual studies comparing brain-derived neurotrophic factor levels before and after antipsychotic treatment in patients with schizophrenia. CI = confidence interval; Tx = treatment.

Several studies have also shown that atypical, rather than typical, antipsychotics promote cell survival and elevated BDNF levels.^{24–28} Olanzapine was especially validated for its neuroprotective effects,^{29,30} possibly through activation of a BDNF signaling pathway,^{28,31–33} although this was not agreed in one study.³⁴

On the other hand, the effects on the expression of BDNF caused by risperidone in preclinical studies have been controversial. Risperidone reversed ketamine³⁵ or rotenone³⁶-induced decreases in the levels of BDNF mRNA expression. However, it has been shown that both risperidone and haloperidol significantly decrease the expression of BDNF protein in both the cortex and the hippocampus of rats.³⁷ In addition, Keilhoff et al showed that although risperidone improved cell survival in rat hippocampus, it did not change the expression of BDNF.³⁸ Compared with olanzapine, the lack of significant changes in BDNF level as a result of risperidone

treatment may relate to its stronger D2 antagonism, a closer pharmacodynamic property. Even so, it is also possible that blood BDNF level represents a therapeutic marker in a subset of patients. For example, Lee and Kim showed that plasma BDNF levels were lower pre- and post-risperidone treatment in the nonresponding group compared with the much-improved group.¹⁹

Although the findings of the current analysis suggest blood BDNF level as a plausible biomarker of the clinical status of schizophrenia in a subset of patients, caution needs to be taken before further interpretations can be made. Lack of disease specificity is likely to be a major drawback in using BDNF level as a diagnostic marker as reduced BDNF level has been reported in several other disorders, such as bipolar disorder,³⁹ major depression,⁴⁰ and eating disorders.⁴¹ In addition, the significance of the result was undermined by inconsistency in severity and drug

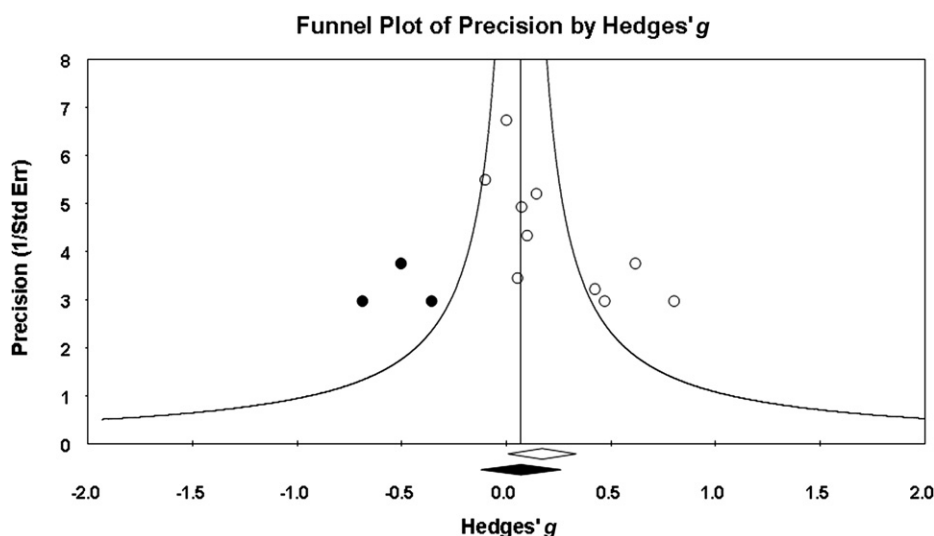


Figure 3 Funnel plot examining publication bias in studies comparing brain-derived neurotrophic factor levels before and after antipsychotic treatment in patients with schizophrenia. The plot describes the effect sizes (Hedges' *g*) of studies vs. their precision (inverse of standard error). Published studies are depicted as open circles. Black circles represent potentially missing studies that were inputted based on the trim-and-fill method. The white diamond represents the pooled effect size (ES = 0.171, 95% CI = 0.008–0.334, *p* = 0.040) of the originally included studies. The black diamond represents the pooled effect size (ES = 0.070, 95% CI = -0.122 to 0.261, *p* = 0.305) of the 10 originally included studies and three potentially missing studies.

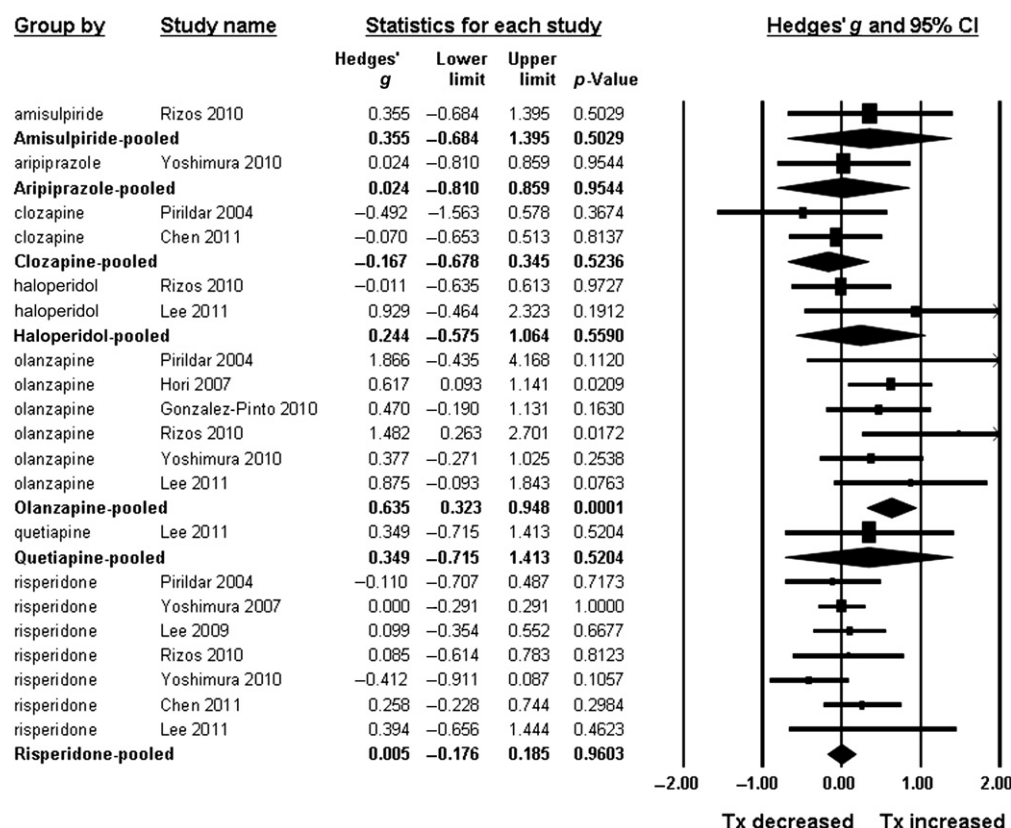


Figure 4 Forest plot showing pooled results and individual studies comparing brain-derived neurotrophic factor levels before and after antipsychotic treatment in patients with schizophrenia. The overall effect was divided by individual antipsychotics. CI = confidence interval; Tx = treatment.

response in patients among studies. Although current preliminary results support a role for peripheral BDNF as a biomarker of the treatment process for selected antipsychotic drugs, they need to be confirmed by further studies with larger sample sizes and a stronger association between treatment response and peripheral BDNF levels.

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