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Effects of antidepressant and antipsychotic medication on peripheral brain-derived neurotrophic factor concentration: Systematic review and meta-analysis

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) is an important regulatory protein in the pathophysiology of psychiatric disorders. Several studies have reported the relationship between peripheral BDNF concentrations and the use of psychoactive drugs. However, the results remain controversial. This study aimed to evaluate the effects of psychoactive drugs on BDNF concentrations and to explore the association between changes in BDNF concentrations and improvements in clinical scores. A systematic review and meta-analysis were conducted. Six electronic databases, including PubMed, Scopus, Medline, Web of Science, Google Scholar and Science Direct, were searched. Changes in BDNF concentrations were compared before and after psychoactive treatment, using the standardized mean difference (SMD) and 95 % confidence interval (95 % CI). Twenty-three studies were included. A significant increase in serum BDNF concentrations was observed after treatment with antipsychotics (SMD=0.43; 95 %CI: 0.26, 0.60) and antidepressants (SMD=0.49; 95 %CI: 0.23, 0.74). However, the plasma BDNF concentration was not affected by antidepressant and antipsychotic medication. Although an improvement in clinical scores was observed after treatment, no significant association was observed between changes in BDNF concentrations and the changes in the Positive and Negative Syndrome Scale (PANSS) and the Hamilton Depression Rating Scale (HAM-D) scores. In conclusion, antidepressants and antipsychotics increase serum BDNF concentrations.

1. Introduction

Neurotrophins (NTs) are a group of homodimeric growth factors expressed in both brain and peripheral tissues, and play a crucial role in regulating cell proliferation, migration and maturation (Ivanisevic and Saragovi, 2013; Martinowich et al., 2007). Among all neurotrophins, brain-derived neurotrophic factor (BDNF) stands out for its high level of

expression in the brain and potent effects on synapses (Lu et al., 2014). It is secreted by several cell types, mainly by neurons, in the cerebral cortex, hippocampus and basal forebrain. BDNF can also be secreted by glial cells particularly astrocytes (Pöyhönen et al., 2019).

BDNF has been identified as a significant factor in the modification of synaptic transmission (Huang and Reichardt, 2001; Park and Poo, 2013). Given its crucial role in maintaining normal central nervous

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system functioning, any alteration in BDNF levels, distribution, structure, or activity, may lead to neuronal dysfunction. This dysregulation of BDNF may be linked to the onset of neurodegenerative diseases (Greenberg et al., 2009). Consequently, BDNF signalling is involved in several neurodegenerative disorders and implicated in a huge variety of cellular processes that impact behaviour (Park and Poo, 2013).

This factor was associated with several disorders, including schizophrenia and major depressive disorders (MDD) (Autry and Monteggia, 2012). There is substantial evidence indicating that BDNF is involved in the pathophysiology of MDD, as individuals with MDD often exhibit abnormally low levels of BDNF compared to those without the disorder (Sen et al., 2008). This decrease in BDNF levels may contribute to impaired neuroplasticity and neuronal functioning. Moreover, decreased BDNF levels could disrupt synaptic function, leading to impaired neural connectivity and impaired information processing, which are observed in schizophrenia (Toyooka et al., 2002).

Several studies have evaluated the effects of psychoactive drugs on serum or plasma BDNF concentrations, but the results have been conflicting and controversial.

Antidepressants have been found to affect the BDNF concentrations. However, the changes in BDNF concentrations do not occur uniformly for all antidepressants (Arumugam et al., 2017). Some clinical studies have reported that the decrease in BDNF concentrations in MDD patients could be reversed after a period of antidepressant treatment, while others have not observed such changes (Brunoni et al., 2008; Deuschle et al., 2013; Hellweg et al., 2008; Matriciano et al., 2009; Molendijk et al., 2011; Yoshimura et al., 2007). These findings suggest that different antidepressant molecules may have varying effects on peripheral BDNF concentrations during treatment.

The studies on antipsychotics have shown the same controversy over the effects of antipsychotics on BDNF (Chiou and Huang, 2017).

Due to these conflicting results and the varying effects of psychoactive drugs on peripheral BDNF levels found in studies with different characteristics, we performed a systematic review and meta-analysis, that aimed to assess the effects of psychoactive drugs on peripheral BDNF concentrations and to evaluate the association between changes in BDNF concentrations and improvement in clinical outcomes.

2. Materials and methods

It was a systematic review and meta-analysis. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the number CRD42022321506.

2.1. Search strategy

Six databases were consulted by two authors (TM and ZT) independently: Medline, Cochrane, Scopus, Science Direct, Google Scholar and Web of Science. The search terms were settled as follows: ("brain-derived neurotrophic factor" OR "BDNF") AND ("psychotropic drugs" OR "psychoactive drugs" OR "antidepressant drugs" OR "antipsychotic drugs" OR "benzodiazepine" OR "anxiolytic drugs"). As many trials are not published, clinical trial registries for ongoing and unpublished studies were screened using ClinicalTrials.gov.

2.2. Study eligibility

Prospective studies and clinical trials on the effect of psychoactive drugs on BDNF concentrations were included.

The inclusion criteria were:

- Studies evaluating at least one psychoactive drug corresponding to one of the following Anatomical Therapeutic Chemical (ATC) classifications: N05 (psycholeptics) and N06A (antidepressants).

- Studies where psychoactive drugs were used in a well-defined psychiatric illness, according to the Diagnostic and Statistical Manual of Mental Disorders.
- Studies examining BDNF concentrations in serum or plasma before and after the use of psychoactive drugs.
- Studies that reported mean and standard deviation of BDNF concentrations before and after treatment exposure.

The non-inclusion criteria were studies concerning animals or *in vitro* studies, case studies, studies where patients underwent electroconvulsive therapy or deep brain stimulation, and studies that evaluated BDNF Val66Met polymorphism on response to psychoactive treatment.

2.3. Study selection

The studies were selected using Rayyan. Two reviewers (TM and ZT) independently applied the eligibility criteria, starting by examining the titles and abstracts of each study first, then the full text of the studies. Discrepancies were resolved by two other reviewers (JJ and NC).

2.4. Risk of bias assessment

Assessment tools from the Cochrane Collaboration were used to evaluate the risk of bias in the selected studies. The evaluation of the risk of bias was done independently by two authors (TM and ZT).

The Risk of Bias 2 (RoB 2) tool was used for randomized studies. For non-randomized studies, the Risk of Bias In Non-Randomized Studies - of Intervention (ROBINS-I) tool was used. Only studies assessed as having a "low/moderate risk of bias" or "low/some concerns" by the ROBINS-I and RoB 2 tools respectively were included in the quantitative synthesis of the meta-analysis.

2.5. Data extraction

For each study data were extracted independently by two authors (TM and ZT), involving two reviewers in the case of disagreement (JJ and NC).

The following variables were extracted:

- Sociodemographic variables: author's name, publication year, country, age, sex, and study design.
- Clinical variables and exposure: type of psychiatric disease, diagnostic classification used according to the Diagnostic and Statistical Manual of Mental Disorders (DSM).
- Type of psychoactive drug and its corresponding Anatomical Therapeutic Chemical (ATC) classification, psychoactive drug dose, duration of psychoactive drug use, sample size at baseline and after treatment.
- Biological outcome and measurement: BDNF blood sample, duration of follow-up, mean and standard deviation of BDNF concentrations before and after treatment, unit of BDNF measure, technique of BDNF concentrations measurement.
- Clinical outcomes and psychiatric assessment scales: Positive and Negative Scale Score (PANSS) and Hamilton Depression Rating Scale Score (HAM-D).

Concerning exposure, in studies evaluating more than one psychoactive drug, data were extracted for all patients, regardless of the type of psychoactive drug, and then for each type of psychoactive drug separately.

Regarding outcomes, the meta-analysis used the longest time point from studies that measured BDNF concentrations at multiple times after treatment.

2.6. Statistical analysis

All statistical analyses were performed using STATA software (version 17.0; Stata Corporation, College Station, Texas, USA). P-value less than 0.05 was considered statistically significant.

A random effects model with a restricted maximum likelihood method was applied. Standardized mean differences (SMDs) and their 95 % confidence intervals (95 % CIs) were calculated for each study. In our study, SMD refers to the difference in BDNF mean concentrations in the group of patients before and after taking the psychoactive drugs divided by the pooled standard deviation. Cohen’s method was used as a measure of the effect size. A pooled SMD (and its 95 % CIs) was then calculated in the meta-analysis.

The heterogeneity level was investigated using chi squared-based Q statistic (Cochran’s Q chi-square) test and the percentage of variation by I² Index. Stratified analyses were performed to explore whether the effect of psychoactive drugs on BDNF differs across the different strata. The effect of psychoactive drugs on BDNF concentrations was examined within each stratum: blood sample source (serum or plasma), AD (antidepressants) or AP (antipsychotics) drug used, and its corresponding ATC group, duration of treatment and BDNF measurement technique used. Univariate meta-regression analyses were performed to identify potential sources of heterogeneity between studies and to investigate the relationship between the predictor variables and the effect size. The following variables were tested separately in the meta-regression: study

design, number of participants at baseline, mean age, gender, duration of treatment, blood sample source, BDNF measurement technique used, laboratory ELISA kit. Finally because studies that report significant or positive results are more likely to be published than studies that report non-significant or negative results, we searched for publication bias (Dwan et al., 2013). Publication bias was assessed using Egger’s test and Begg’s test and represented by funnel plots.

3. Results

3.1. Study selection

A total of 4390 articles were identified by the search strategy. After checking for duplicates, 3635 articles were retained. Of these, 3457 were not relevant on review of the titles and abstracts. The remaining 178 articles were retrieved and reviewed in full text, and 148 were excluded. A total of 30 articles met the inclusion criteria. Of these 30 articles, only 23 were included in the meta-analysis after evaluation of the risk of bias. The flowchart for the selection and inclusion of studies was presented in Fig. 1.

3.2. Risk of bias

After evaluating the risk of bias using the RoB assessment tool for six RCTs (four antidepressant and two antipsychotic studies), the overall

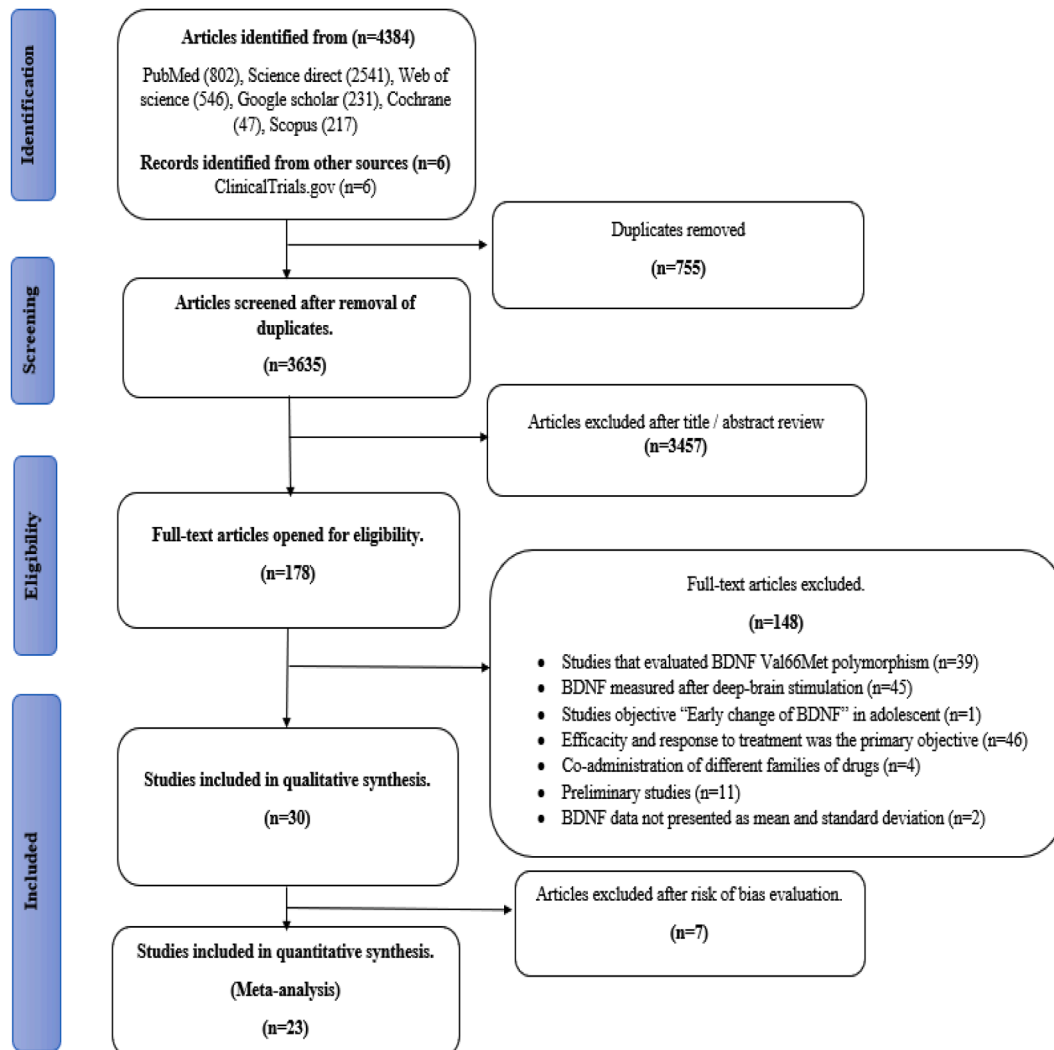


Fig. 1. Flowchart summarizing study identification and selection.

risk was high in one study and with some concerns in five other studies. Methods used for random sequence generation were detailed in about 80 % of the assessed studies. Nonetheless, there was some concerns risk of bias due to inadequate allocation concealment, studies were single blinded or did not provide sufficient information about blinding. A low risk of bias in the measurement of outcome (change in BDNF) was noted in all the studies, and only 30 % of studies had some concerns with reporting results.

The risk of bias of the twenty-four NRCTs was assessed using the ROBINS-I tool. Six studies were found to have a high risk of bias, five with a moderate risk of bias and the remaining thirteen with a low risk of bias. All studies demonstrated a low risk of bias in classifying interventions, adhering to the intended interventions, and selecting the reported results domains. About 30 % of studies were assessed as having moderate risk of bias in confounding domains, due to the lack of information on the analysis method used to control for confounding bias.

The results of risk of bias assessment per item presented as percentages across all assessed studies (RCTs and NRCTs) were presented in Fig. 2 (A and B respectively).

3.3. Characteristics of included studies

In the 23 studies included in the meta-analysis, patients taking antipsychotics had a diagnosis of schizophrenia, while patients taking antidepressants were diagnosed with MDD. The mean age of patients was less than 50 years old in both antidepressant and antipsychotic studies. The percentage of women using antipsychotics was 48.5 %, compared with 67.0 % in studies of antidepressants.

Descriptive analysis of included antipsychotic and antidepressant studies were shown in Table 1. The other characteristics of the included studies are summarized in Table S1 and Table S2.

3.4. Standardized mean difference

The fourteen antipsychotic studies were pooled together to assess the effect of antipsychotic drugs on BDNF concentrations before and after

Table 1

Descriptive analysis of included antipsychotic and antidepressant studies.

Variables	Antipsychotic studies (n = 14) n (%)	Antidepressant studies (n = 9) n (%)
Age, mean ± SD	30.9 ± 5.9	43.3 ± 6.6
Gender,% of females	48.5	67.0
Disease		
Schizophrenia	14 (100.0)	NA
Major depressive disorder	NA	9 (100.0)
BDNF blood sample		
Serum	8 (57.1)	7 (77.8)
Plasma	5 (35.7)	2 (22.2)
Serum and plasma	1 (7.2)	None
Psychoactive drug duration, week		
<6	4 (28.6)	2 (22.2)
6- 8	4 (28.6)	6 (66.7)
>8	6 (42.8)	1 (11.1)

NA: not applicable.

treatment (Chen and Huang, 2011; Chiou and Huang, 2017; González-Pinto et al., 2010; Han et al., 2021; Kudlek Mikulic et al., 2017; Lee et al., 2011; Lee and Kim, 2009; Noto et al., 2021; Rizos et al., 2010; Wu et al., 2018, 2020; Yoshimura et al., 2012, 2007; Zhang et al., 2018). The random effect model was applied. A significant increase in BDNF concentrations after antipsychotic treatment (SMD= 0.43; 95 % CI: 0.26, 0.60; $p < 0.001$) was found. The weighted percentages reflecting the contribution of each study to the overall analysis ranged from 4.0 % to 10.7 %.

Changes in BDNF concentrations after antipsychotic treatment were shown in Fig. 3.

The analysis of 9 included antidepressant drug studies, provided SMD and its corresponding 95 %CI for each study (Aydemir et al., 2006; Başterzi et al., 2009; Deuschle et al., 2013; Fornaro et al., 2015; Hellweg et al., 2008; Matriciano et al., 2009; Wolkowitz et al., 2011; Yasui-Furukori et al., 2011; Yoshimura et al., 2007). The overall SMD

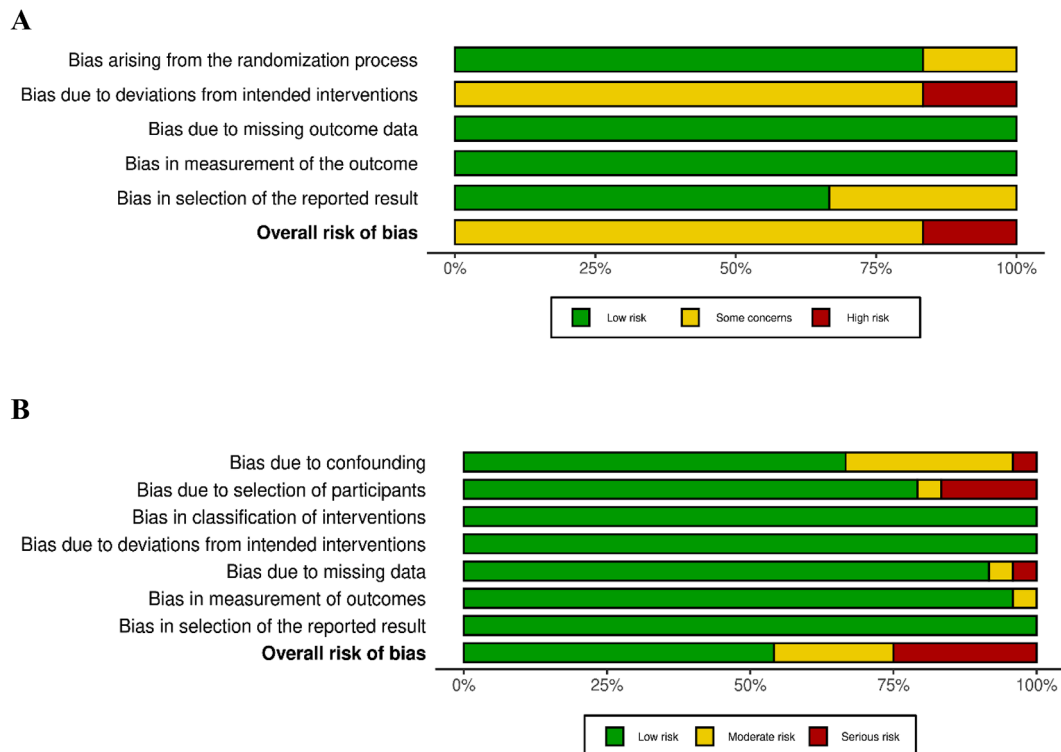


Fig. 2. A: Summary plot of RoB –2 tool for RCT. B: Summary plot of ROBINS-I for NRCTs.

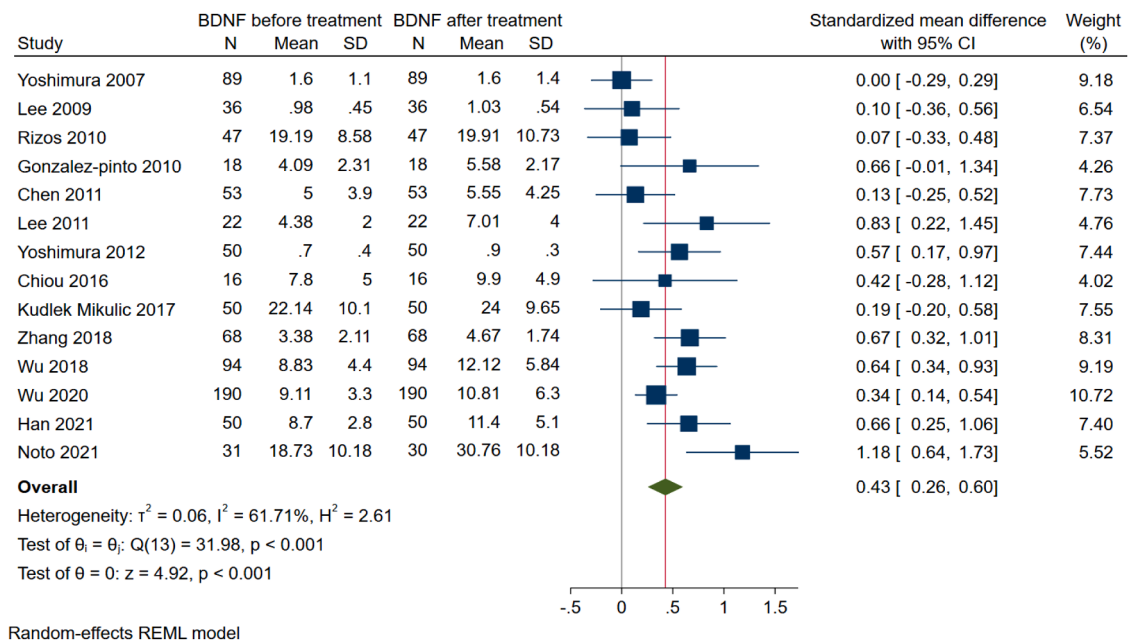


Fig. 3. Forest plot of BDNF concentrations of antipsychotic drug studies.

comparing BDNF concentrations before and after antidepressant treatment using the random effect model was found to be statistically significant (SMD=0.49; 95 % CI: 0.23, 0.74; $p < 0.001$). BDNF concentrations increased significantly after antidepressant treatment. The weighted percentages reflecting the contribution of each study to the overall analysis were ranged from 8.6 % to 13.8 %.

Changes in BDNF concentrations after antidepressant treatment were shown in Fig. 4.

3.5. Stratified analysis

For the blood sample source, a significant increase in BDNF concentrations was observed only in serum. This increase was also observed using two different ELISA techniques, Emax Promega and Quantikine R&D. When considering the ATC classification, only the classes “Diazepines, Oxazepines, Thiazepines and Oxepines”, “Other antipsychotic” and “SSRI” showed a significant increase in BDNF concentrations. The

molecules found to increase BDNF concentrations were sertraline among antidepressants, and risperidone and olanzapine among antipsychotics.

Furthermore, patients treated for more than 6 weeks showed a significant increase in BDNF concentrations. Moreover, studies carried out in the Asian population have demonstrated a significant increase in BDNF concentrations. Stratified analyses were presented in Figs. 5 and 6 respectively.

3.6. Meta-regression

In univariate meta-regression model, several tested variables were not associated with changes in BDNF concentrations, as represented by SMDs. These variables were: randomization, sample size at baseline, gender distribution, BDNF blood sample source, and sensitivity of the BDNF measurement technique.

However, three variables were found to be significantly associated with changes in BDNF concentrations: mean age with a negative

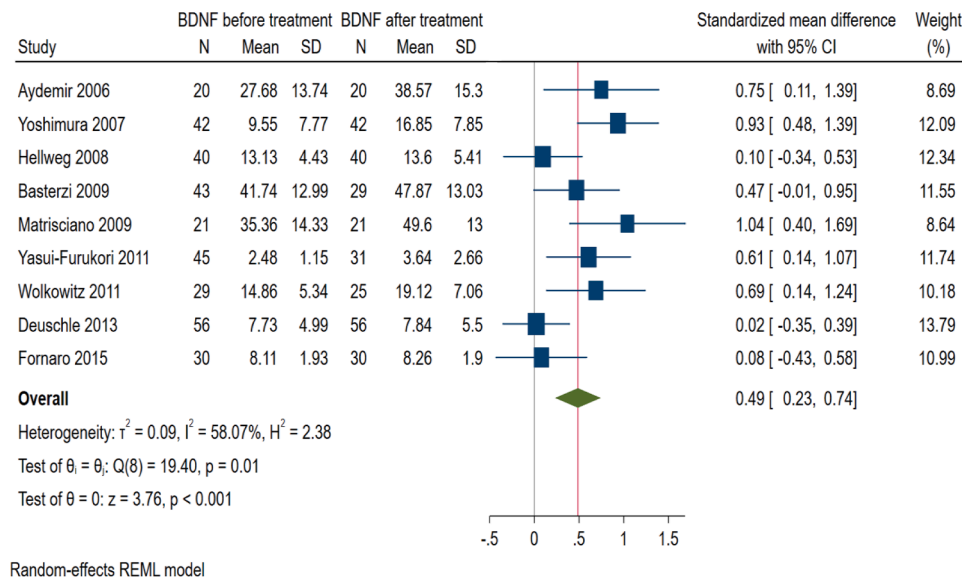


Fig. 4. Forest plot of BDNF concentrations of antidepressant drug studies.

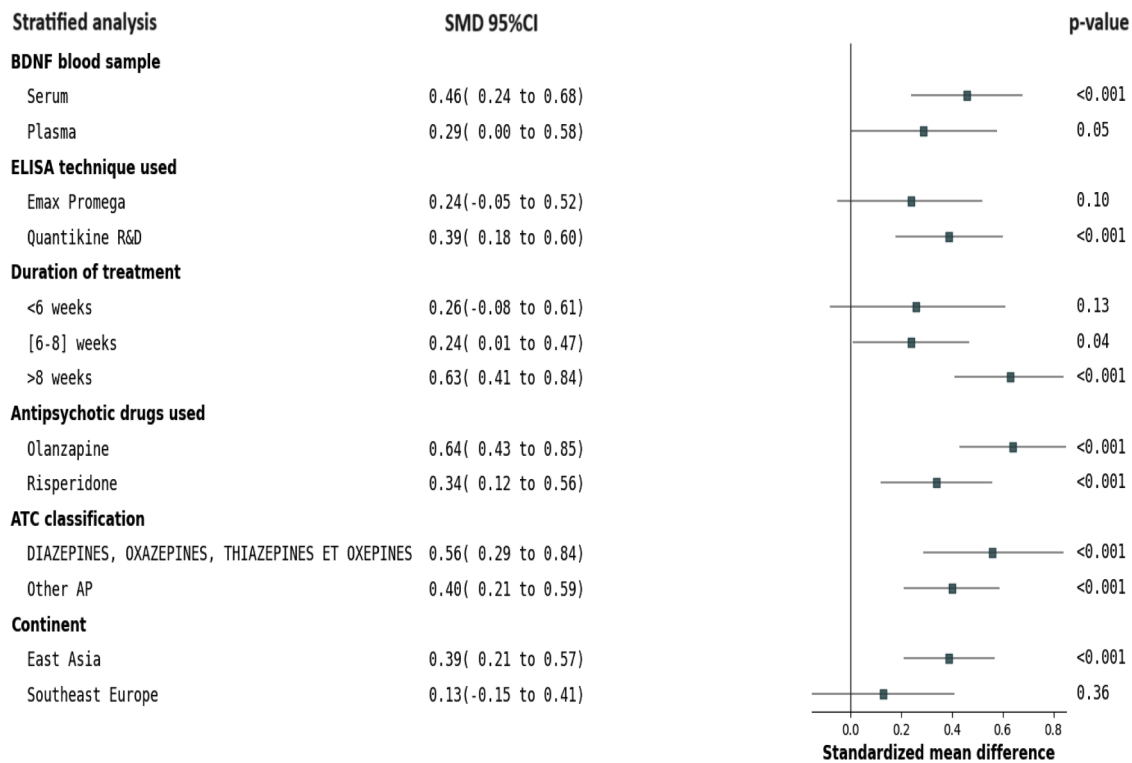


Fig. 5. Stratified analysis of antipsychotic drug studies.

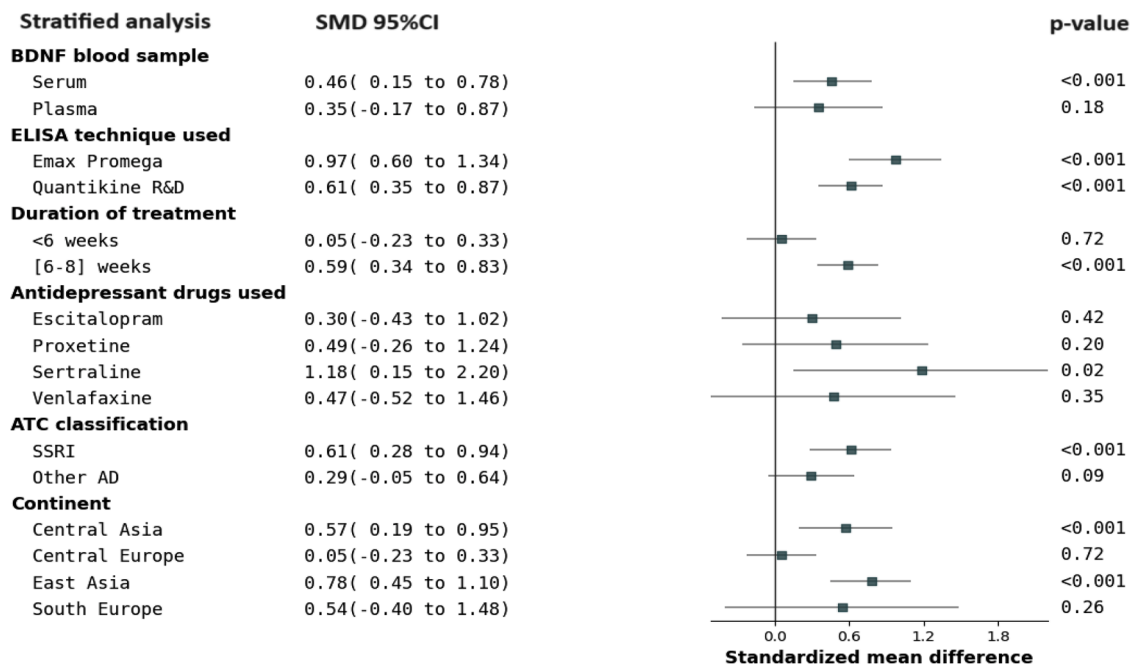


Fig. 6. Stratified analysis of antidepressant drug studies.

coefficient of correlation (-0.03 ; $p = 0.005$), duration of antipsychotic drug use with a positive coefficient of correlation (0.20 ; $p < 0.021$) and laboratory kit used with a positive coefficient of association (0.16 ; $p = 0.009$) in the case of antipsychotic studies.

In the case of antidepressant studies, only duration of treatment showed a positive correlation with BDNF concentrations (0.53 ; $p = 0.006$). Table S3 and Table S4.

3.7. Publication bias

In antipsychotic drug studies, both Begg's and Egger's test were not significant. Their results are respectively (Kendall's score= 7.00 ; SE= 18.26 ; $z = 0.33$; $p = 0.74$) and (Beta1= 1.72 ; SE= 1.28 ; $z = 1.34$; $p = 0.18$) suggesting no publication bias. For antidepressant studies, the Egger test was significant (Beta1= 5.39 ; SE= 2.59 ; $z = 2.08$; $p = 0.03$), while Begg's test was not (Kendall's score = 18 ; SE= 9.59 ; $z = 1.77$; $p = 0.07$). We used funnel plots to represent publication bias Figure S1 and

Figure S2.**3.8. Correlation between BDNF concentration changes and clinical improvement**

The random effects model analysis revealed an improvement in clinical scores after antipsychotic treatment when comparing Positive and Negative Syndrome Scale (PANSS) scores before and after antipsychotic treatment (SMD = -1.96 ; 95 % CI: -2.59 , -1.32 ; $p < 0.001$). Furthermore, an improvement in clinical scores was also observed after antidepressant treatment when comparing Hamilton Depression Rating Scale score (HAM-D) before and after antidepressant treatment (SMD = -2.84 ; 95 % CI: -3.85 , -1.82 ; $p < 0.001$).

However, correlation between variation in BDNF concentrations and changes in the PANSS and HAM-D scores after treatment revealed a non-significant correlation with PANSS ($r = -0.03$; $p = 0.69$) or HAM-D ($r = -0.04$; $p = 0.85$) scores, respectively.

4. Discussion

This meta-analysis on the effects of psychoactive drugs on peripheral BDNF concentrations included 14 studies on antipsychotics and 9 on antidepressants. Pooling data from these studies into a quantitative synthesis revealed a significant increase in peripheral BDNF concentrations after treatment with both antipsychotics and antidepressants.

Antipsychotic drugs exert their therapeutic effects by modulating various neurotransmitter systems, including dopamine and serotonin (Konradi and Heckers, 2001). Antidepressants work by blocking the reuptake of monoamines (like serotonin and noradrenaline) into the presynaptic neuron. This results in higher levels of these monoamines in the synaptic cleft, leading to enhanced stimulation of postsynaptic receptors and increased postsynaptic neurotransmission (Andrade and Rao, 2010).

Moreover, it has been demonstrated that antidepressants of diverse classes directly bind to a region composed of two TrkB transmembrane domains. This binding enhances the receptor's presence on the cell surface and boosts its sensitivity for BDNF (Casarotto et al., 2021). The exact mechanism by which these medications increase BDNF concentrations remains not fully elucidated. One hypothesis suggests that by targeting neurotransmitter systems, antidepressant medications may influence signalling pathways that lead to an increase in BDNF (Levy et al., 2018).

A moderate level of heterogeneity was found for both included antipsychotic and antidepressant studies. Several factors may contribute to the observed heterogeneity in this meta-analysis, such as study characteristics, patients' characteristics, clinical factors, and other medical-related factors. To investigate potential sources of heterogeneity in our study, stratified analyses and meta-regression were performed.

A significant increase in serum BDNF concentrations following both antipsychotic and antidepressant treatment was found. However, a non-significant increase was observed specifically in plasma BDNF concentrations for both antipsychotics and antidepressants. This disparity in BDNF concentrations between serum and plasma can be attributed to several factors. Firstly, platelets represent a major storage site of BDNF in peripheral blood. During the coagulation process, platelet activation leads to the release of BDNF into the serum. Consequently, serum BDNF represents total peripheral BDNF, including BDNF released from platelets during clotting (Begliuomini et al., 2007; Fujimura et al., 2002). Moreover, the choice of collection tubes can have an impact on BDNF assay results. Begliuomini et al. 2007 found that the use of lithium heparinized tubes which contain heparin that acts as an anticoagulant, may interfere with BDNF assay, whereas EDTA (Ethylene Diamine Tetra-acetic Acid) tubes do not (Begliuomini et al., 2007). Furthermore, variations in centrifugation conditions, such as speed and duration of centrifugation, can influence the amount of platelets suspended in plasma and subsequently impact BDNF concentrations

(Bocchio-Chiavetto et al., 2010).

Concerning the duration of treatment, a non-significant increase in BDNF concentrations was observed for the group receiving treatment for less than 6 weeks. The groups receiving treatment for 6 to 8 weeks and more than 8 weeks showed a significant increase in BDNF concentrations. One possible explanation for the observed findings is the complex synthesis process of BDNF which can take time to become measurable (Bathina and Das, 2015).

Regarding the ATC classification stratified analysis, both the "Diazepines, Oxazepines, Thiazepines and Oxepines" as well as "Other antipsychotic" ATC classes showed a significant increase in BDNF concentrations following treatment. In antidepressant studies, the "SSRI" class showed a significant increase in BDNF concentrations, however, "Other antidepressants" did not.

Regarding antipsychotics, the reasons why only olanzapine and risperidone have been associated with increases in BDNF concentrations may be due to several factors. Firstly, they were the only antipsychotic medications that were identified and analyzed in the specific analysis. Additionally, the different effects on BDNF could be attributed to the unique affinity profile of each medication for neurotransmitter receptors. For example, olanzapine has been found to boost BDNF mRNA expression through various mechanisms, such as adjusting GluR2 protein levels and blocking 5-HT_{2A} receptors (Bai et al., 2003). For antidepressants, only sertraline was found to be associated with an increase in BDNF concentrations compared to escitalopram, paroxetine, and venlafaxine. This difference may be attributed to the specific pharmacological characteristics of these medications. Research has indicated that various classes of antidepressants can have different impacts on BDNF transcription, release, receptor activation, and secondary messengers (Matrisciano et al., 2009).

Sertraline's higher selectivity for serotonin receptors, in contrast to the broader affinity profiles of escitalopram, paroxetine, and venlafaxine, could explain its rapid effect on increasing BDNF concentrations. In addition, the affinity of sertraline for the σ_1 receptor and its rapid action on increasing serum BDNF concentrations may explain its effect found in our meta-analysis on BDNF increments (Lowther et al., 1995).

In contrast, there is no demonstrated σ_1 -receptor affinity for escitalopram (Fabre and Hamon, 2003). This distinction may account for why we did not observe an effect for this particular medication.

These differences should be interpreted with caution, as they don't imply that the other molecules do not affect the BDNF concentrations. Moreover, the effect on BDNF can vary from one medication to another, even if they belong to the same therapeutic class. Multiple factors, including the pharmacodynamic, pharmacokinetic, chemical, and structural properties of each drug and their specific effects on neurochemical systems and receptor interactions, may contribute to these differences.

A meta-analysis conducted in 2020 by Semahegn et al., showed that almost half of patients with major psychiatric disorders exhibited non-adherence to their prescribed psychotropic medications. These findings underscore challenges that patients face in adherence to psychotropic treatment and to the recommended dosing intervals (Semahegn et al., 2020). Additionally, variations in the number of studies within each stratum, differences in drug doses, treatment duration, severity of the disease and individual response variations among patients may influence the observed effects on BDNF.

A significant increase in BDNF concentrations was observed after antidepressant and antipsychotic treatment in studies conducted in Asia. Pivac et al. conducted a study in 2009 that investigated the distribution of the BDNF Val66Met (Methionine 66 Valine) polymorphism in Caucasian (Croatian) and Asian (Korean) healthy participants and revealed a significant ethnic difference. Among the Caucasian participants, the most frequent genotype observed was Val/Val. They displayed a different distribution of "Met" (Methionine) and "Val" (Valine) alleles. Conversely, for Korean participants, it was Met/Val and had a similar distribution of "Met" and "Val" alleles (Pivac et al., 2009). These

findings highlight distinct patterns in the distribution of the *Val66Met* polymorphism between this ethnic group. In addition, the frequency of the Met-allele in the *Val66Met* can vary widely across populations. A huge range of Met-allele values was reported from 0.5 % in sub-Saharan Africans to 19.9 % in Europeans and 43.6 % in Asian groups. Furthermore, within European populations, there are variations in the frequency of the Met-allele. (Petryshen et al., 2010; Vulturar et al., 2016). Additionally, polymorphisms of the BDNF receptor, such as those of *TrkB* (tyrosine receptor kinase B) and *P75NTR* (p75 neurotrophin receptor) have been associated with antidepressant efficacy (Colle et al., 2015). These findings emphasize the importance of considering genetic factors and ethnic diversity when studying the implication of the BDNF *Val66Met* polymorphism. Further research is needed to explore the functional implications of these genetic variations and their specific impact on response to psychoactive drugs.

Moreover, Stratified analysis on the ELISA technique used resulted in a notable reduction of heterogeneity within each stratum and overall, for both antipsychotic and antidepressant studies ($I^2=50.9\%$ and $I^2=0.0\%$) respectively. The reduction of heterogeneity to zero in the antidepressant studies within each stratum after stratified analysis provides important insights into the impact of the ELISA technique on the variation observed. These results underline the importance of standardizing the ELISA technique in future studies to minimize the potential bias introduced by variations in measurement methods.

In this meta-analysis, a negative correlation was found between changes in BDNF concentrations and patient age, suggesting that as patients get older, their BDNF concentrations tend to decrease. This finding aligns with previous research indicating that BDNF expression and signalling decline with age (Erickson et al., 2010).

The positive correlation found between duration of treatment and BDNF implies that longer treatment duration may be associated with increased BDNF concentrations.

The analysis of studies on antipsychotic drugs revealed a significant decrease in the PANSS scale, indicating an improvement in both positive and negative symptoms in patients with schizophrenia. This finding aligns with the established efficacy of antipsychotic drugs in managing these symptoms. However, it's important to note that individual responses to antipsychotic medication may vary (Nnadi and Malhotra, 2007). Similarly, the analysis of antidepressant studies demonstrated a significant decrease in HAM-D score, indicating an improvement in depressive symptoms following antidepressant treatment. The observed decrease in HAM-D score reflects the efficacy of antidepressants in alleviating depressive symptoms. However, only four studies were considered in the analysis due to missing of the required data.

Concerning the association between changes in BDNF concentrations and changes in clinical scale scores, a non-significant correlation was observed with both Positive and Negative Syndrome Scale Score (PANSS) and Hamilton Depressive Rating Scale score (HAM-D). This means that the increase in BDNF concentrations did not show a significant correlation with PANSS and HAM-D. Varma et al. have also found no association between patients' BDNF concentrations and HAM-D scores (Sözeri-Varma et al., 2011). However, Emon et al. found significant negative correlations between serum BDNF and HAM-D in both drug-naïve and drug-treated MDD patients (Emon et al., 2020). These different findings can be attributed to several factors related to study-specific characteristics, patient characteristics and treatment-related factors.

Finally, our meta-analysis only included studies that reported the mean and standard deviation of BDNF concentrations before and after treatment. This selection was based on the limitations of methods that estimate the mean and standard deviation from the median, interquartile range, and sample size, which may introduce methodological discrepancies and impact the reliability of our meta-analysis findings, as emphasized by Wan et al. (Wan et al., 2014).

To the best of our knowledge, this is the first meta-analysis to investigate the effect of psychoactive drugs, including both

antidepressants and antipsychotics, on peripheral BDNF concentrations. Multiple stratified analyses and meta-regressions were carried out, identifying potential sources of heterogeneity, and exploring correlations. Moreover, the meta-analysis focused on patients with specific psychiatric disorders, such as schizophrenia and depression, resulting in a more focused and homogeneous sample.

Limitations of this study were the lack of standardized dosing between studies and patients due to ethical reasons, and the variation in treatment duration between the included studies. These differences can potentially impact the comparability of results. Additionally, the included studies exhibit variations in sample sizes and demographic characteristics. The use of different BDNF measurement kits with varying sensitivities could potentially influence the accuracy and comparability of BDNF measurements across studies.

Further studies evaluating the effect of psychoactive drugs that influence BDNF concentrations (as identified in this meta-analysis) on cancer outcomes, such as survival of cancer patients could be of interest, particularly considering the results of recent studies suggesting a protective effect of BDNF on cancer survival (Tarhini et al., 2024).

5. Conclusions

In conclusion, this meta-analysis showed a significant increase in serum but not in plasma BDNF concentrations after treatment of antidepressant and antipsychotic medication. These findings highlight the potential of psychoactive drugs including antidepressants and antipsychotics to significantly increase serum BDNF concentrations. However, various factors can influence the association between psychoactive drug use and peripheral BDNF, such as the duration of psychoactive drug use, the type of drugs used, the serum or plasma BDNF sample, the measurement technique used, and even population characteristics such as ethnicity and age. Considering these factors is crucial for interpreting the findings and understanding the full extent of the relationship between psychoactive drugs and BDNF concentrations.

CRedit authorship contribution statement

Tassadit Merabtine: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Zeinab Tarhini:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Pierre-Marie Preux:** Writing – review & editing, Validation. **Niki Christou:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Jeremy Jost:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2024.115946](https://doi.org/10.1016/j.psychres.2024.115946).

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