INPLASY PROTOCOL

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Corresponding author:
Yachen Shi

yachen_shi@163.com

Author Affiliation:
Affiliated ZhongDa Hospital, School of Medicine, Southeast University

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The authors report no biomedical financial interests or potential conflicts of interest.

The value of peripheral neurotrophins for diagnosis and antidepressant treatment response in depression: a systematic review and meta-analysis

Shi, YC[1]; Luan, D[2]; Song, RZ[3]; Zhang, ZJ[4].

Review question / Objective: **Current meta-analysis aimed to investigate the MDD diagnostic value of peripheral neurotrophins levels in cross-sectional studies and the association between peripheral neurotrophins levels and the response to antidepressant treatment in longitudinal studies.**
Condition being studied: **The neurotrophin hypothesis indicates that neurotrophic factors is important for the pathophysiology of major depressive disorder (MDD) and alterations in peripheral neurotrophins levels have potential clinical application for MDD. The association between MDD and aberrant peripheral neurotrophic factor levels has been examined in numerous meta-analyses. However, few meta-analyses assesses the association between neurotrophic factors levels and treatment response. With emerging studies on the peripherial neurotrophic factors levels in MDD patients, we conduct a comprehensive and methodologically strict meta-analysis in the present study to update the evidences on the clinical application of peripheral neurotrophic factors in MDD including diagnosis and response to antidepressant treatment.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 August 2020 and was last updated on 18 August 2020 (registration number INPLASY202080077).

INTRODUCTION

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METHODS

Search strategy: (1) "depressive disorder" and synonyms; (2) "neurotrophic factor" and synonyms, including its components (e.g., BDNF); (3) "serum/plasma" and synonyms.

Participant or population: All the included studies were conducted in adult patients (aged ≥ 18 years). All patients undergone depressive disorder [e.g., MDD and treatment-resistant depression (TRD)] diagnosed according to the international diagnosis tools (e.g., Diagnostic and Statistical Manual of Mental Disorders).

Intervention: Subjests with depressive disorders at cross-sectional level and depressive disorder patients accepted an effective treatment.

Comparator: All the included studies were conducted in adult patients (aged ≥ 18 years), and all controls were healthy subjests and had never received any antidepressant treatment.

Study designs to be included: A cross-sectional study contained an depressive cohort and a control cohort or an longitudinal study with antidepressant treatment.

Eligibility criteria: Studies were screened based on the following inclusion criteria: (1) all patients undergone depressive disorder [e.g., MDD and treatment-resistant depression (TRD)] diagnosed according to the international diagnosis tools (e.g., Diagnostic and Statistical Manual of Mental Disorders); (2) any kind of neurotrophic factors, including BDNF, GDNF, IGF-2, VEGF, NGF, FGF-2, and S100 protein (S100B), were measured in serum and/or plasma; (3) a cross-sectional study contained an depressive cohort and a control cohort or an longitudinal study with antidepressant treatment reported a cut-off value of a standardized posttreatment symptom assessment for dividing patients into responders and nonresponders; (4) any detection methods of neurotrophic factors or any antidepressant treatment methods were allowed. Exclusion criteria were as follows: (1) studies conducted in patients with other neuropsychiatric disorders (e.g., schizophrenia, bipolar depression, Alzheimer's disease, Parkinson's disease, etc.), unless separate data for unipolar depression patients could be obtained; (2) depression occurs as a result of posttraumatic stress disorder, stroke, cerebral trauma, diabetes, perimenopause syndrome, perinatal depression, alcohol use disorder, and cancer.

Information sources: Published studies were systematically searched from the PubMed and Web of Science databases up to February 2020. And we contacted the primary authors of partial studies for missing data, and when the authors could not provide the original data, data were also extracted from bar chart or scatter diagram using GETDATA Graph Digitizer.

Main outcome(s): The Change in serum and/or plasma level of neurotrophic factors, including BDNF, GDNF, IGF-2, VEGF, NGF, FGF-2, and S100 protein, between patients and controls and between responders and nonresponders.

Additional outcome(s): None.

Quality assessment / Risk of bias analysis: The methodological quality of cross-sectional studies was assessed by the Newcastle Ottawa Scale (NOS), which contained three primary items: selection, comparability, and exposure. Every item contained some subordinate items and the total score of each study ranged from zero to nine. In addition, the Cochrane risk of bias tool including seven factors, was used to assess methodological quality of included longitudinal studies, and an adapted assessment parameters was used to quantify the methodological quality: low risk of bias = 1, unclear risk of bias = 2, and high risk of bias = 3. Therefore, the total score of each longitudinal study ranges from 7 to 21, with a lower total score indicating a higher quality. The assessment was conducted by two independent researchers and the disparities were resolved by consensus.

Strategy of data synthesis: For each neurotrophic factor, the standard mean difference (SMD) and 95% confidence interval (CI) were used to assess the effect sizes (ESs) expressing the difference between two groups. The SMD value greater than 0 indicated that the neurotrophic factor levels were higher in depression patients than healthy controls or responders than nonresponders.

Subgroup analysis: Random-effects meta-regression and subgroup analyses were performed to explore sources of heterogeneity based on the following potential confounders: mean age, gender distribution (proportion of females), medication status on study-entry (drug-free/treatment/mixed), sample type (serum/plasma), neurotrophic factor detection methods (ELISA/other), treatment type (single treatment/combined treatment or pharmacotherapy/physicotherapeutics), length of treatment, study quality, publication year.

Sensibility analysis: When the significant pooled SMD was detected, sensitivity analyses were performed to assess whether a single study can affect the stability of results by deleting one study from analyses each time.

Language: English.

Country(ies) involved: China.

Keywords: Antidepressive treatment, Assessment, Depression, Diagnosis, Meta-analysis, Neurotrophin.

Contributions of each author:
Author 1 - Yachen Shi - performed selection of studies, initial screening, full-text analysis and drafted the manuscript.
Author 2 - Di Luan - performed selection of studies, initial screening, and provided statistical expertise.
Author 3 - Ruize Song - performed selection of studies and extracted the data.
Author 4 - Zhijun Zhang - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy and provide feedback and approved the final manuscript.