CRD summary
The review evaluated whether brain-derived neurotropic factor blood levels correlated with improvement in major depression. Brain-derived neurotropic factor blood levels were significantly higher after treatment with antidepressants than before, but remained higher in healthy people. Given the limited evidence of uncertain quality, the presence of heterogeneity and the review process limitations, the authors' conclusions should be interpreted with caution.

Authors' objectives
To evaluate whether brain-derived neurotropic factor levels in blood correlate with improvement in major depression.

Searching
MEDLINE, SciELO (Scientific Electronic Library Online) and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to February 2008 for studies published in English. Search terms were reported. The bibliographies of each retrieved article and conference abstracts were handsearched. Attempts were made to find unpublished studies by contacting clinical experts, searching the CRISP (Computer Retrieval of Information on Scientific Projects) database and searching for abstracts.

Study selection
Clinical trials or case-control studies that reported mean brain-derived neurotropic factor level (with standard deviation) in blood in patients with major depression pre- and post-antidepressant treatment, or that compared brain-derived neurotropic factor level in blood with healthy controls, were eligible for inclusion.

The mean age of the participants was 40 years (range 32 to 56), and the mean proportion of males was 36% (range 13 to 75%). The depression treatments used included: venlafaxine (75-225 mg daily); escitalopram (10mg daily); paroxetine (20-40mg daily); milnacipran (50-150mg daily); electroconvulsive therapy; repetitive transcranial magnetic stimulation; and vagal nerve stimulation. Most of the included studies used a Promega ELISA kit to measure brain-derived neurotropic factor in serum. Studies measured serum or plasma brain-derived neurotropic factor or both.

It appeared that two independent researchers performed the study selection.

Assessment of study quality
Methodological quality was assessed for use of selection criteria, case-control matching and evidence of an intention to treat analysis.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Mean brain-derived neurotropic factor blood levels, with standard deviations, were extracted for each group. When a study measured mean brain-derived neurotropic factor levels at more than one time point, the mean value after the longest time was generally used. When a study did not report the mean blood brain-derived neurotropic factor and standard deviation, they were calculated (where possible) or authors were contacted for the relevant information (or when other data were missing). The drug-free period before each study was divided into three categories: less than two weeks; two to four weeks; and more than four weeks.

Data were extracted independently by two reviewers, using a structured form. Discrepancies were resolved by consensus and using a third reviewer when necessary.
Methods of synthesis
Random-effects and fixed-effect models were used to calculate pooled standardised mean difference (SMD) and standard deviation (SD), weighted by the inverse variance of each study. Study heterogeneity was evaluated with a $\chi^2$ test. A sensitivity analysis and cumulative regression were also performed. Publication bias was assessed using Egger’s test. Meta-regression was performed using a random-effects model to examine prespecified variables. The main comparison was between patients with major depression pre- and post-treatment, but two further analyses were performed comparing depressed patients pre-treatment versus healthy people and depressed patients post-treatment versus healthy people.

Results of the review
Nineteen studies (23 datasets, n=1,504 participants, range 10 to 79) were included in the review, including 10 case-control studies and 13 clinical trials (mostly non controlled). Loss to follow-up was only reported for one study (40%). The test for heterogeneity was significant, so a random-effects model was used for all meta-analysis.

Brain-derived neurotropic factor level was significantly higher after antidepressant treatment than before in depressed patients (SMD 0.62, 95% CI 0.36 to 0.88; $I^2=61\%$). A sensitivity analysis showed the result did not significantly change after the exclusion of any one study, Egger’s test was not significant, indicating an absence of publication bias. A meta-regression showed that age, gender, baseline depression, case-control versus clinical trial, ELISA kit used, and type of antidepressant treatment were not associated with outcome (i.e. $p>0.05$). There was a significant association between brain-derived neurotropic factor level and: depression symptoms change ($p=0.02$); period of treatment ($p=0.01$); previous drug use with a two week cut-off ($p=0.004$); and previous drug use with a four week cut-off ($p=0.02$).

Brain-derived neurotropic factor level was significantly higher in healthy people than in patients with depression before treatment (SMD 0.91, 95% CI 0.70 to 1.1) and was also higher for healthy people compared with patients with depression after treatment (SMD 0.34, 95% CI 0.02 to 0.66), indicating that brain-derived neurotropic factor level was significantly higher in healthy people. Meta-regression found significant associations between brain-derived neurotropic factor level both baseline depression ($p=0.02$, pre-treatment versus healthy people) and age ($p=0.02$, post-treatment versus healthy people).

Further subgroup analyses were available as online supplementary material. A subgroup analysis compared drug treatment (eight studies) versus non-drug treatment studies (six studies) and found that, for both types of study, brain-derived neurotropic factor level was significantly higher post-treatment in depressed patients but there was significant heterogeneity in the drug treatment studies (SMD 0.64, 95% CI 0.34 to 0.93; $I^2=64\%$) compared with the non-drug treatment studies (SMD 0.32, 95% CI 0.02 to 0.61; $I^2=5\%$).

Authors’ conclusions
Different antidepressive treatments were associated with an increase in brain-derived neurotropic factor levels, suggesting that this neuropeptide might be ‘a final common pathway’ in major depressive disorder treatment. Further brain-derived neurotropic factor studies are needed on major depression to explore its role in neurogenesis and neuroplasticity.

CRD commentary
The review addressed a well-defined question supported by appropriate inclusion criteria. Relevant databases were searched and unpublished studies were considered, but only studies published in English were included, so it is possible that some relevant studies may have been missed. However, publication bias was assessed and none was found. The authors reported that no studies in languages other than English were identified.

Study quality was assessed but the authors did not differentiate between study designs (before-after studies and randomised controlled trials), reporting was minimal and unclear (it was not clear how many patients were included in the overall meta-analyses), and quality assessment results were not used in interpreting the review results. Although data extraction was carried out with efforts to reduce error and bias, it was not clear whether this process applied to other aspects of the review process. Relevant study details were reported for the majority of studies but some details were not clear; the details of studies not included in meta-analyses were not reported, making it difficult to assess all the evidence. Incomplete data was provided for the included studies. Details of length of follow-up and duration of
treatment were not provided, and loss to follow-up was only reported for one study. Statistical heterogeneity was assessed and there was evidence for heterogeneity. It was not clear whether the statistical method used for the meta-analysis was appropriate as it was used to derive the standardised mean difference for all studies combined, with no separation by study design.

In view of potential limitations arising from the review process, the small size and uncertain quality of the included studies, and the presence of significant heterogeneity, the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors identified a need for further studies in to evaluate whether brain-derived neurotropic factor plasma levels are more sensitive to acute or sub acute depression symptoms change compared with serum brain-derived neurotropic factor levels, or whether they are related to methodological issues. The authors also recommended further studies to investigate whether brain-derived neurotropic factor blood levels directly reflect brain-derived neurotropic factor brain metabolism, such as whether brain-derived neurotropic factor blood levels are related to an increase in the volume of hippocampus and amygdala. Brain-derived neurotropic factor could be used together with depression rating scales to evaluate antidepressive therapies.

**Funding**

Not stated.

**Bibliographic details**


**PubMedID**

18752720

**DOI**

10.1017/S1461145708009309

**Original Paper URL**

http://journals.cambridge.org/action/displayAbstract?aid=2539260

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Adolescent; Adult; Aged; Brain-Derived Neurotrophic Factor /metabolism /physiology; Data Interpretation, Statistical; Depressive Disorder, Major /genetics /metabolism /psychology; Female; Humans; Male; Middle Aged; Neuronal Plasticity /physiology; Quality Control; Young Adult

**AccessionNumber**

12009101649

**Date bibliographic record published**

31/03/2009

**Date abstract record published**

03/02/2010
**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.