Introduction

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that regulates neuronal survival and growth during development. Effects of BDNF on neuronal transmission in the hippocampus, cortex, cerebellum and basal forebrain are important for learning and memory processes [1]. Reduced BDNF may affect synaptic efficiency and connectivity in schizophrenia that is hypothesized to underpin signs and symptoms of the disorder. Due to the difficulty measuring brain levels of BDNF in living people, most studies in this summary have measured levels of BDNF in the periphery (i.e. from blood serum samples).

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. As part of a wider search for all topics included in the library, reviews on BDNF in schizophrenia were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. The decision to include or exclude reviews was conducted in duplicate by two independent reviewers with any disagreements settled by discussion. All quality assessments and data extraction have been completed in duplicate by two reviewers who were not masked to review authors.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (formerly the QUOROM statement) which describes a preferred way to present a meta-analysis [2]. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. For instance, a low possibility of bias would be assigned to reviews checking over 66% of items, a medium possibility between 33 and 66% and a high possibility would be given to reviews checking less than 33%. Reviews rated as having a high possibility of reporting bias have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomized controlled trials (RCT) may be downgraded to moderate, low or very low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[3]. The resulting table represents an objective summary of the available evidence, although the conclusions
TECHNICAL COMMENTARY

Chemical Alterations – Peripheral Brain-derived Neurotrophic Factor

are solely the opinion of staff of the Schizophrenia Research Institute.

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Results

We found two reviews that met our inclusion criteria [1, 4]. Click on review ID for a link to the review’s abstract.

See PRISMA checklist for review quality assessments.

Conclusions

• Moderate quality evidence suggests reduced blood BDNF levels in patients compared to healthy controls, regardless of medication dosage or medication status. Normal age related BDNF decline was greater in patients than controls.

• High quality evidence suggests a moderate increase in blood BDNF levels in patients after treatment with olanzapine.
MJ Green, SL Matheson, A Shepherd, CS Weickert and VJ Carr

Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis

Molecular Psychiatry (2010), 1–13

View review abstract online

<table>
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<th>Comparison</th>
<th>BDNF levels in patients with schizophrenia compared to healthy controls</th>
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<td>Summary of evidence</td>
<td>Moderate quality evidence suggests reduced blood BDNF levels in patients compared to healthy controls, regardless of medication status or medication dosage. Normal age related BDNF decline was greater in patients than controls.</td>
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**Blood BDNF levels**

Results showed a significant, moderate reduction in blood BDNF levels in schizophrenia patients when compared with age and sex matched controls

17 studies, N = 2084

\[ g = -0.594, 95\% \text{ CI } -0.930 \text{ to } -0.257, p = 0.001 \]

\[ I^2 = 91.5\%, p < 0.001 \]

With one study outlier removed, a significant effect remains

16 Studies, N = 2065, \( g = -0.458, 95\% \text{ CI } -0.770 \text{ to } -0.146, p = 0.004 \)

\[ I^2 = 90\%, p < 0.001 \]

Meta-regression showed greater reduction in BDNF levels with increasing patient age, 16 Studies, N = 2065, \( b = -0.01749, p < 0.001 \)

Meta-regression found no effect of medication dosage (mean chlorpromazine equivalents), 8 Studies, N = not reported, \( b = -0.00026, p < 0.370 \)

**Subgroup analysis of medicated vs. drug naïve patients**

Significant, moderate reduction in blood BDNF levels both medicated and drug naïve patients

**Drug naïve subgroup**: 7 studies, N = 517, \( g = -0.446, 95\% \text{ CI } -0.850 \text{ to } -0.043, p = 0.030 \)

\[ I^2 = 75\%, p < 0.001 \]

**Medicated subgroup**: 13 studies, N = 1678, \( g = -0.401, 95\% \text{ CI } -0.765 \text{ to } -0.036, p = 0.031 \)

\[ I^2 = 91\%, p < 0.001 \]
Subgroup analysis of females vs. males
Results showed a significant, moderate reduction in blood BDNF levels in both female and male patients (with one outlier removed from the male analysis)

Females: 7 studies, N = 593, \( g = -0.450, 95\% \text{ CI} -0.781 \text{ to } -0.118, p = 0.008 \)
\( \tau^2 = 70\% , p < 0.001 \)

Males: 10 studies, N = 1033, \( g = -0.227, 95\% \text{ CI} -0.728 \text{ to } -0.274, p = 0.375 \)
\( \tau^2 = 91\% , p < 0.001 \)

Males with one outlier removed: 9 studies, N = 973, \( g = -0.446, 95\% \text{ CI} -0.818 \text{ to } -0.074, p = 0.019 \)
\( \tau^2 = 82\% , p < 0.001 \)

No significant difference in effect was reported between gender subgroups
Before outlier removed, \( Q_B = 0.528, p = 0.467 \)
With outlier removed, \( Q_B = 0.000, p = 0.989 \)

Consistency in results\(^\dagger\) Inconsistent

Precision in results\(^\$\) Precise

Directness of results\(^\|\) Direct

Lin P-Y
Increase in brain-derived neurotrophic factor in patients with schizophrenia treated with olanzapine: a systematic review and meta-analysis

View review abstract online

Comparison
BDNF levels in patients with schizophrenia before and after treatment with antipsychotics.

Summary of evidence
High quality evidence (consistent, precise, direct) suggests a moderate increase in blood BDNF levels in patients following treatment with olanzapine. Other antipsychotics were not associated with a similar increase.

Blood BDNF levels
Chemical Alterations – Peripheral Brain-derived Neurotrophic Factor

Results showed a significant, small increase in blood BDNF levels in schizophrenia patients following treatment with antipsychotics

10 studies, N = 399, g = 0.171, 95% CI 0.008 to 0.334, p = 0.04

Q = 11.69, p = 0.232, I² = 23%

Meta-regression showed that this effect was not moderated by patient age (p = 0.59), gender (p = 0.815), duration of illness (p = 0.509), time of treatment (p = 0.326), or source of sample (p = 0.759).

Subgroup analyses stratified by type of antipsychotic medication found a significant increase in BDNF levels only following olanzapine treatment

- **Olanzapine**: 6 studies, g = 0.635, 95%CI 0.323 to 0.948, p = 0.0001
- **Risperidone**: 7 studies, g = 0.005, 95%CI -0.176 to 0.185, p = 0.612

No difference in BDNF levels were found following treatment with amisulpride (1 study), aripiprazole (1 study), clozapine (2 studies), haloperidol (2 studies), or quetiapine (1 study).

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent</th>
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<tr>
<td>Precision in results</td>
<td>Precise</td>
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<td>Directness of results</td>
<td>Direct</td>
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**Explanation of acronyms**

- $b$ = correlation coefficient, BDNF = Brain derived neurotrophic factor, CI = confidence interval, d = Cohen’s d and $g$ = Hedges’ $g$ = standardized mean differences (see below for interpretation of effect size), $I^2$ = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, $Q_w$ = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), $Q_B$ = test for between group differences (heterogeneity between groups of studies for an outcome of interest), vs = versus
Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials which are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[5].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomized trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study’s mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[5].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A large effect is considered if RR > 2 or < 0.5 and a very large effect if RR > 5 or < 0.2[6]. InOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios
measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforeseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardized (b) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardized regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

\[ I^2 = \left( \frac{Q - df}{Q} \right) \times 100\% \]

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[6].

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) which is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. \( I^2 \) is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. \( I^2 \) can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[5];

\[ I^2 = \left( \frac{Q - df}{Q} \right) \times 100\% \]

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Many thanks to Dr Melissa Green for reviewing the original version of this summary of evidence.

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Chemical Alterations – Peripheral Brain-derived Neurotrophic Factor

References