

Infectious agents

Introduction

Several markers of infectious agents have been investigated in people with bipolar disorder due to their neurological interactions.

Infectious agents include *Toxoplasma gondii* and Borna Disease Virus. *Toxoplasma gondii* is a parasitic protozoa usually hosted by domestic cats and other warm-blooded animals. Borna Disease Virus is the key causative component of Borna disease, a neurological syndrome primarily affecting animals, but sometimes humans.

Any association between these infectious agents and risk of subsequent bipolar disorder remains unclear.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) that are published in English from the year 2010, and that report results separately for people with a diagnosis of a bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. When multiple copies of review topics were found, only the most recent and/or comprehensive review was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ([PRISMA](#)) checklist that describes a preferred way to present a meta-analysis¹. Reviews with less than 50% of items checked 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 randomised controlled trials (RCTs) may be downgraded to moderate or 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, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)². The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found three systematic reviews that met our inclusion criteria³⁻⁵.

- Moderate to high quality evidence suggests a small effect of increased markers for borna disease virus in people with bipolar disorder compared to controls.
- Moderate to high quality evidence suggests a small effect of increased markers for *Toxoplasma gondii* in people with bipolar disorder, particularly those under 40 years of age, compared to controls. There were no differences in herpesviruses antibodies.

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Azami M, Jalilian FA, Mojarad MRA, Mohammadi Y, Tardeh Z

The association between borna disease virus and mood disorders: A systematic review and meta-analysis

Archives of Neuroscience 2018; 5(2): e57779

[View review abstract online](#)

Comparison	Markers of borna disease virus in people with bipolar disorder vs. controls.
Summary of evidence	Moderate to high quality evidence (large sample, consistent, imprecise, direct) suggests a small effect of increased markers for borna disease virus in people with bipolar disorder.
Borna disease virus	
<p><i>A significant, small effect of increased markers for borna disease virus in people with bipolar disorder;</i></p> <p>7 studies, N = 440, OR = 1.99, 95%CI 1.29 to 3.08, $p = 0.002$, $I^2 = 0\%$, $p = 0.856$</p> <p>Authors report no evidence of publication bias.</p>	
Consistency in results[‡]	Consistent
Precision in results[§]	Imprecise
Directness of results	Direct

Snijders GJLJ, van Mierlo HC, Boks MP, Begemann MJH, Sutterland AL, Litjens M, Ophoff RA, Kahn RS, de Witte LD

The association between antibodies to neurotropic pathogens and bipolar disorder: A study in the Dutch Bipolar (DB) Cohort and meta-analysis

Translational Psychiatry 2019; 9: 311

[View online review abstract](#)

Comparison	Neurotropic pathogen levels in people with bipolar disorder.
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Summary of evidence	Moderate to high quality evidence (large sample, some inconsistency, mostly precise, direct) finds a small increase in toxoplasma gondii antibodies in people with bipolar disorder who are < 40 years, with no differences in herpesviruses antibodies.
Herpesviruses	
<i>There were no significant differences between groups;</i>	
Herpes simplex virus-1: 7 studies, N = 2,671, OR = 0.92, 95%CI 0.73 to 1.14, $p = 0.44$, $I^2 = 18%$, $p > 0.05$	
Herpes simplex virus-2: 5 studies, N = 1,756, OR = 1.22, 95% CI 0.86 to 1.75, $p = 0.25$, $I^2 = 17%$, $p > 0.05$	
Cytomegalovirus: 9 studies, N = 2,948, OR = 1.19, 95%CI 0.85 to 1.64, $p = 0.30$, $I^2 = 56%$, $p < 0.02$	
Toxoplasma gondii	
<i>There were no significant differences between groups;</i>	
11 studies, N = 6,834, OR = 1.40, 95%CI 0.95 to 1.90, $p = 0.09$, $I^2 = 72%$, $p < 0.001$	
<i>However, subgroup analysis found significant increase in toxoplasma gondii in studies with a mean age < 40 years (small effect);</i>	
< 40yrs: 5 studies, N = 1,839, OR = 1.78, 95%CI 1.09 to 2.89, $p = 0.02$, $I^2 = 0%$, $p > 0.05$	
> 40yrs: 5 studies, N = 2,412, OR = 1.12, 95%CI 0.71 to 1.77, $p = 0.64$, $I^2 = 82%$, $p < 0.05$	
Consistency in results	Consistent for herpes simplex virus-1 and -2, and for < 40yrs subgroup analysis.
Precision in results	Precise for herpes simplex virus-1 only.
Directness of results	Direct

Sutterland AL, Fond G, Kuin A, Koeter MWJ, Lutter R, van Gool T, Yolken R, Szoke A, Leboyer M, de Haan L

Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis

Acta Psychiatrica Scandinavica 2015; 132: 161-179

[View review abstract online](#)

Comparison	Toxoplasma gondii antibodies in people with bipolar disorder vs. controls.
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Summary of evidence	Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests small effect of increased markers for <i>Toxoplasma gondii</i> in people with bipolar disorder.
<i>Toxoplasma gondii</i> antibodies	
<p><i>A significant, small effect of increased markers for <i>Toxoplasma gondii</i> in people with bipolar disorder;</i></p> <p>11 studies, N = 16,997, OR = 1.52, 95%CI 1.06 to 2.18, $p = 0.024$, $I^2 = 67%$, p not reported</p> <p>Authors report no evidence of publication bias.</p>	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = degree of heterogeneity across study results not explained by chance, N = number of participants, OR = odds ratio, p = probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus.

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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 that 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 small⁶.

† 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 that are correctly identified

(100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that 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 randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that 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 medium effect, and 0.8 and over represents a large treatment effect⁶.

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, an 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. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if $RR > 2$ or < 0.5 and a large effect if $RR > 5$ or < 0.2 ⁷. InOR stands for logarithmic OR where a InOR 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 are an indication of

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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. Unstandardised (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. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that 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 substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

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

§ 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, this criteria should be relaxed⁸.

|| 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 that 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 so is 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.

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