TECHNICAL COMMENTARY

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Heart disease

Introduction

People with bipolar disorder show increased rates of co-occurring conditions compared to people without bipolar disorder. Heart disease is a common co-occurring disorder. It is unclear if the increased risk of heart disease is a consequence of the metabolic impact of medications or unhealthy lifestyle choices, or most likely, a combination of both.

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 2010 that report results separately for people with bipolar or related disorder. Reviews were identified by searching MEDLINE, EMBASE and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and/or comprehensive review was included. Reviews with pooled data are given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. Reviews rated as having 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 randomized 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 criteria[3-5].

- Moderate quality evidence suggests small increases in cardiovascular disease, congestive heart failure, and death due to cardiovascular disease in people with bipolar disorder. Results were adjusted for other variables that may have explained these associations.
- Moderate to low quality evidence also suggests a large effect of reduced heart rate variability.
- High quality evidence suggests no differences in rates of myocardial infarction between people with or without bipolar disorder.

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Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, Thapa-Chhetri N, Fornaro M, Gallicchio D, Collantoni E, Pigato G, Favaro A, Monaco F, Kohler C, Vancampfort D, Ward PB, Gaughran F, Carvalho AF, Stubbs B

Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls

World Psychiatry 2017; 16: 163-80

View review abstract online

Comparison	**Cardiovascular disease in people with bipolar disorder vs. people without bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent and imprecise, direct) suggests significant increases in cardiovascular disease, congestive heart failure, and death as a result of cardiovascular disease in people with bipolar disorder, with results adjusted for other variables that may have explained these associations.**

Cardiovascular disease

A small, significant increase in cardiovascular disease was found in people with bipolar disorder in unadjusted and adjusted longitudinal data (adjusted for other potential explanatory variables), and in unadjusted, but not adjusted cross-sectional data;

Longitudinal studies

Unadjusted: 12 studies, N = 1,098,899, RR = 1.50, 95%CI 1.28 to 1.75, $p < 0.0001$, $I^2 = 76\%$

Adjusted: 10 studies, N = 7,058,915, HR = 1.57, 95%CI 1.28 to 1.93, $p < 0.0001$, $I^2 = 91\%$

Cross-sectional studies

Unadjusted: 4 studies, N = 1,545,672, OR = 1.73, 95%CI 1.11 to 2.71, $p = 0.02$, $I^2 = 91\%$

Adjusted: 4 studies, N = 1,425,775, OR = 1.28, 95%CI 0.90 to 1.80, $p = 0.17$, $I^2 = 52\%$

Death due to cardiovascular disease

A small, significant increase in death due to cardiovascular disease was found in people with bipolar disorder in adjusted, but not in unadjusted longitudinal data;

Longitudinal studies

Unadjusted: 5 studies, N = 393,442, RR = 1.31, 95%CI 0.94 to 1.83, $p = 0.11$, $I^2 = 75\%$

Adjusted: 3 studies, N = 179,651, HR = 1.65, 95%CI 1.10 to 2.47, $p = 0.02$, $I^2 = 88\%$

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Coronary heart disease
A small, significant increase in coronary heart disease was found in people with bipolar disorder in unadjusted longitudinal and cross-sectional data, but not in adjusted data; Longitudinal studies Unadjusted: 4 studies, N = 9,255,482, RR = 1.95, 95%CI 1.20 to 3.17, $p = 0.007$, $I^2 = 96\%$ Adjusted: 4 studies, N = 6,808,812, HR = 1.16, 95%CI 0.76 to 1.78, $p = 0.49$, $I^2 = 87\%$ Cross-sectional studies Unadjusted: 3 studies, N = 1,544,275, OR = 1.75, 95%CI 1.11 to 2.77, $p = 0.02$, $I^2 = 94\%$ Adjusted: 1 study, N = 1,424,378, OR = 1.06, 95%CI 0.85 to 1.31, $p = 0.49$, $I^2 = N/A$
Congestive heart failure
A large, significant increase in congestive heart failure was found in people with bipolar disorder in unadjusted and adjusted longitudinal data, and a small effect was found in unadjusted, but not adjusted cross-sectional data; Longitudinal studies Unadjusted: 1 study, N = 2,418,067, RR = 11.52, 95%CI 9.37 to 23.14, $p < 0.0001$, $I^2 = N/A$ Adjusted: 1 study, N = 1,397, HR = 2.27, 95%CI 1.49 to 3.45, $p < 0.0001$, $I^2 = N/A$ Cross-sectional studies Unadjusted: 1 study, N = 1,424,378, OR = 1.38, 95%CI 1.03 to 1.84, $p = 0.03$, $I^2 = N/A$ Adjusted: 1 study, N = 1,424,378, OR = 1.11, 95%CI 0.80 to 1.54, $p = 0.53$, $I^2 = N/A$

Consistency in results	Inconsistent
Precision in results	Mostly imprecise
Directness of results	Direct

Faurholt-Jepsen M, Kessing LV, Munkholm K

Heart rate variability in bipolar disorder: A systematic review and meta-analysis

Neuroscience and Biobehavioral Reviews 73: 68-80

View review abstract online

Comparison	**Heart rate variability in people with bipolar disorder vs. people without bipolar disorder.**

Summary of evidence	**Moderate to low quality evidence (large sample, inconsistent, imprecise, direct, low quality studies) suggests a large effect of reduced heart rate variability in people with bipolar disorder.**
Heart rate variability	
A large, significant effect of reduced heart rate variability in people with bipolar disorder; 10 studies, N = 1,581, *g* = -1.77, 95%CI -2.46 to -1.09, *p* < 0.001 More recent publication year, larger studies and higher study quality were associated with a smaller effect size. Authors report that the studies were generally of low quality and that there was a lack of consideration of potential confounding factors.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Prieto ML, Cuellar-Barboza AB, Bobo WV, Roger VL, Bellivier F, Leboyer M, West CP, Frye MA

Risk of myocardial infarction and stroke in bipolar disorder: a systematic review and exploratory meta-analysis

Acta Psychiatrica Scandinavica 2014; 130: 342-53

View review abstract online

Comparison	**Myocardial infarction in people with bipolar disorder vs. people without bipolar disorder.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests no differences in rates of myocardial infarction between people with bipolar disorder and people without bipolar disorder.**
Myocardial infarction	
No significant differences between groups; 4 studies, N = 13,091,210, RR = 1.09, 95%CI 0.96 to 1.24, *p* = 0.20, I^2 = 6%	

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Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *g* = Hedges *g*, a measure of standardised mean difference, HR = hazard ratio, IRR = incidence rate ratio, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = relative risk, 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 small[6].

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† 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 moderate effect, and 0.8 and over represents a large effect[6].

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 medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[7]. lnOR 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

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between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen 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.

‡ Inconsistency refers to differing estimates of 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 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[6];

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

§ 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[8].

‖ 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 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.

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