TECHNICAL COMMENTARY

Mortality

NeuRA Discover. Conquer. Cure.
BIPOLAR DISORDERS LIBRARY

Introduction

The life expectancy of people with a mental illness may be reduced compared to the general population. The reasons are largely unclear but may in part be related to lifestyle factors such as weight gain, smoking, unhealthy diet and low physical activity. Bipolar disorder may also be associated with increased suicide rates when compared to the general population. This topic assesses the current evidence describing mortality rates in people with bipolar disorder.

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 a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases 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 that describes a preferred way to present a meta-analysis[1]. 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 two systematic reviews that met our inclusion criteria[3, 4].

- Moderate to high quality evidence suggests a medium-sized effect of increased risk of all-cause mortality in people with bipolar disorder compared to population rates.
- There were large effects of increased risk of suicide or other violent death, medium-sized effects of increased risk of death from respiratory disease or infections, and small effects of increased risk of death from cardiovascular disease, circulatory disease or cancer.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Hayes JF, Miles J, Walters K, King M, Osborn DP (2015):

A systematic review and meta-analysis of premature mortality in bipolar affective disorder

Acta Psychiatrica Scandinavica 2015; 131: 417-25

View review abstract online

Comparison	**Rates and causes of mortality in people with bipolar disorder vs. general population rates.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly consistent and precise, direct) suggests a medium-sized effect of increased risk of all-cause mortality in people with bipolar disorder compared to population rates.** **There were large effects of increased risk of suicide or other violent death, medium-sized effects of increased risk of death from respiratory disease or infections, and small effects of increased risk of death from circulatory disease or cancer.**

Mortality

Medium-sized increased risk of all-cause mortality in people with bipolar disorder;

26 studies, N = 220,134, SMR = 2.05, 95%CI 1.89 to 2.23, $p < 0.05$, $I^2 = 96\%$, $p < 0.001$

Heterogeneity could not be explained by year of publication, sample size, decade of data collection, population type or geographical region.

Large increased risk of any unnatural death in people with bipolar disorder;

12 studies, N = 159,434, SMR = 7.42, 95%CI 6.43 to 8.55, $p < 0.05$, $I^2 = 96\%$, $p < 0.001$

Very large increased risk of suicide in people with bipolar disorder;

15 studies, N = 46,756, SMR = 14.44, 95%CI 12.43 to 16.78, $p < 0.05$, $I^2 = 87\%$, $p < 0.001$

Large increased risk of other violent death in people with bipolar disorder;

5 studies, N = 22,641, SMR = 3.68, 95%CI 2.77 to 4.90, $p < 0.05$, $I^2 = 89.5\%$, $p < 0.001$

Small increased risk of any natural death in people with bipolar disorder;

12 studies, N = 159,434, SMR = 1.64, 95%CI 1.47 to 1.83, $p < 0.05$, $I^2 = 98\%$, $p < 0.001$

Medium-sized increased risk of death from respiratory disease in people with bipolar disorder;

5 studies, N = 22,609, SMR = 2.92, 95%CI 2.00 to 4.23, $p < 0.05$, $I^2 = 94\%$, $p < 0.001$

Medium-sized increased risk of death from infections in people with bipolar disorder;

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

5 studies, N = 22,895, SMR = 2.25, 95%CI 1.70 to 3.00, $p < 0.05$, $I^2 = 45\%$, $p = 0.12$ *Small increased risk of death from circulatory disease in people with bipolar disorder;* 14 studies, N = 153,948, SMR = 1.73, 95%CI 1.54 to 1.94, $p < 0.05$, $I^2 = 95\%$, $p < 0.001$ *Small increased risk of death from cancer in people with bipolar disorder;* 10 studies, N = 27,693, SMR = 1.14, 95%CI 1.10 to 1.21, $p < 0.05$, $I^2 = 56\%$, $p = 0.03$	
Consistency in results‡	Inconsistent, apart from infections
Precision in results§	Mostly precise
Directness of results‖	Direct

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	**Death due to cardiovascular disease in people with bipolar disorder vs. people without bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a small, significant increase in the rate of death as a result of cardiovascular disease in people with bipolar disorder, with results adjusted for other variables that may have explained this association.**
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; 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, $p = 0.02$, $I^2 = 88\%$	
Consistency in results	Inconsistent

Mortality

Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, HR = hazard 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, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = risk ratio, SMR = standardised mortality rate

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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.

---

†Different effect measures are reported by different reviews.

Median rate ratio refers to the ratio between prevalence or incidence rates of two groups, based on the median rather than the mean. The median is often used as a better measure of central tendency than the mean when data are skewed. Harmonic means are also used when data are skewed and are appropriate for rate data.

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) 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 medium effect, and 0.8 and over represents a large treatment 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, 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[6]. 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 between variables. They are an 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. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent 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.

Prevalence refers to how many existing cases there are at a particular point in time.

Mortality

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).

‡ 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 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 relaxed[7].

‖ 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Hayes JF, Miles J, Walters K, King M, Osborn DP (2015): A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta Psychiatrica Scandinavica* 131: 417-25.
4. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P*, et al.* (2017): 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* 16: 163-80.
5. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
6. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
7. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au