TECHNICAL COMMENTARY

Predominent polarity

Introduction

Bipolar disorder is characterised by recurrent episodes of depression and mania, hypomania, or mixed symptoms. Some, but not all, people with bipolar disorder show a predominance of either depression or manic episodes.

A major depressive episode is a period of at least two weeks in which a person has at least five of the following symptoms (including one of the first two): intense sadness or despair; feelings of helplessness, hopelessness or worthlessness; loss of interest in activities once enjoyed; feelings of guilt, restlessness or agitation; sleeping too little or too much; slowed speech or movements; changes in appetite; loss of energy; difficulty concentrating, remembering or making decisions; and/or thoughts of death or suicide.

A manic episode is a period of at least one week when a person is high spirited or irritable in an extreme way most of the day for most days. A manic episode involves changes in normal behaviour such as showing exaggerated self-esteem or grandiosity, less need for sleep, talking more than usual, talking more loudly and quickly, being easily distracted, doing many activities at once, scheduling more events in a day than can be accomplished, embarking on risky behaviour, uncontrollable racing thoughts, and/or quickly changing ideas or topics. These changes in behaviour are significant and clear to friends and family and are severe enough to cause major dysfunction.

A hypomanic episode is similar to a manic episode but the symptoms are less severe and need only last four days in a row. Hypomanic symptoms do not lead to the major problems that mania often causes, and the person is still able to function.

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. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. 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 reviews assessing the same topic were found, only the most recent and/or comprehensive review was included.

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 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

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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 mania and depression predominance is similar in studies assessing symptoms retrospectively. However, mania episodes were less prevalent than depression episodes when episodes are measured prospectively over the course of bipolar disorder.
- Factors associated with depression predominance are; type II bipolar disorder, melancholia symptoms, a depressive onset of illness, suicide attempts, mixed episodes, delayed diagnosis of bipolar disorder, and being married.
- Factors associated with mania predominance are; type I bipolar disorder, a mania onset of illness, onset of illness with psychotic features, younger onset of illness, and substance use.

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Carvalho AF, McIntyre RS, Dimelis D, Gonda X, Berk M, Nunes-Neto PR, Cha DS, Hyphantis TN, Angst J, Fountoulakis KN

Predominant polarity as a course specifier for bipolar disorder: a systematic review

Journal of Affective Disorders 2014; 163: 56-64

View review abstract online

Comparison	**Factors associated with predominance of symptoms in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (consistent, direct, large samples, unable to assess precision) suggests mania and depression predominance is similar in studies assessing symptoms retrospectively.** **Factors associated with depression predominance are; type II bipolar disorder, melancholia symptoms, a depressive onset of illness, suicide attempts, mixed episodes, delayed diagnosis of bipolar disorder, and being married.** **Factors associated with mania predominance are; type I bipolar disorder, a mania onset of illness, onset of illness with psychotic features, younger onset of illness, substance use.**
Factors associated with predominance	
19 studies (16 retrospective), N = 77,989 Any predominant polarity: median = 52.7% Mania predominance: median = 26% Depressive predominance: median = 21% *Factors associated with depressive predominance;* Diagnosis of type II bipolar disorder: 4 studies, N = 834 Melancholic symptoms: 2 studies, N = 828 A depressive onset of illness: 4 studies, N = 2233 More suicide attempts: 5 studies, N = 2049 More mixed episodes: 3 studies, N = 1286 Delayed diagnosis of bipolar disorder: 2 studies, N = 1077 Being married: 2 studies, N = 1097	

Factors not associated with depressive predominance; Having a comorbid psychiatric illness: 7 studies, N = 3257 Rapid cycling: 5 studies, N = 3118 *Factors with mixed results;* Female sex: 2 studies, N = 1532, found a relationship, 5 studies, N = 737 found no relationship *Factors associated with mania predominance;* Diagnosis of type I bipolar disorder: 4 studies, N = 1257 A mania onset of illness: 3 studies, N = 2084 Younger onset of illness: 3 studies, N = 1701 More substance use: 2 studies, N = 828 Onset of illness with psychotic features: 2 studies, N = 1532 *Factors not associated with mania predominance;* Having a comorbid psychiatric illness: 7 studies, N = 3257 Rapid cycling: 5 studies, N = 3118 *Factors with mixed results;* Male sex: 1 study, N = 604 found a relationship, 4 studies, N = 2056 found no relationship More hospitalisation: 2 studies, N = 773 found a relationship, 1 study, N = 124 found no relationship

Consistency in results‡	Consistent, apart from female gender.
Precision in results§	Unable to assess; no CIs were reported.
Directness of results‖	Direct

Miller S, Dell'Osso B, Ketter TA

The prevalence and burden of bipolar depression

Journal of Affective Disorders 2014; 169 Suppl 1: S3-11

View review abstract online

Comparison	**Prevalence of depression vs. mania symptoms in people with bipolar disorder, from prospective studies.**
Summary of evidence	**Moderate to high quality evidence (consistent, direct, large sample, unable to assess precision) shows depression symptoms are around three times more prevalent than mania symptoms over**

	the course of bipolar disorder.
Prevalence of depression vs. mania symptoms	
Depressive symptoms were more prevalent over time than mood elevation/mixed symptoms; 5 prospective studies, N = 1,071, follow-up over 1 to 13 years Depression symptoms average = 34.1% over time Mania/elevated/mixed symptoms average = 12.3% over time	
Consistency in results	Authors report data are consistent regardless of study location or methodology.
Precision in results	Unable to assess; confidence intervals were not reported.
Directness of results	Direct

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 tath 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].

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† Different effect measures are reported by different reviews.

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 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.

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).

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.

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‡ 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[5];

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

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§ 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 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.

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