TECHNICAL COMMENTARY

Depression

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Introduction

Bipolar disorder is characterised by recurrent episodes of depression and mania, hypomania, or mixed symptoms. 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.

Long-term studies have found that depressive symptoms are usually more pervasive than mood elevation or mixed symptoms. Depressive symptoms have also been consistently associated with greatest impairments in social and occupational functioning.

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 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 six systematic reviews that met our inclusion criteria[3-8].

- High quality evidence shows early age of onset is associated with increased severity of depression in people with bipolar disorder.

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

Depression

- Moderate to high quality evidence shows depression episodes are around three times more predominant than mania, elevated, or mixed episodes over the course of bipolar disorder (1-13 years). In studies measuring predominance retrospectively, the rates of depression and mania episodes are similar.
- 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.
- Moderate quality evidence suggests the clinical features associated more often with bipolar depression than unipolar depression in children or youth include; more psychiatric comorbidities and behavioural problems (oppositional disorder, conduct disorder, anxiety disorders, irritability, suicidal/self-harm, social impairment, and substance use); earlier onset of mood symptoms; more severe depression; and having a family history of psychiatric illness.
- Moderate to low quality evidence suggests the cumulative rate of conversion from unipolar depression to bipolar disorder increases from 3.78% at 1-year assessment to 12.87% at 10-year assessment. The yearly rate of conversion from unipolar depression to bipolar disorder decreases from 3.83% at 1-year assessment to 0.78% at 10-year assessment.
- Moderate quality evidence finds no differences in levels of anhedonia (reduced capacity for pleasure) between people with bipolar disorder and people without a mental illness. Levels of anhedonia were higher only in people with schizophrenia, major depression (not remitted), substance use, and Parkinson's disease.

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

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	**Predominance of depression vs. mania episodes in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (consistent, direct, large samples, unable to assess precision) suggests depression and mania episode 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.**

Depressive episode polarity

19 studies (16 retrospective), N = 77,989

Any predominant polarity: median = 53%

Depressive predominance: median = 21%

Mania predominance: median = 26%

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 with mixed results;

Female sex: 2 studies, N = 1532, found a relationship, 5 studies, N = 737 found no relationship

Factors not associated with depressive predominance;

Having a comorbid psychiatric illness: 7 studies, N = 3257 Rapid cycling: 5 studies, N = 3118	
Consistency in results‡	Consistent, apart from female sex.
Precision in results§	Unable to assess; no CIs reported.
Directness of results‖	Direct

Joslyn C, Hawes DJ, Hunt C, Mitchell PB

Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review

Bipolar Disorders 2016; 18: 389-403

View review abstract online

Comparison	**Relationship between age at onset and depression severity in people with bipolar disorder.**
Summary of evidence	**High quality evidence (consistent, precise, direct, large sample) shows early age of onset is associated with increased severity of depression.**
Age of onset and depression symptoms	
Significant, medium-sized effect of early age of onset and increased depression severity; More severity depression: 3 studies, N = 1,076, g = 0.42, 95%CI 0.30 to 0.55, $p < 0.001$, $I^2 = 0\%$	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Kessing LV, Willer I, Andersen PK, Bukh JD

Rate and predictors of conversion from unipolar to bipolar disorder: A systematic review and meta-analysis

Bipolar Disorders 2017; 19: 324-35

View review abstract online	
Comparison	**Conversion rates over time from unipolar depression to bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (large sample, direct, unable to assess consistency or precision) suggests the cumulative rate of conversion from unipolar depression to bipolar disorder increases from 3.78% at 1 year assessment to 12.87% at 10 year assessment.** **The yearly rate of conversion from unipolar depression to bipolar disorder decreases from 3.83% at 1 year assessment to 0.78% at 10 year assessment.**
Conversion rates	
11 studies, N = 77,066 *The cumulative risk of conversion increased, and the yearly rate of conversion decreased over time;* 1 year cumulative % = 3.78, 2 year cumulative % = 6.74, 5 year cumulative % = 9.41, 10 year cumulative % = 12.87 1 year rate = 3.85%, 1-2 year rate = 3.13%, 2-5 year rate = 0.97%, 5-10 year rate = 0.78% Authors report no consistent associations between conversion rates and having a family history of bipolar disorder, or younger age at first depression diagnosis. Authors report no evidence of publication bias.	
Consistency in results	No measure of consistency is reported.
Precision in results	Unable to assess.
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 mania vs. depression episodes in people with bipolar disorder assessed over time.**
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/elevated or mixed symptoms over the course of bipolar disorder (1-13 years).
Prevalence of mania vs. depression 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 Mania/elevated/mixed symptoms: mean = 12.3% of the time Depression symptoms: mean = 34.1% of the 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

Trostheim M, Eikemo M, Meir R, Hansen I, Paul E, Kroll SL, Garland EL, Leknes S

Assessment of Anhedonia in Adults with and without Mental Illness: A Systematic Review and Meta-analysis

JAMA Network Open 2020; 3: e2013233

View review abstract online

Comparison	**Anhedonia in people with bipolar disorder vs. people without a mental illness.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) finds no differences in levels of anhedonia between people with bipolar disorder and people without a mental illness. Levels of anhedonia were higher only in people with schizophrenia, major depression (not remitted), substance use, and Parkinson's disease.**
Anhedonia **Measured using the Snaith-Hamilton Pleasure Scale**	
There were no differences in anhedonia between people with bipolar disorder and people without a mental illness; 5 studies, N = 477, g = 0.40, 95%CI -0.20 to 1.00, $p > 0.05$, I^2 = 87% Authors report increased anhedonia in people with schizophrenia, major depression, substance	

use, and Parkinson's disease (compared to no mental illness).	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Uchida M, Serra G, Zayas L, Kenworthy T, Faraone SV, Biederman J

Can unipolar and bipolar pediatric major depression be differentiated from each other? A systematic review of cross-sectional studies examining differences in unipolar and bipolar depression

Journal of Affective Disorders 2015; 176: 1-7

View review abstract online

Comparison	**Clinical differences in children and adolescents with unipolar depression vs. bipolar depression.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, unable to assess precision, direct) suggests the clinical features associated more often in children or youth with bipolar depression than in children or youth with unipolar depression include; more psychiatric comorbidities and behavioural problems (oppositional disorder, conduct disorder, anxiety disorders, irritability, suicidal/self-harm, social impairment, and substance use); earlier onset of mood symptoms; more severe depression; and having a family history of psychiatric illness.**

Clinical features

4 studies, N = 1,476

3/4 studies found significantly higher rates of psychiatric comorbidities in children/youth with bipolar disorder, including oppositional defiant disorder, conduct disorder, anxiety disorders, and substance use (in adolescents only).

3/4 studies found significantly higher rates of first degree relatives with any psychiatric illness in children/youth with bipolar disorder.

3/4 studies found significantly earlier onset of mood symptoms in children/youth with bipolar disorder.

2/4 studies found significantly greater severity, and more frequent episodes, of depression in children/youth with bipolar disorder.

2/4 studies found significantly more sadness, aggression, irritability, hopelessness, and suicidal or

self-injurious behaviors in children/youth with bipolar disorder. 2/4 studies found significantly higher level of impairment, including difficulties with peers and family members, and severe behavioral problems in school in children/youth with bipolar disorder.	
Consistency in results	Results appear inconsistent.
Precision in results	Unable to assess; no CIs are reported
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, Hedges' *g* = standardised mean differences, 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), vs. = versus

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 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[9].

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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[9].

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[10]. 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.

‡ 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[9];

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

§ 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 relaxed[11].

‖ 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

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