TECHNICAL COMMENTARY

Mixed states

Introduction

Bipolar disorder is characterised by recurrent episodes of depression and mania or hypomania. Some people with bipolar disorder also show episodes of mixed states. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines mixed states as having three or more manic or hypomanic symptoms within a depressive episode, or depressive symptoms within a manic or hypomanic episode.

A 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

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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 four systematic reviews that met our inclusion criteria[3-6].

- Moderate quality evidence suggests the prevalence of mixed states in people with bipolar disorder is around 35%, which is significantly more prevalent than in people with major depression (around 24%).
- Moderate quality evidence finds the prevalence of mixed states in children with bipolar disorder is around 55%. There were high rates of comorbidities in these children, particularly ADHD, oppositional defiant disorder, and anxiety disorders.
- Moderate quality evidence finds the prevalence of mixed states during hypomania is around 27% and the prevalence of mixed states during bipolar depression is around 18%.
- Moderate quality evidence finds small to medium-sized increases in unemployment, rapid cycling, anxiety disorders, and a history of suicide attempts in people with bipolar disorder with mixed features compared to those without mixed features. These clinical correlates were particularly apparent in people in a hypo/manic episode, along with less severe mania and less family history of bipolar disorders.

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Bartoli F, Crocamo C, Carra G

Clinical correlates of DSM-5 mixed features in bipolar disorder: A meta-analysis

Journal of Affective Disorders 2020; 276: 234-40

View review abstract online

Comparison	**Correlation between clinical features in people with bipolar disorder and mixed states vs. people with bipolar disorder without mixed states.**
Summary of evidence	**Moderate quality evidence (large samples, some inconsistency, imprecise, direct) finds small to medium-sized increases in unemployment, rapid cycling, anxiety disorders, and a history of suicide attempts in people with bipolar disorder with mixed features compared to those without mixed features. These clinical correlates were particularly apparent in people in a hypo/manic episode, along with less severe mania and less family history of bipolar disorders.**

Clinical correlates of mixed states

Small to medium-sized effects of higher rates of the following clinical correlates in people with bipolar disorder with mixed features;

More unemployment: 4 studies, N = 1,026, OR = 0.65, 95%CI 0.47 to 0.90, $p < 0.05$, $I^2 = 0\%$

Rapid cycling: 3 studies, N = 653, OR = 2.89, 95%CI 1.30 to 6.45, $p < 0.05$, $I^2 = 0\%$

Anxiety disorders: 4 studies, N = 1,443, OR = 1.81, 95%CI 1.14 to 2.88, $p < 0.05$, $I^2 = 55\%$

History of suicide attempts: 7 studies, N = 2,768, OR = 1.77, 95%CI 1.09 to 2.90, $p < 0.05$, $I^2 = 79\%$

There were no associations with age, gender, marital status, age at onset, symptom severity, family history of bipolar disorder, comorbid substance use disorders, co-occurring psychotic features, or medication status.

Subgroup analysis of current mood state showed people with bipolar disorder with mixed features who were currently in a hypo/manic episode reported more rapid cycling, anxiety disorders, history of suicide attempts, less severe mania, and less family history of bipolar disorders. The only clinical correlate found in people with bipolar disorder with mixed features currently in a depressive episode was more unemployment.

Consistency in results	Inconsistent for anxiety and suicide attempts.
Precision in results	Imprecise
Directness of results	Direct

Janiri D, Conte E, De Luca I, Simone MV, Moccia L, Simonetti A, Mazza M, Marconi E, Monti L, Chieffo DPR, Kotzalidis G, Janiri L, Sani G

Not only mania or depression: Mixed states/mixed features in paediatric bipolar disorders

Brain Sciences 2021; 11: 434

View review abstract online

Comparison	**Prevalence of mixed states in children with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, appears inconsistent and imprecise, direct) finds the prevalence of mixed states in children with bipolar disorder is around 55%. There were high rates of comorbidities in these children, particularly ADHD, oppositional defiant disorder, and anxiety disorders.**
Prevalence of mixed states in children	
Around half of children with bipolar disorder report mixed states; 11 studies, N = 1,365, prevalence = 55.2%, 95%CI 40.10% to 70.3% There were high rates of comorbidities in children with bipolar disorder and mixed states, particularly ADHD, oppositional defiant disorder, and anxiety disorders.	
Consistency in results	Appears inconsistent
Precision in results	Appears imprecise
Directness of results	Direct

Na KS, Kang JM, Cho SE

Prevalence of DSM-5 mixed features: A meta-analysis and systematic review

Journal of Affective Disorders 2021; 282: 203-10

View review abstract online

Comparison	**Prevalence of mixed states in people with bipolar disorder during a hypo/manic episode and during a depressive episode.**

Summary of evidence	**Moderate quality evidence (large sample, appears inconsistent and imprecise, direct) finds the prevalence of mixed states during hypomania is around 27% and the prevalence of mixed states during bipolar depression is around 18%.**
Prevalence of mixed states	
Rates of mixed states in people with bipolar disorder; Hypo/manic: 8 studies, N = 5,151, prevalence = 26.8%, 95%CI 17.0% to 39.5%, I^2 not reported Bipolar depression: 7 studies, N not reported, prevalence = 18.2%, 95%CI 11.4% to 27.8%, I^2 = 97%	
Consistency in results	Inconsistent
Precision in results	Appears imprecise
Directness of results	Direct

Vazquez GH, Lolich M, Cabrera C, Jokic R, Kolar D, Tondo L, Baldessarini RJ

Mixed symptoms in major depressive and bipolar disorders: A systematic review

Journal of Affective Disorders 2018; 225: 756-60

View review abstract online

Comparison	**Prevalence of mixed states in people with bipolar disorder vs. major depressive disorder.**
Summary of evidence	**Moderate quality evidence (inconsistent, imprecise, direct, large sample) suggests the prevalence of mixed states in people with bipolar disorder is around 35%, which is significantly more prevalent than in people with major depression (around 24%).**
Prevalence of mixed states	
A small, significant effect of higher rates of mixed states in people with bipolar disorder; 17 studies, N = 19,198, RR = 1.59, 95%CI 1.27 to 2.00, $p < 0.0001$, I^2 = 84% Prevalence in bipolar disorder = 35% Prevalence in major depressive disorder = 24%	
Consistency in results	Inconsistent

Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

ADHD = attention deficit hyperactivity disorder, CI = confidence interval, 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 = risk ratio, vs. = versus

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[7].

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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[7].

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[8]. 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[7];

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

§ 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[9].

‖ 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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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. Vazquez GH, Lolich M, Cabrera C, Jokic R, Kolar D, Tondo L*, et al.* (2018): Mixed symptoms in major depressive and bipolar disorders: A systematic review. *Journal of Affective Disorders* 225: 756-60.
4. Bartoli F, Crocamo C, Carra G (2020): Clinical correlates of DSM-5 mixed features in bipolar disorder: A meta-analysis. *Journal of Affective Disorders* 276: 234-40.
5. Na KS, Kang JM, Cho SE (2021): Prevalence of DSM-5 mixed features: A meta-analysis and systematic review. *Journal of Affective Disorders* 282: 203-10.
6. Janiri D, Conte E, De Luca I, Simone MV, Moccia L, Simonetti A*, et al.* (2021): Not only mania or depression: Mixed states/mixed features in paediatric bipolar disorders. *Brain Sciences* 11: 434.
7. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
8. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
9. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*

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