TECHNICAL COMMENTARY

Mood cycling

Introduction

Bipolar disorder is characterised by recurrent episodes of depression and mania or hypomania. The duration of mood episodes varies between patients, from several days to several months, with usually a period of remission in between. The frequency of mood changes (cycling) also varies between patients, with four or more episodes per year classified as rapid cycling.

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

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].

- High quality evidence suggests less treatment response in people with continuous cycling bipolar disorder compared to people without continuous cycling.

- Moderate to low quality evidence suggests the mean annual prevalence of rapid cycling in people with bipolar disorder is around 18%, and the lifetime prevalence is around 31%, indicating rapid cycling is a transitory phenomenon. Factors associated with rapid cycling include longer course of illness, earlier age at onset, substance use, and suicidality.

- Moderate quality evidence suggests manic episodes peak during spring/summer and, to a lesser extent, in autumn. Depressive episodes peak in early winter and, to a lesser extent, in summer. Mixed episodes peak in early spring or mid/late summer.

- Moderate to low quality evidence suggests there are menstrual cycle-related mood changes in 44% to 68% of women with bipolar disorder. 25% to 77% of women with bipolar disorder met the criteria for premenstrual syndrome, and 15% to 27% met the criteria for premenstrual dysphoric disorder.

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Carvalho AF, Dimellis D, Gonda X, Vieta E, McLntyre RS, Fountoulakis KN

Rapid cycling in bipolar disorder: a systematic review

Journal of Clinical Psychiatry 2014; 75: e578-86

View review abstract online

Comparison	Prevalence and features associated with rapid cycling in bipolar disorder.
Summary of evidence	Moderate to low quality evidence (large sample, direct, unable to assess consistency or precision) suggests the mean annual prevalence of rapid cycling in people with bipolar disorder is around 18%, and the lifetime prevalence is around 31%, indicating rapid cycling is a transitory phenomenon. Factors associated with rapid cycling include longer course of illness, earlier age at onset, substance use, and suicidality.

Prevalence and factors relating to rapid cycling
110 studies, N ~9,000 *Rapid cycling is related to;* Longer course of illness Earlier age at onset Drug and alcohol abuse Increased suicidality Mean annual prevalence rate of rapid cycling among bipolar patients is around 18%, and the lifetime prevalence rate is around 31%. Authors conclude that rapid cycling is a transitory phenomenon rather than a stable pattern.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Geoffroy PA, Bellivier F, Scott J, Etain B

Seasonality and bipolar disorder: a systematic review, from admission rates to seasonality of symptoms

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Journal of Affective Disorders 2014; 168: 210-23	
View review abstract online	
Comparison	**Relationship between seasonality and bipolar mood changes.**
Summary of evidence	**Moderate quality evidence (large sample, direct, consistent, unable to assess precision) suggests manic episodes peak during spring/summer and, to a lesser extent, in autumn. Depressive episodes peak in early winter and, to a lesser extent, in summer. Mixed episodes peak in early spring or mid/late summer.**
Seasonality	
51 studies, over 100,000 participants Manic episodes peaked during spring/summer and, to a lesser extent, in autumn. Depressive episodes peaked in early winter and, to a lesser extent, in summer. Mixed episodes peaked in early spring or mid/late summer.	
Consistency in results	Authors report results are consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Teatero ML, Mazmanian D, Sharma V **Effects of the menstrual cycle on bipolar disorder** **Bipolar Disorders 2014; 16: 22-36** View review abstract online	
Comparison	**Relationship between seasonality and bipolar mood changes.**
Summary of evidence	**Moderate to low quality evidence (large sample, direct, unable to assess consistency or precision) suggests there are menstrual cycle-related mood changes in 44% to 68% of women with bipolar disorder. 25% to 77% of women with bipolar disorder met the criteria for premenstrual syndrome, and 15% to 27% met the criteria for premenstrual dysphoric disorder.**
Seasonality	
11 prospective studies (N = 686) found menstrual cycle-related mood changes were reported in 44% to 65% of women with bipolar disorder.	

10 retrospective studies (N = 2,559) found menstrual cycle-related mood changes were reported by 64% to 68% of women with bipolar disorder. 25% to 77% of women with bipolar disorder met the criteria for premenstrual syndrome, and 15% to 27% met the criteria for premenstrual dysphoric disorder.	
Consistency in results	Authors report results are consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Tundo A, De Crescenzo F, Gori D, Cavalieri P

Long-term treatment response to continuous cycling course in bipolar disorders: A meta-analysis

Journal of Affective Disorders 2018; 241: 367-70

View review abstract online

Comparison	**Long-term (1+ years) treatment response in people with bipolar disorder and continuous mood cycling vs. no continuous mood cycling.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests less treatment response in people with continuous cycling bipolar disorder.**
Treatment response	
A significant effect of less treatment response in people with continuous cycling bipolar disorder; 6 studies, N = 671, RD = -0.17, 95%CI -0.25 to -0.09, *p* < 0.0001, I^2 = 3% Continuous cycling: response rate = 34.0%, no continuous cycling: response rate = 49.3%	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I² = 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), RD = risk difference, 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 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. I² 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. I² 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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