TECHNICAL COMMENTARY

First-episode bipolar disorder

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Introduction

The onset of bipolar disorder can be hard to identify, as early symptoms may be difficult to distinguish from normal mood fluctuations. Correct diagnosis and treatment is important because untreated illness may have an inherently 'toxic' effect, contributing to psychological deterioration and poor prognosis. An initial diagnosis of bipolar disorder usually follows the first distinct episode of mania, but may come after a long period of inappropriate treatments for other mood disorders.

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 for people with bipolar and 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 reviews assessing the same topic were found, only the most recent and comprehensive reviews were included. Reviews with pooled data are prioritised 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 matters 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 the mean interval between onset of symptoms of bipolar disorder and management of the disorder is around 6 years. Early age of onset of symptoms and bipolar II vs. bipolar I disorder were associated with longer treatment delays.
- Moderate to low quality evidence finds the rates of symptom and functioning improvement and rates of relapse following a first hospitalisation for bipolar disorder vary widely between studies. For symptom improvement, sample rates varied between 26% and 98%, for functioning improvement, sample rates varied between 35% and 87%, and for relapse, sample rates varied between 21% and 74%.

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Dagani J, Signorini G, Nielssen O, Bani M, Pastore A, Girolamo GD, Large M

Meta-analysis of the Interval between the Onset and Management of Bipolar Disorder

Canadian Journal of Psychiatry 2017; 62: 247-58

View review abstract online

Comparison	**Time between age of onset and age of treatment in people with first-episode bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests the mean interval between onset of bipolar disorder and treatment is around 6 years. Factors associated with longer treatment delays include; early onset of symptoms and bipolar II disorder.**

Duration of untreated illness

The interval between the onset of bipolar disorder and its management was ~6 years;

27 studies, N = 9,415, mean = 5.8 years, 95%CI 4.8 to 6.8 years

The following factors accounted for some of the heterogeneity observed;

Studies with an earlier mean age of symptom onset and studies with a higher proportion of people with bipolar II disorder had a longer interval.

Studies reporting the age of symptom onset defined by an episode of bipolar disorder reported a longer interval than studies reporting first symptoms, and studies that reported the onset of symptoms had a longer interval than studies that used less well specified definitions of illness onset.

Studies reporting age at first diagnosis reported a longer interval than studies reporting first hospitalisation, and studies reporting age at first hospitalisation reported a longer interval than studies recording age at first treatment.

Studies that used a defined method, such as a life chart approach (collection of retrospective and prospective data recorded by a patient or a clinician) to ascertain onset of bipolar disorder reported a longer interval between onset and management than studies that did not specify how onset was ascertained. More recently published studies reported a longer interval.

There were no differences in effect size according to;

Proportion of males, proportion of patients with substance or alcohol use disorder, method of diagnosis or study reporting quality.

Consistency in results‡	Authors report the data are inconsistent.
Precision in results§	Appears precise.
Directness of results‖	Direct

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McMurrich S, Sylvia LG, Dupuy JM, Peckham AD, Peters AT, Deckersbach T, Perlis R H

Course, outcomes, and psychosocial interventions for first-episode mania

Bipolar Disorders 2012; 14: 797-808

View review abstract online

Comparison	**Symptoms, functioning and relapse after a first hospitalisation for bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (small samples, appears inconsistent, unable to assess precision, direct) suggests rates of symptom and functioning improvement, and relapse rates vary widely between studies. For symptoms, rates varied between 26 and 98%, for functioning rates varied between 35% and 87%, and for relapse, rates varied between 21% and 74%.**
Symptoms, functioning and relapse	
1 study (N = 166), found 98% of the sample had syndromic recovery, 72% had symptom recovery, and 43% had functional recovery by 2 years. 20% of the sample had relapsed to mania or depression by 4 years, and 19% had a phase switch with no recovery by 4 years. 1 study (N = 71) found 85% of the sample had syndromic recovery, 43% had symptom recovery, 39% had functional recovery, and 52% had relapsed by 12 months. 1 study (N = 109) found 56% of the sample had syndromic recovery, 35% had symptom recovery, and 35% had functional recovery by 12 months. 1 study (N = 24) found 79% of the sample had syndromic recovery by 6 months and 26% by 4 years, 79% had functional recovery by 6 months and 87% by 4 years, and 21% had relapsed by 6 months and 74% by 4 years.	
Consistency in results	Unable to assess; appears inconsistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, N = number of participants, vs. = versus

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Explanation of technical terms

*Bias has the potential to affect reviews of both RCT and 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[5].

† Different effect measures are reported by different reviews.

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. 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).

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 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

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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.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) which 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 (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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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. Dagani J, Signorini G, Nielssen O, Bani M, Pastore A, Girolamo GD*, et al.* (2017): Meta-analysis of the Interval between the Onset and Management of Bipolar Disorder. *Canadian Journal of Psychiatry* 62: 247-58.
4. McMurrich S, Sylvia LG, Dupuy JM, Peckham AD, Peters AT, Deckersbach T*, et al.* (2012): Course, outcomes, and psychosocial interventions for first-episode mania. *Bipolar Disorders* 14: 797-808.
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*.