TECHNICAL COMMENTARY

Age at illness onset

Introduction

Age of onset of bipolar disorder varies between around 18 and 30 years. Differences observed in the age of onset may be influenced by genetic or environmental risk factors, or sex. Understanding the factors that impact on age at the onset of symptoms could lead to better understanding of the risk factors for the disorder and earlier and improved intervention strategies for patients.

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 a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. Reviews with pooled data were given priority for inclusion. When multiple copies of reviews assessing the same topic were found, only the most recent 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 rated as having < 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 matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are 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 one review that met inclusion criteria[3].

- High quality evidence shows early age of onset was associated with increased severity of depression.

- Moderate to high quality evidence suggests early age of onset was associated with having a comorbid personality disorder and longer delay to treatment.

- Moderate quality evidence suggests early age of onset was associated with suicide attempts, comorbid anxiety disorder, substance use disorder, and alcohol use disorders.

- There were no associations between early age of onset and severity of mania symptoms, first polarity of mania, psychotic symptoms, rapid cycling or mixed bipolar episodes.

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	Symptom severity, prognosis and clinical features associated with age at onset.
Summary of evidence	**High quality evidence (consistent, precise, direct, large sample) shows early age of onset was associated with increased severity of depression.**
	Moderate to high quality evidence (inconsistent or imprecise, direct, large samples) suggests early age of onset was associated with having a comorbid personality disorder and longer delay to treatment.
	Moderate quality evidence (inconsistent and imprecise, direct, large samples) suggests early age of onset was associated with suicide attempts, comorbid anxiety disorder, substance use disorder, and alcohol use disorders.
	There were no associations between early age of onset and severity of mania symptoms, first polarity of mania, psychotic symptoms, rapid cycling or mixed bipolar episodes.

Symptom severity, prognosis and clinical features

Significant, small to medium-sized effects of early age of onset with the following factors;

Attempted suicide: 6 studies, N = 4,045, OR = 1.68, 95%CI 1.29 to 2.18, $p < 0.001$, $I^2 = 58\%$

Severe depression: 3 studies, N = 1,076, g = 0.42, 95%CI 0.30 to 0.55, $p < 0.001$, $I^2 = 0\%$

Longer delay to treatment: 3 studies, N = 1,415, g = 0.39, 95%CI 0.15 to 0.64, $p < 0.001$, $I^2 = 76\%$

Anxiety disorder: 10 studies, N = 4,841, OR = 1.72, 95%CI 1.34 to 2.19, $p < 0.001$, $I^2 = 64\%$

Personality disorders: 4 studies, N = 1,746, OR = 2.34, 95%CI 1.85 to 2.95, $p < 0.001$, $I^2 = 0\%$

Substance use disorder: 10 studies, N = 4,808, OR = 1.80, 95%CI 1.39 to 2.35, $p < 0.001$, $I^2 = 50\%$

Alcohol use disorder: 9 studies, N = 4,752, OR = 1.35, 95%CI 1.04 to 1.76, $p = 0.023$, $I^2 = 62\%$

No associations were found with severity of mania symptoms, first polarity mania, psychotic symptoms, rapid cycling, or mixed episodes.

Consistency in results	Consistent for severity of depression and personality disorders only.
Precision in results	Precise for severity of depression and delay to treatment only.

Directness of results	Direct

Explanation of acronyms

CI = confidence cnterval, *g* = Hedges's *g,* standardised mean difference, I² = 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)

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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 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[4].

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† Different effect measures are reported by different reviews.

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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[4].

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, a 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. A 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[5]. 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.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an

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indirect 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 independent 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 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 considerable heterogeneity and over this is considerable heterogeneity. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[4];

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

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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, these criteria should be relaxed[6].

‖ 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 and is therefore 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.

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. Joslyn C, Hawes DJ, Hunt C, Mitchell PB (2016): Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review. *Bipolar Disorders* 18: 389-403.
4. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
5. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
6. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*.

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