TECHNICAL COMMENTARY

Age at illness onset

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Introduction

Age at onset of bipolar disorder varies. Differences observed in the age at 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 with detailed literature search, methodology, and inclusion/exclusion criteria that were published in full text, in English, from the year 2010. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Reviews with pooled data are prioritized for inclusion. Reviews reporting fewer than 50% of items on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[1]) checklist have been excluded from the library. The evidence was graded guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach[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 three systematic reviews that met inclusion criteria[3-5].

- Moderate quality evidence suggests the median age at onset of bipolar disorder is around 33 years old.
- Moderate to high quality evidence finds a trimodal distribution, with 45% of people with bipolar disorder showing an early-onset age (~17 years), 35% showing a mid-onset age (~26 years), and 20% showing a late-onset age (~42 years).
- High quality evidence shows younger age at onset was associated with increased severity of depression.
- Moderate to high quality evidence suggests younger age at onset was associated with having a comorbid personality disorder and longer delay to treatment.
- Moderate quality evidence suggests younger age at onset was associated with more suicide attempts, comorbid anxiety disorder, substance use disorder, and alcohol use disorders.
- There were no associations between age at onset and severity of mania symptoms, first polarity of mania, psychotic symptoms, rapid cycling, or mixed bipolar episodes.

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Bolton S, Warner J, Harriss E, Geddes J, Saunders KEA

Bipolar disorder: Trimodal age-at-onset distribution

Bipolar Disorders 2021; 23: 341-56

View review abstract online

Comparison	**Age at onset of bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large sample, some consistency, direct, unable to assess precision) finds a trimodal distribution for the age at onset of bipolar disorder, with 45% showing an early-onset age (~17 years), 35% showing a mid-onset age (~26 years), and 20% showing a late-onset age (~42 years).**
Age at onset	
21 studies, N = 22,981 *14 studies (67%) found a trimodal age at onset distribution;* 45% found an early-onset age = 17.3 years 35% found a mid-onset age = 26 years 20% found a late-onset age = 41.9 years *5 studies (24%) found a bimodal age at onset distribution;* 66% found an early-onset age = 24.3 years 34% found a late-onset age = 46.3 years The remaining two studies had mixed results between trimodal and bimodal.	
Consistency in results	Authors state the findings were reasonably consistent.
Precision in results	Unable to assess; CIs not 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	**Symptom severity, prognosis and clinical features associated with early age at onset.**
Summary of evidence	**High quality evidence (consistent, precise, direct, large sample) shows early age at onset was associated with increased severity of depression. Moderate to high quality evidence (inconsistent or imprecise, direct, large samples) finds early age at onset was associated with having a comorbid personality disorder and longer delay to treatment. Moderate quality evidence (inconsistent and imprecise, direct, large samples) finds early age at onset was associated with suicide attempts, comorbid anxiety disorder, substance use disorder, and alcohol use disorders.** **There were no associations between early age at 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 at 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

Solmi M, Radua J, Olivola M, Croce E, Soardo L, Salazar de Pablo G, Il Shin J, Kirkbride JB, Jones P, Kim JH, Kim JY, Carvalho AF, Seeman MV, Correll CU, Fusar-Poli P

Age at onset of mental disorders worldwide: large-scale meta-analysis of

192 epidemiological studies

Molecular Psychiatry 2021

Link to review abstract

Comparison	**Age of onset of bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency, appears imprecise, direct) suggests the median age at onset of bipolar disorder is around 33 years old.**
Age at onset	
40 population studies Median age at onset = 33 years, IQR 22 to 49 years 14 years: 5.1% 18 years: 13.7% 25 years: 32.0%	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Appears imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *g* = Hedges' *g,* standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IQR = interquartile range, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant)

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[6].

† 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[6].

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[7]. 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

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.

‡ 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. 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 considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[6];

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

§ 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, these criteria should be relaxed[8].

‖ 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

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