TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.

BIPOLAR DISORDERS LIBRARY

Attention Deficit Hyperactivity Disorder

Introduction

Attention deficit hyperactivity disorder (ADHD) is a behavioural disorder characterised by inattention, hyperactivity, and impulsivity. The estimated prevalence in children under 18 years in the general population is around 5%. It is more prevalent in males than in females. ADHD can persist into adulthood with an estimated prevalence of 2.5% of ADHD in the adult general population. The DSM-5 requires that ADHD in adults began in childhood, with inattentive or hyperactive-impulsive symptoms needing to be present before age 12.

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. 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 review topics were found, only the most recent and/or comprehensive review was included. Reviews with pooled data were 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 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 three systematic reviews that met our inclusion criteria[3-5].

- Moderate to high quality evidence finds around 17% of adults with bipolar disorder also have ADHD. Prevalence of ADHD was higher in small than in large studies and was higher in studies from Western Asia (Turkey and Iran) than in studies from America or Europe.
- Conversely, around 8% of adults with ADHD also have bipolar disorder. Prevalence of bipolar disorder was higher in studies using the DSM than the ICD, and in studies from America than studies from Europe or

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Taiwan. Age of bipolar disorder onset occurred earlier in those with ADHD than in those without ADHD.

- Moderate quality evidence finds around 10% of children and youth with ADHD go on to develop bipolar disorder. This represents a large increase in the risk of bipolar disorder in children and youth with ADHD when compared to children and youth without any psychiatric disorder.
- Moderate quality evidence finds a small increased risk of ADHD in people with bipolar disorder compared to people with major depression, and a medium-sized increased risk of ADHD in people with any mood disorder compared to people without any mood disorder. Prevalence of ADHD ranged from 17% in adults with bipolar disorder to 43% in adolescents with bipolar disorder, to 73% in children with bipolar disorder.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Brancati GE, Perugi G, Milone A, Masi G, Sesso G

Development of bipolar disorder in patients with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis of prospective studies

Journal of Affective Disorders 2021; 293: 186-96

View review abstract online

Comparison	**Rates of bipolar disorder in children and youth with ADHD vs. children and youth without a psychiatric disorder.** **Age ranged from 6 to 18 years. Data is gained from longitudinal, prospective studies, with follow-up between 4 and 33 years.**
Summary of evidence	**Moderate quality evidence (large sample size, some inconsistency, imprecise, direct) finds the prevalence of bipolar disorder in children and youth with ADHD is around 10%. This represents a large increase in risk of bipolar disorder in children and youth with ADHD compared to children and youth without a psychiatric disorder.**
Bipolar disorder in ADHD	
Overall prevalence of bipolar disorder in youth and children with ADHD; 10 studies, N = 1,248, prevalence = 10%, 95%CI 0.6% to 15%, I^2 = 82% *A large, significant effect of greater risk of bipolar disorder in children and youth with ADHD than in children and youth without a psychiatric disorder;* 6 studies, N = 1,124, RR = 8.97, 95%CI 4.26 to 18.87, $p < 0.0001$, Qp = 0.9014 There were no moderating effects of age, gender, or follow-up duration.	
Consistency in results‡	Consistent for control analysis, inconsistent for prevalence.
Precision in results§	Imprecise
Directness of results‖	Direct

Sandstrom A, Perroud N, Alda M, Uher R, Pavlova B

Prevalence of attention-deficit/hyperactivity disorder in people with mood

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

disorders: A systematic review and meta-analysis

Acta Psychiatrica Scandinavica 2021; 143: 380-91

View review abstract online

Comparison	**Risk of ADHD in people with bipolar disorder vs. controls, and vs. major depression.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) finds a small effect of greater risk of ADHD in people with bipolar disorder compared to people with major depression, and a medium-sized increased risk of ADHD in people with any mood disorder compared to people without a mood disorder. Prevalence of ADHD ranged from 17% in adults with bipolar disorder to 43% in adolescents with bipolar disorder, to 73% in children with bipolar disorder.**

ADHD in bipolar disorder

Overall prevalence of ADHD in people with bipolar disorder;

92 studies, N = 17,089

Prevalence of ADHD in children with bipolar disorder: 73%, 95%CI 66% to 79%

Prevalence of ADHD in adolescents with bipolar disorder: 43%, 95%CI 35% to 50%

Prevalence of ADHD in adults with bipolar disorder: 17%, 95%CI 95%CI 14% to 20%

A small, significant effect of greater risk of ADHD in people with bipolar disorder than in people with major depression;

11 studies, N = 12,438, RR = 1.72, 95%CI 1.20 to 2.47, $p = 0.003$, $I^2 = 82.80\%$

A medium-sized, significant effect of greater risk of ADHD in people with any mood disorder than in people without a mood disorder;

15 studies, N = 57,934, RR = 3.42, 95%CI 2.81 to 4.16, $p < 0.001$, $I^2 = 59.70\%$

Studies of children with bipolar disorder who had a younger mean age, greater proportion of males, and older editions of DSM reported higher rates of ADHD. Studies of adolescents with bipolar disorder from North America showed higher prevalence rates than studies from the rest of the world.

Consistency in results	Authors report data are inconsistent
Precision in results	Imprecise
Directness of results	Direct

Schiweck C, Arteaga-Henriquez G, Aichholzer M, Edwin Thanarajah S, Vargas-Caceres S, Matura S, Grimm O, Haavik J, Kittel-Schneider S, Ramos-Quiroga JA, Faraone SV, Reif A

Comorbidity of ADHD and adult bipolar disorder: A systematic review and meta-analysis

Neuroscience and Biobehavioral Reviews 2021; 124: 100-23

View review abstract online

Comparison	**Rates of bipolar disorder in adults with lifetime or current ADHD, and rates of lifetime or current ADHD in adults with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds around 17% of adults with bipolar disorder also have ADHD. Prevalence of ADHD was higher in small than large studies and was higher in studies from Western Asia (Turkey and Iran) than in studies from America or Europe. Conversely, around 8% of adults with ADHD also have bipolar disorder. Prevalence of bipolar disorder was higher in studies using the DSM than the ICD, and in studies from America than studies from Europe or Taiwan. Age of bipolar disorder onset occurred earlier in patients with ADHD than in patients without ADHD.**

ADHD and bipolar disorder

71 studies, N = 646,766

Around 17% of adults with bipolar disorder also have ADHD;

17.11%, 95%CI 13.05% to 21.59%

Prevalence was higher in smaller than larger studies, and in studies from Western Asia (Turkey and Iran) than studies from America or Europe (trend effect for Europe).

Around 8% of adults with ADHD also have bipolar disorder;

7.95%, 95%CI 5.31% to 11.06%

Prevalence was higher in studies using the DSM than the ICD, and in studies from America than studies from Europe or Taiwan. Age of bipolar disorder onset occurred earlier in patients with ADHD than in patients without ADHD.

There were no moderating effects of current age, sex, bipolar disorder type (I or II), ADHD diagnosis (lifetime or current).

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

NeuRA Discover. Conquer. Cure.

BIPOLAR DISORDERS LIBRARY

Attention Deficit Hyperactivity Disorder

Consistency in results	Authors report data are inconsistent
Precision in results	Appears precise
Directness of results	Direct

Explanation of acronyms

ADHD = attention deficit hyperactivity disorder, CI = confidence interval, DSM = Diagnostic and Statistical Manual of Mental Disorders, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), ICD = International Classification of Diseases, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = risk ratio, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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. Brancati GE, Perugi G, Milone A, Masi G, Sesso G (2021): Development of bipolar disorder in patients with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis of prospective studies. *Journal of Affective Disorders* 293: 186-96.
4. Sandstrom A, Perroud N, Alda M, Uher R, Pavlova B (2021): Prevalence of attention-deficit/hyperactivity disorder in people with mood disorders: A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica* 143: 380-91.
5. Schiweck C, Arteaga-Henriquez G, Aichholzer M, Edwin Thanarajah S, Vargas-Caceres S, Matura S*, et al.* (2021): Comorbidity of ADHD and adult bipolar disorder: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews* 124: 100-23.
6. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
7. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
8. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*