TECHNICAL COMMENTARY

Childhood bipolar disorder

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Introduction

Roughly 2% of youth under the age of 18 experience bipolar disorder. For 55 to 60% of adults with bipolar disorder, the pathology begins in childhood and adolescence with displays of subthreshold forms or prodromal signs of the disorder. Early age at onset is associated with more severe symptoms and poor prognosis.

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 seven systematic reviews that met our inclusion criteria[3-9].

- Moderate quality evidence suggests the most common mania symptoms reported in youths with bipolar disorder are (in decreasing order); increased energy, irritability, mood lability, distractibility, goal-directed activity, euphoric/elated mood, pressured speech, hyperactivity, racing thoughts, poor judgment, grandiosity, inappropriate laughter, decreased need for sleep, and flight of ideas.
- Moderate quality evidence suggests the clinical features associated more often in children or youth with bipolar depression than in children or youth with unipolar depression include; more psychiatric comorbidities and behavioural problems (oppositional disorder, conduct disorder, anxiety disorders, irritability, suicidal/self-

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harm, social impairment, and substance use); earlier onset of mood symptoms; more severe depression; and having a family history of psychiatric illness.

- Moderate to high quality evidence suggests irritability, aggression, and low insight are more common in youths than adults with bipolar disorder. Odd appearance, grandiosity, flight of ideas, decreased sleep, and increased sexual interest are more common in adults than youths with bipolar disorder. There were no differences in rapid speech, motor features or elevated mood.
- Moderate to high quality evidence suggests having a positive family history of any mood disorder is associated with greater likelihood of switching to mania in children with major depression. Moderate quality evidence suggests having subthreshold symptoms of mania, emotional dysregulation, or behaviour problems are also associated with greater likelihood of switching to mania in children with major depression.
- Moderate to low quality evidence suggests a medium-sized increased risk of suicide ideation in children and adolescents with bipolar disorder.
- Moderate quality evidence suggests around 14% of youth treated with antipsychotics for any diagnosis had bipolar disorder. Among youth with bipolar disorder, 44% were on antipsychotics. There were significant increases in antipsychotic use over time in youth with bipolar disorder, with no increases in antipsychotic use over time in youth with depression.
- For children with subthreshold bipolar symptoms compared to controls, moderate quality evidence found greater severity of functional impairment, mania and depression symptoms, disruptive behaviour, suicidal ideation and attempts, and more mood and substance use disorders. Compared to children with a diagnosis of bipolar disorder, children with subthreshold symptoms showed less severe functional impairment, mania and psychosis symptoms, suicidal ideation and attempts, and less service use.

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Cervesi C, Park SY, Galling B, Molteni S, Masi G, Gerhard T, Olfson M, Correll CU

Extent, time course, and moderators of antipsychotic treatment in youth with mood disorders: Results of a meta-analysis and meta-regression analyses

Journal of Clinical Psychiatry 2017; 78: 347-57

View review abstract online

Comparison	**Rates of bipolar disorder vs. other mood disorders in youth on antipsychotic treatment.**
Summary of evidence	**Moderate quality evidence (large sample size, unable to assess consistency, precise, direct) suggests around 14% of youth treated with antipsychotics for any diagnosis had bipolar disorder. Among youth with bipolar disorder, 44% were on antipsychotics. There were significant increases in antipsychotic use over time in youth with bipolar disorder, with no increases in antipsychotic use over time in youth with depression.**
Bipolar disorder	
41 studies (N = 518,919) found a quarter of antipsychotic-treated youth had a mood disorder; All mood disorders = 24.5% Bipolar spectrum disorders = 13.6% Depression spectrum disorders = 10.9% Among youth with bipolar spectrum disorders, 44% received antipsychotics Among youth with depression spectrum disorders, 4.6% received antipsychotics *There was a small, significant effect of increases in rates over time, particularly for bipolar disorder;* All mood disorders = 17.3% in 2000 to 24.5% in 2006, OR = 1.50, 95%CI 1.26 to 1.79, $p < .0001$ Bipolar spectrum disorders = 11.1% in 2001 to 16.3% in 2006, $p < .0001$ Depression spectrum disorders = 9.1% in 2001 to 9.2% in 2007, $p = 0.77$	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise for increases over time; unable to assess other rates.
Directness of results	Direct

das Neves Peixoto FS, de Sousa DF, Luz DCRP, Vieira NB, Goncalves Junior J,

Santos GCA, da Silva FCT, Rolim Neto ML

Bipolarity and suicidal ideation in children and adolescents: A systematic review with meta-analysis

Annals of General Psychiatry 2017; 16: 22

View review abstract online

Comparison	**Suicide ideation in children and adolescents with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, imprecise, direct) suggests a medium-sized increased risk of suicide ideation in children and adolescents with bipolar disorder.**
Mania symptoms	
Significant, medium-sized increased risk of suicidal ideation in children and adolescents with bipolar disorder; 16 studies, N not reported, RR = 2.94, 95%CI 2.29 to 3.78, p = 0.001 A history of self-harm, psychiatric hospitalisations, mixed episodes and psychosis were associated with increased risk.	
Consistency in results	Appears inconsistent.
Precision in results	Imprecise
Directness of results	Direct

Safer DJ, Zito JM, Safer AM

Age-grouped differences in bipolar mania

Comprehensive Psychiatry 2012; 53: 1110-7

View review abstract online

Comparison	**Mania symptoms in youth vs. adults with bipolar disorder type I.**
Summary of evidence	**Moderate to high quality evidence (precise, direct, large sample, unable to assess consistency) suggests irritability, aggression, and low insight is more common in youths than adults with bipolar disorder. Odd appearance, grandiosity, flight of ideas, decreased sleep, and increased sexual interest are more common**

	in adults than youths with bipolar disorder.
Mania symptoms	
4 studies, N = 457 youth (mean age 14yrs), N = 649 adults (mean age 39yrs) *The following symptoms were significantly more common in youth than adults with bipolar disorder;* Irritability: 16.7%, 95%CI 16.3% to 17.2% vs. 13.9%, 95%CI 13.5% to 14.3% Aggression: 15.0%, 95%CI 14.5% to 15.5% vs. 8.7%, 95%CI 8.3% to 9.2% Low insight: 4.7%, 95%CI 4.3% to 5.1% vs. 2.7%, 95%CI 2.4% to 3.0% *The following symptoms were significantly more common in adults than youth with bipolar disorder;* Odd appearance: 3.4%, 95%CI 3.1% to 3.7% vs. 4.1%, 95%CI 3.8% to 4.3% Grandiosity: 10.3%, 95%CI 9.7% to 10.9% vs. 15.8%, 95%CI 15.2% to 16.4% Flight of ideas: 7.0%, 95%CI 6.8% to 7.2% vs. 7.8%, 95%CI 7.5% to 8.0% Decreased sleep: 5.8%, 95%CI 5.5% to 6.1% vs. 7.8%, 95%CI 7.5% to 8.1% Increased sexual interest: 3.5%, 95%CI 3.1% to 3.8% vs. 5.3%, 95%CI 5.0% to 5.6% There were no significant differences between youth and adults in rapid speech, increased motor or elevated mood. Authors report similar findings for studies with mixed bipolar disorder diagnoses (I, II, and not otherwise specified).	
Consistency in results	Unable to assess; no measure of heterogeneity is reported.
Precision in results	Appears precise.
Directness of results	Direct

Uchida M, Serra G, Zayas L, Kenworthy T, Hughes B, Koster A, Faraone SV, Biederman J

Can manic switches be predicted in pediatric major depression? A systematic literature review

Journal of Affective Disorders 2015; 172: 300-6

View review abstract online

Comparison	**Features associated with manic switches in children and youth with major depression disorder followed for 1-11yrs.**
Summary of evidence	**Moderate to high quality evidence (direct, large sample,**

	consistent, unable to assess precision) suggests a positive family history of any mood disorder is associated with greater likelihood of switching to mania in children with major depression. **Moderate quality evidence (direct, large sample, inconsistent, unable to assess precision) suggests subthreshold symptoms of mania, emotional dysregulation, and behaviour problems are associated with greater likelihood of switching to mania in children with major depression.**
Manic switches	
7 studies, N = 985 children and youth (aged 6-18 yrs) The average rate of manic switching was 28.3% *Factors associated with manic switches include;* 4/4 studies reported a positive family history of a mood disorder 2/4 studies reported subthreshold symptoms of mania 2/4 studies reported emotional dysregulation 2/4 studies reported behaviour problems 2/4 studies reported psychotic symptoms Authors report course of illness, severity of depression, and comorbid conduct disorder provided inconsistent results.	
Consistency in results	Consistent for subthreshold symptoms of mania only.
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Uchida M, Serra G, Zayas L, Kenworthy T, Faraone SV, Biederman J

Can unipolar and bipolar pediatric major depression be differentiated from each other? A systematic review of cross-sectional studies examining differences in unipolar and bipolar depression

Journal of Affective Disorders 2015; 176: 1-7

View review abstract online

Comparison	**Clinical differences in children and adolescents with unipolar depression vs. bipolar depression.**

Summary of evidence	**Moderate quality evidence (large sample, inconsistent, unable to assess precision, direct) suggests the clinical features associated more often in children or youth with bipolar depression than in children or youth with unipolar depression include; more psychiatric comorbidities and behavioural problems (oppositional disorder, conduct disorder, anxiety disorders, irritability, suicidal/self-harm, social impairment, and substance use); earlier onset of mood symptoms; more severe depression; and having a family history of psychiatric illness.**
Clinical features	
4 studies, N = 1,476 3/4 studies found significantly higher rates of psychiatric comorbidities in children/youth with bipolar disorder, including oppositional defiant disorder, conduct disorder, anxiety disorders, and substance use (in adolescents only). 3/4 studies found significantly higher rates of first-degree relatives with any psychiatric illness in children/youth with bipolar disorder. 3/4 studies found significantly earlier onset of mood symptoms in children/youth with bipolar disorder. 2/4 studies found significantly greater severity, and more frequent episodes, of depression in children/youth with bipolar disorder. 2/4 studies found significantly more sadness, aggression, irritability, hopelessness, and suicidal or self-injurious behaviors in children/youth with bipolar disorder. 2/4 studies found significantly higher level of impairment, including difficulties with peers and family members, and severe behavioral problems in school in children/youth with bipolar disorder.	
Consistency in results	Results appear inconsistent.
Precision in results	Unable to assess; no CIs are reported
Directness of results	Direct

Van Meter AR, Burke C, Kowatch RA, Findling RL, Youngstrom EA

Ten-year updated meta-analysis of the clinical characteristics of pediatric mania and hypomania

Bipolar Disorders 2016; 18: 19-32

View review abstract online

Comparison	**Prevalence of mania symptoms in children and youth with bipolar**

	disorder.
Summary of evidence	**Moderate quality evidence (direct, large sample, inconsistent, unable to assess precision) suggests the most common mania symptoms reported in youths with bipolar disorder are (in decreasing order); increased energy, irritability, mood lability, distractibility, goal-directed activity, euphoric/elated mood, pressured speech, hyperactivity, racing thoughts, poor judgment, grandiosity, inappropriate laughter, decreased need for sleep, and flight of ideas.**
Mania symptoms	
20 studies, N = 2,226 youths Increased energy: 8 studies, prevalence = 79%, 95%CI 61% to 93%, I^2 = 98% Irritability: 19 studies, prevalence = 77%, 95%CI 64% to 88%, I^2 = 97 Mood lability: 6 studies, prevalence = 76%, 95%CI 55% to 92%, I^2 = 98 Distractibility: 17 studies, prevalence = 74%, 95%CI 61% to 85%, I^2 = 97 Goal-directed activity: 9 studies, prevalence = 72%, 95%CI 56% to 86%, I^2 = 97 Euphoric/elated mood: 19 studies, prevalence = 64%, 95%CI 53% to 75%, I^2 = 96% Pressured speech: 18 studies, prevalence = 63%, 95%CI 49% to 77%, I^2 = 97% Hyperactive: 8 studies, prevalence = 62%, 95%CI 40% to 81%, I^2 = 98 Racing thoughts: 15 studies, prevalence = 61%, 95%CI 49% to 72%, I^2 = 97 Poor judgment: 17 studies, prevalence = 61%, 95%CI 45% to 76%, I^2 = 98 Grandiosity: 19 studies, prevalence = 57%, 95%CI 44 to 69%, I^2 = 97 Inappropriate laughter: 6 studies, prevalence = 57%, 95%CI 33% to 79%, I^2 = 97 Decreased need for sleep: 19 studies, prevalence = 56%, 95%CI 46% to 67%, I^2 = 95 Flight of ideas: 12 studies, prevalence = 54%, 95%CI 42% to 66%, I^2 = 95 Increased productivity: 4 studies, prevalence = 47%, 95%CI 33% to 63%, I^2 = 91 Increased creativity: 3 studies, prevalence = 41%, 95%CI 23% to 62%, I^2 = 95 Uninhibited people-seeking: 7 studies, prevalence = 41%, 95%CI 27% to 56%, I^2 = 96 Hypersexuality: 12 studies, prevalence = 32%, 95%CI 23% to 42%, I^2 = 94 Hallucinations: 10 studies, prevalence = 31%, 95%CI 17% to 46%, I^2 = 96 Delusions: 5 studies, prevalence =24%, 95%CI 1% to 62%, I^2 = 98 *Significant predictors of mania symptoms;* Male gender predicted increased energy, pressured speech, hyperactivity, grandiosity, and uninhibited people-seeking. Increased age was associated goal-directed activity.	

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Increased year of data collection was associated with hyperactivity. Increased study quality predicted distractibility, uninhibited people seeking, and hyperactivity.	
Consistency in results	Authors report results were inconsistent.
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Vaudreuil CAH, Faraone SV, Di Salvo M, Wozniak JR, Wolenski RA, Carrellas NW, Biederman J

The morbidity of subthreshold pediatric bipolar disorder: A systematic literature review and meta-analysis

Bipolar Disorders 2019; 21: 16-27

View review abstract online

Comparison 1	**Mood and behavioural outcomes in children with subthreshold bipolar symptoms vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency, mostly imprecise, direct) suggests greater severity of functional impairment, mania and depression symptoms, disruptive behaviour, suicidal ideation and attempts and more mood and substance use disorders in children with subthreshold symptoms than controls. There were no differences in levels of anxiety, psychosis or service use.**
Mood and behavioural outcomes	
4 studies, N = 1,369 *Subthreshold pediatric BP was associated with more;* Functional impairment: SMD = 0.61, 95%CI 0.25 to 0.97, $p < 0.05$ Mania symptoms: SMD = 1.88, 95%CI 1.38 to 2.38, $p < 0.05$ Depression: SMD = 0.66, 95%CI 0.52 to 0.80, $p < 0.05$ Disruptive behaviour: RR = 1.75, 95%CI 1.17 to 2.62, $p < 0.05$ Mood disorders: RR = 1.78, 95%CI 1.29 to 2.79, $p < 0.05$ Substance use disorders: RR = 2.27, 95%CI 1.23 to 4.21, $p < 0.05$ Suicidal ideation and attempts: RR = 7.66, 95%CI 1.71 to 34.33, $p < 0.05$	

There were no significant differences in levels of anxiety, psychosis, or service use.	
Comparison 2	**Mood and behavioural outcomes in children with subthreshold bipolar symptoms vs. children with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency, mostly imprecise, direct) suggests greater severity of functional impairment, mania and psychosis symptoms, suicidal ideation and attempts and more service use in children with bipolar disorder compared to children with subthreshold symptoms. There were no differences in depressive symptoms or mood or substance use disorders.**
Mood and behavioural outcomes	
6 studies, N = 1,585 *Pediatric bipolar disorder was associated with more;* Functional impairment: SMD 0.30, 95%CI 0.09 to 0.51, $p < 0.05$ Mania symptoms: SMD = 0.54, 95%CI 0.14 to 0.95, $p < 0.05$ Psychosis symptoms: RR = 2.01, 95%CI 1.56 to 2.73, $p < 0.05$ Suicidal ideation and attempts: RR = 1.62, 95%CI 1.04 to 2.52, $p < 0.05$ Service use: RR = 1.914, 95%CI 1.09 to 3.35, $p < 0.05$ There were no significant differences in depression symptoms, mood or substance use disorders.	
Consistency in results	Unable to assess; no measure of heterogeneity was reported.
Precision in results	Mostly imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = extent of inconsistency of findings across studies in the meta-analysis, N = number of participants, OR = odds ratio, RR = risk ratio, SMD = standardised mean 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[10].

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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[10].

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[11]. 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. 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[10];

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

§ 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[12].

‖ 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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