TECHNICAL COMMENTARY

Pharmaceutical treatments for children and adolescents

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Introduction

Bipolar disorder is a chronic psychiatric illness that can have devastating effects on individuals and their families. It is the sixth leading cause of disability worldwide, with prevalence estimated to be around 1% in the general adult population.

The age of onset of bipolar disorder typically occurs during early adulthood, although onset can occur in childhood or adolescence. Bipolar disorder in childhood and adolescence is commonly associated with impairment in multiple domains, including increased risk of psychiatric hospitalisation, antisocial behaviour, addictions, and suicidal behaviour. There is a need to optimise treatments for early-onset patients for whom medication use could be long-term, with concerns about potential overuse and side effects in a population who are undergoing relevant biological, psychological, and social maturational changes.

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, the most recent and/or comprehensive review was 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, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having 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 six reviews that met our inclusion criteria[3-8].

- Moderate quality evidence suggests combined treatment with an anticonvulsant or lithium plus a second-generation antipsychotic was significantly more effective for clinical response than individual treatments.
- Moderate to high quality evidence suggests a medium-sized effect of improved mania

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symptoms with second-generation antipsychotics aripiprazole, olanzapine, risperidone and ziprasidone compared to placebo. Moderate quality evidence suggests no differences in depression symptoms between quetiapine and placebo.

- Moderate to low quality evidence suggests a small effect of improved mania symptoms with mood stabilisers divalproex, lithium, oxcarbazepine and topiramate compared to placebo.
- Second generation antipsychotics may cause more weight gain and drowsiness than mood stabilisers, while mood stabilisers may cause more akathisia (inner restlessness).

Biederman J, Petty CR, Woodworth KY, Lomedico A, O'Connor KB, Wozniak J, Faraone SV

How informative are open-label studies for youth with bipolar disorder? A meta-analysis comparing open-label versus randomized, placebo-controlled clinical trials

Journal of Clinical Psychiatry 2012; 73: 358-65

View review abstract online

Comparison	**Comparison of results from open-label and randomised trials of treatments for youth with bipolar disorder.** **Trials were predominantly of second-generation antipsychotics (aripiprazole, risperidone, olanzapine, quetiapine, ziprasidone) or mood stabilisers (divalproex).** **Open-label trials ran for longer than RCTs (11.5 vs. 3.6 weeks). The mean sample age was older in RCTs than in open-label trials (13.2 vs. 9.4 years). There were more males in open-label trials than in RCTs (70 vs. 52%).**
Summary of evidence	**Moderate to low quality evidence (inconsistent, indirect, precise, large samples) suggests small improvements in mania symptoms with second-generation antipsychotics aripiprazole, risperidone, olanzapine, quetiapine, ziprasidone or mood stabiliser divalproex.**
Mania **Measured on the Young Mania Rating Scale (YMRS)**	
Small, significant improvement on the YMRS from baseline to endpoint, with no significant differences in effect sizes between study designs; 8 open-label trials, N = 269, SMD = 1.72, 95%CI 1.34 to 2.10, $p < 0.001$, $I^2 = 66.4\%$, $p < 0.001$ 6 RCTs, N = 652, SMD = 2.32, 95%CI 1.99 to 2.65, $p < 0.001$, $I^2 = 80.5\%$, $p < 0.001$ *Small, significant effect of greater improvement on the YMRS with treatment compared to placebo;* 6 RCTs, N = 652, SMD = 0.71, 95%CI 0.50 to 0.90, $p < 0.001$, $I^2 = 69\%$, $p = 0.002$ Authors report no evidence of publication bias.	
Risks	Not reported.
Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Indirect comparisons (mixed drugs/classes).

Correll CU, Sheridan EM, DelBello MP

Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials

Bipolar Disorders 2010; 12: 116-41

View review abstract online

Comparison	**Acute treatment (≤ 12 weeks) with either antipsychotics or mood stabilisers vs. placebo in youth with bipolar disorder.** **Trials were predominantly industry sponsored (88.9%). Trial duration was 3 to 8 weeks.**
Summary of evidence	**Moderate to low quality evidence (direct, medium to large samples, unable to assess consistency or precision) suggestions a medium-sized effect of improved overall and mania symptoms with second-generation antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone) and a small effect of improved mania symptoms with mood stabilisers (divalproex, lithium, oxcarbazepine and topiramate).**

Overall symptoms

Measured on the Clinical Global Impression-Bipolar Disorder scale (CGI-BP)

A significant, medium-sized effect of improved overall symptoms with second-generation antipsychotics compared to placebo;

All second-generation antipsychotics: 5 RCTs, N = 1,140, ES = 0.63, 95%CI 0.50 to 0.76, $p < 0.05$

Aripiprazole: number of studies & N not reported, ES = 0.79, 95%CI 0.54 to 1.04, $p < 0.05$

Olanzapine number of studies & N not reported, ES = 0.48, 95%CI 0.15 to 0.81, $p < 0.05$

Quetiapine: number of studies & N not reported, ES = 0.48, 95%CI 0.22 to 0.73, $p < 0.05$

Risperidone: number of studies & N not reported, ES = 0.73, 95%CI 0.4 to 1.06, $p < 0.05$

Ziprasidone: number of studies & N not reported, ES = 0.47, 95%CI 0.2 to 0.75, $p < 0.05$

A significant, small effect of improved overall symptoms with mood stabilisers compared to placebo when studies were combined, but not when medications were analysed separately;

All mood stabilisers: number of studies & N not reported, ES = 0.47, CI not reported, $p < 0.05$

Divalproex: number of studies & N not reported, ES = 0.54, CI not reported, $p > 0.05$

Lithium: number of studies & N not reported, ES = 0.41, CI not reported, $p > 0.05$

Mania symptoms

Measured on the Young Mania Rating Scale (YMRS)

A significant, medium-sized effect of improved mania symptoms with second-generation antipsychotics compared to placebo; All second-generation antipsychotics: 5 RCTs, N = 1,140, ES = 0.65, 95%CI 0.53 to 0.78, $p < 0.05$ NNT for remission (≤ 12 on YMRS) = 3.7, 95%CI 3.1 to 4.7, $p < 0.05$ Aripiprazole: number of studies & N not reported, ES = 0.69, 95%CI 0.44 to 0.94, $p < 0.05$ NNT for remission = 3.2, 95%CI 2.5 to 4.3, $p < 0.05$ Olanzapine: number of studies & N not reported, ES = 0.75, 95%CI 0.41 to 1.08, $p < 0.05$ NNT for remission = 4.1, 95%CI 2.7 to 8.3, $p < 0.05$ Quetiapine: number of studies & N not reported, ES = 0.60, 95%CI 0.35 to 0.86, $p < 0.05$ NNT for remission = 4.2, 95%CI 3.1 to 11.0, $p < 0.05$ Risperidone: number of studies & N not reported, ES = 0.81, 95%CI 0.48 to 1.14, $p < 0.05$ NNT for remission = 3.7, 95%CI 2.4 to 6.8, $p < 0.05$ Ziprasidone: number of studies & N not reported, ES = 0.48, 95%CI 0.21 to 0.76, $p < 0.05$ NNT not reported *A significant, small effect of improved mania symptoms with mood stabilisers compared to placebo;* All mood stabilisers: 4 RCTs, N = 469, ES = 0.24, 95%CI 0.06 to 0.41, $p < 0.05$ Divalproex: number of studies & N not reported, ES = 0.28, 95%CI 0.01 to 0.54, $p < 0.05$ Lithium: number of studies & N not reported, ES = 0.31, CI not reported, $p < 0.05$ Oxcarbazepine: number of studies & N not reported, ES = 0.11, CI not reported, $p < 0.05$ Topiramate: number of studies & N not reported, ES = 0.51, CI not reported, $p < 0.05$	
Risks	Second generation antipsychotics caused more weight gain than mood stabilisers (ES = 0.53 vs. 0.10) and more drowsiness (NNH = 4.7 vs. 9.5). Second generation antipsychotics caused less akathisia (inner restlessness) than mood stabilisers (NNH = 20.4 vs. 10.2), likely due to lower doses⁄slower titration.
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; CI not standardised.
Directness of results	Direct

Duffy A, Heffer N, Goodday SM, Weir A, Patten S, Malhi GS, Cipriani A

Efficacy and tolerability of lithium for the treatment of acute mania in children with bipolar disorder: A systematic review: A report from the ISBD-IGSLi joint task force on lithium treatment

Bipolar Disorders 2018; 20(7): 583-93 View review abstract online	
Comparison 1	**Lithium vs. placebo in children or adolescents with bipolar I disorder.**
Summary of evidence	**Moderate to low quality evidence (small sample, precise, direct) suggestions a trend effect if greater improvement of mania symptoms with lithium.**
Mania symptoms	
A trend effect of greater improvement with lithium treatment; 1 RCT, N = 81, SMD = -0.42, 95%CI -0.88 to 0.04, p = 0.07	
Comparison 2	**Lithium vs. sodium divalproex in children or adolescents with bipolar I disorder.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) suggestions no differences in mania symptoms between lithium and sodium divalproex.**
Mania symptoms	
No significant differences between groups; 3 RCTs, N = 253, SMD = -0.07, 95%CI -0.31 to 0.18, p = 0.60, I^2 = 0%, p = 0.48	
Comparison 3	**Lithium vs. risperidone in children or adolescents with bipolar I disorder.**
Summary of evidence	**Moderate quality evidence (small to medium-sized sample, precise, direct) suggestions a large effect of greater improvement in mania symptoms with risperidone.**
Mania symptoms	
A significant, large effect of greater improvement with risperidone; 1 RCT, N = 179, SMD = 0.85, 95%CI 0.53 to 1.15, p < 0.00001	
Risks	Common side of lithium included nausea, vomiting, frequent urination, excessive thirst, and increased thyrotropin levels. Drop-out rates were comparable between lithium and placebo or sodium divalproex, but were higher than with risperidone.
Consistency in results	Consistent where applicable (sodium divalproex comparison).
Precision in results	Precise

Directness of results	Direct

Liu HY, Potter MP, Woodworth KY, Yorks DM, Petty CR, Wozniak JR, Faraone SV, Biederman J

Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis

Journal of the American Academy of Child & Adolescent Psychiatry 2011; 50: 749-62.e39

View review abstract online

Comparison	**Comparison of results from open-label and randomised trials of treatments for youth with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, appears precise, indirect) suggestions a small to medium-sized effect of improved mania symptoms with second-generation antipsychotics. Moderate to low quality evidence (large sample, appears precise, open-label trials, indirect, inconsistent,) suggests a 50% response rate for mania with second-generation antipsyhotics, mood stabilisers, anticonvulsants and naturopathic treatments.** **Low quality evidence (small trials) is unable to determine the benefits of treatments for depression or ADHD in children with bipolar disorder.**

Mania symptoms

Response rate measured on the Young Mania Rating Scale (YMRS; ≥ 50% decrease)

8 RCTs (N = 1738)

A small to medium-sized, significant effect of greater rate of response with treatment than with placebo;

OR = 2.24, $p < 0.001$, $I^2 = 0$ %, $p = 0.88$

Subgroup analysis showed that this effect was accounted for by second-generation antipsychotics. Findings were not significant for divalproex and were modestly significant for the other anticonvulsants. There were no changes in the effect size according to mean study age.

Authors report no evidence of publication bias.

11 open-label studies (N = 928)

Overall rate of response from baseline was significant at around 50%;

Response rate = 50.6%, $p < 0.001$, $I^2 = 70.9\%$, $p < 0.001$

Meta-regression showed no significant difference in the rate of response between drug classes

(second-generation antipsychotics, mood stabilisers, other anticonvulsants, and naturopathic treatments) or between specific drug compounds. There were no changes in response rate according to mean study age. Authors report no evidence of publication bias.	
Depression symptoms	
1 open-label trial (N = 28, mean age 9 years) reported a 43% response rate after treatment with carbamazepine. 1 open-label trial (N = 18, mean age 9 years) reported a 22% response rate after treatment with divalproex in the subgroup with depressive symptoms (N = 9). 1 open-label trial (N = 19, mean age 12 years) reported a 60% response rate after treatment with aripiprazole in the subgroup with depressive symptoms (N = 11). 1 open-label trial (N = 15, mean age 5 years) reported a 36% response rate after treatment with olanzapine or risperidone in the subgroup with depressive symptoms (N = 11). 1 open-label trial (N = 30, mean age 10 years) reported a 48% response rate after treatment with risperidone in the subgroup with depressive symptoms (N = 22). 1 open-label trial (N = 21, mean age 10 years) reported a 50% response rate after treatment with ziprasidone in the subgroup with depressive symptoms (N = 14). 1 open-label trial (N = 20, mean age 9 years) reported a 40% response rate after treatment with omega-3 fatty acids.	
ADHD symptoms	
1 open-label trial (N = 28, mean age 9 years) reported a 62% response rate after treatment with carbamazepine in the subgroup with ADHD symptoms (N = 27). 1 open-label trial (N = 18, mean age 9 years) reported a 12% response rate after treatment with divalproex in the subgroup with ADHD symptoms (N = 17). 1 open-label trial (N = 15, mean age 5 years) reported a 13-14% response rate after treatment with olanzapine or risperidone in the subgroup with ADHD symptoms (N = 15). 1 open-label trial (N = 19, mean age 12 years) reported a 60% response rate after treatment with aripiprazole in the subgroup with ADHD symptoms (N = 18). 1 open-label trial (N = 30, mean age 10 years) reported a 35% response rate after treatment with risperidone in the subgroup with ADHD symptoms (N = 26). 1 open-label trial (N = 21, mean age 10 years) reported a 33% response rate after treatment with ziprasidone in the subgroup with ADHD symptoms (N = 19).	
Risks	Not reported
Consistency in results	Consistent for RCTs, inconsistent for open-label trials.
Precision in results	Unable to assess; CIs not reported, although forest plot appears precise.

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Directness of results	Indirect for mania symptoms (drug classes combined), direct for individual trials.

Maneeton B, Putthisri S, Maneeton N, Woottiluk P, Suttajit S, Charnsil C, Srisurapanont M

Quetiapine monotherapy versus placebo in the treatment of children and adolescents with bipolar depression: A systematic review and meta-analysis

Neuropsychiatric Disease and Treatment 2017; 13: 1023-32

View review abstract online

Comparison	**Quetiapine vs. placebo for children and adolescents with bipolar depression. Treatment duration = 8 weeks.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, unable to assess precision, consistent, direct) suggests no differences in the effects of quetiapine and placebo for depression in children and adolescents with bipolar disorder.**
Depression symptoms **Children's Depression Rating Scale–Revised (CDRS-R)**	
No significant differences in depression scores between quetiapine and placebo; 2 RCTs, N = 224, WMD = -1.82, 95%CI -5.98 to 2.34, p = 0.39, I^2 = 0%, p = 0.58 Response and remission rates were also not different between groups.	
Risks	There were no differences in discontinuation due to adverse events.
Consistency in results	Consistent
Precision in results	Unable to assess; standardised CIs not reported.
Directness of results	Direct

Yee CS, Hawken ER, Baldessarini RJ, Vazquez GH

Maintenance Pharmacological Treatment of Juvenile Bipolar Disorder: Review and Meta-Analyses

The international journal of neuropsychopharmacology 2019; 22: 531-40

View review abstract online	
Comparison 1	**Any medication (mood-stabilizers or antipsychotics) vs. control (placebo or no treatment) for children and adolescents.**
Summary of evidence	**Moderate quality evidence (medium to large samples, inconsistent, imprecise, direct) suggests greater nonrecurrence of symptoms with active drugs.**
Response	
Meta-analysis of controlled studies showed more nonrecurrence of symptoms with active drugs; 2 RCTs, 1 open label trial, N = 270, OR = 7.14, 95%CI 1.12 to 45.6, p = 0.04, I^2 = 66.3% *There were no significant differences in rates of clinical response;* 3 RCTs, N = 443, OR = 2.88, 95%CI 0.87 to 9.60. p = 0.08, I^2 = 74.5%	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**Any medication for children and adolescents.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess precision or consistency, direct) suggests combined treatment with an anticonvulsant or lithium plus a second-generation antipsychotic was significantly more effective for clinical response than individual treatments.**
Response	
16 trials, N = 1,773 *Combination treatments were significantly more effective for clinical response than individual treatments;* Combined treatments (anticonvulsant or lithium + a second-generation antipsychotic) = 82.7% Anticonvulsants = 53.2% Lithium = 51.1% Second generation antipsychotics = 50.1% Factors associated with increased response were more co-occurring ADHD, polytherapy rather than monotherapy, RCTs rather than nonrandomised uncontrolled trials, and outcome as responder rates rather than nonrecurrence rates. Factors not associated with response were age, trial duration, sex, dropout rate, index episode polarity (most were initially manic), corporate vs. grant support, and reporting year.	
Risks	Adverse events included cognitive dulling, weight-gain, and

	gastrointestinal symptoms.
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Explanation of acronyms

CGI = Clinical Global Improvement scale, CI = confidence interval, ES = effect size, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, NNT = number needed to treat, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, SMD = standardised mean difference, vs. = versus, WMD = weighted mean difference

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[9].

† 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).

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) which 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[9].

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[10]. 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[9];

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

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data 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[11].

‖ 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, which 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.

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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. Maneeton B, Putthisri S, Maneeton N, Woottiluk P, Suttajit S, Charnsil C*, et al.* (2017): Quetiapine monotherapy versus placebo in the treatment of children and adolescents with bipolar depression: A systematic review and meta-analysis. *Neuropsychiatric Disease and Treatment* 13: 1023-32.
4. Biederman J, Petty CR, Woodworth KY, Lomedico A, O'Connor KB, Wozniak J*, et al.* (2012): How informative are open-label studies for youth with bipolar disorder? A meta-analysis comparing open-label versus randomized, placebo-controlled clinical trials. *Journal of Clinical Psychiatry* 73: 358-65.
5. Correll CU, Sheridan EM, DelBello MP (2010): Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disorders* 12: 116-41.
6. Liu HY, Potter MP, Woodworth KY, Yorks DM, Petty CR, Wozniak JR*, et al.* (2011): Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* 50: 749-62.e39.
7. Duffy A, Heffer N, Goodday SM, Weir A, Patten S, Malhi GS*, et al.* (2018): Efficacy and tolerability of lithium for the treatment of acute mania in children with bipolar disorder: A systematic review: A report from the ISBD-IGSLi joint task force on lithium treatment. *Bipolar Disorders* 20: 583-93.
8. Yee CS, Hawken ER, Baldessarini RJ, Vazquez GH (2019): Maintenance Pharmacological Treatment of Juvenile Bipolar Disorder: Review and Meta-Analyses. *The international journal of neuropsychopharmacology* 22: 531-40.
9. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
10. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
11. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*