TECHNICAL COMMENTARY

Treatments for childhood and early-onset schizophrenia

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Introduction

Childhood-onset schizophrenia is defined as onset of schizophrenia prior to the age of 13 years, and early-onset schizophrenia between the ages of 13 and 17 years. This table presents the evidence for pharmaceutical treatments for childhood and early-onset schizophrenia.

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 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version 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 eight reviews that met our inclusion criteria[3-10].

- Compared to first-generation antipsychotics, moderate quality evidence finds a small to medium-sized benefit of second-generation antipsychotics for global and mental state in children and adolescents with schizophrenia.
- Moderate quality evidence finds clozapine was most effective and fluphenazine was least effective for symptoms when compared to placebo and to other antipsychotics (ziprasidone, loxapine, trifluperazine, asenapine, haloperidol, quetiapine, paliperidone, aripiprazole, risperidone, lurasidone, olanzapine, or molindone). There were few significant differences between the other antipsychotics, with only ziprasidone being less effective than olanzapine, molindine and risperidone.

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- Moderate to low quality evidence suggests greater improvement in symptoms with lurasidone than with placebo, but no differences when compared to olanzapine, risperidone, paliperidone extended release, quetiapine, ziprasidone, asenapine, and aripiprazole. There was similar weight gain between lurasidone and placebo, and less weight gain with lurasidone than with olanzapine, quetiapine, risperidone, asenapine, or paliperidone. The odds of all-cause discontinuation were lower with lurasidone than with aripiprazole and paliperidone, with no differences when compared to the other second-generation antipsychotics. Rates of extrapyramidal symptoms and akathisia were similar between lurasidone and the other second-generation antipsychotics.
- For positive symptoms, moderate to high quality evidence suggests medium-sized improvements with olanzapine, risperidone, and asenapine, and small improvements with quetiapine, aripiprazole, and paliperidone over placebo. For negative symptoms, moderate to low quality evidence suggests medium-sized improvements with aripiprazole, asenapine, molindone, olanzapine and risperidone over placebo.
- Moderate quality evidence finds haloperidol, loxapine, risperidone and quetiapine showed the most extrapyramidal symptoms. Olanzapine showed the most weight gain, followed by clozapine, quetiapine, paliperidone, risperidone, asenapine and aripiprazole. Clozapine showed the most sedation, followed by paliperidone, asenapine, loxapine, olanzapine, haloperidol, aripiprazole, and risperidone. Risperidone showed the most prolactin increase, followed by haloperidol, olanzapine, paliperidone, and quetiapine.
- Compared to low dose antipsychotics, moderate to high quality evidence suggests greater improvement in global state in adolescents on standard dose antipsychotics, although there are more side effects with standard doses, including extrapyramidal symptoms, weight gain, somnolence, and prolactin elevation.

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Arango C, Ng-Mak D, Finn E, Byrne A, Loebel A

Lurasidone compared to other atypical antipsychotic monotherapies for adolescent schizophrenia: a systematic literature review and network meta-analysis

European Child & Adolescent Psychiatry 2019; doi.org/10.1007/s00787-019-1425-2

View review abstract online

Comparison	**Lurasidone vs. placebo or other second-generation antipsychotics (olanzapine, risperidone, paliperidone extended release, quetiapine, ziprasidone, asenapine, and aripiprazole).**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, inconsistent, unable to assess precision, indirect) suggests greater improvement in symptoms with lurasidone than with placebo, with no differences compared to the other second-generation antipsychotics. There was similar weight gain between lurasidone and placebo, and less weight gain with lurasidone than with olanzapine, quetiapine, risperidone, asenapine, or paliperidone. The odds of all-cause discontinuation were lower with lurasidone than with aripiprazole and paliperidone, with no differences when compared to other antipsychotics. Rates of extrapyramidal symptoms and akathisia were similar for lurasidone and other atypical antipsychotics.**
Symptoms	
Lurasidone was significantly more efficacious than placebo PANSS: 10 RCTS, N = not reported, MD = -7.95, 95%CrI -11.76 to -4.16, $p < 0.05$ CGI-S: 8 RCTs, N = not reported, MD = -0.44, 95%CrI -0.67 to -0.22, $p < 0.05$ There were no significant differences between lurasidone and aripiprazole, asenapine, clozapine, olanzapine, paliperidone extended-release, quetiapine, risperidone, and ziprasidone.	
Risks	Lurasidone was associated with similar weight gain to placebo and less weight gain than olanzapine, quetiapine, risperidone, asenapine, and paliperidone. The odds of all-cause discontinuation were significantly lower for lurasidone than aripiprazole and paliperidone, with no differences when compared to other antipsychotics. Rates of extrapyramidal symptoms and akathisia were similar for lurasidone and other atypical antipsychotics.

Consistency in results‡	Authors report moderate to high degree of between-trial heterogeneity.
Precision in results§	Unable to assess; MDs are not standardised.
Directness of results‖	Indirect; network meta-analysis.

Ardizzone I, Nardecchia F, Marconi A, Carratelli TI, Ferrara M

Antipsychotic Medication in Adolescents Suffering from Schizophrenia: A Meta-Analysis of Randomized Controlled Trials

Psychopharmacology Bulletin 2010; 43(2): 45-66

View review abstract online

Comparison	**6 to 8 weeks of aripiprazole (10 or 30mg per day), risperidone (1.5-6mg per day) or olanzapine (mean 11.1mg per day) vs. placebo or low-dose risperidone (0.15-0.6mg per day).**
Summary of evidence	**Moderate to high quality evidence (medium to large sample, precise, unable to assess consistency, direct) suggests improvements in global and mental state after 6 to 8 weeks of treatment with aripiprazole, risperidone or olanzapine. Olanzapine resulted more weight gain than risperidone and aripiprazole, and risperidone resulted in more extrapyramidal side effects than aripiprazole.**
Global and mental state	
Significant, medium-sized improvement in symptoms after treatment compared control conditions; PANSS total: 3 RCTs, N = 493, g = -0.415, 95%CI -0.560 to -0.270, $p < 0.0001$ PANSS positive: 3 RCTs, N = 493, g = -0.433, 95%CI -0.578 to -0.288, $p < 0.0001$ PANSS negative: 3 RCTs, N = 493, g = -0.254, 95%CI -0.398 to -0.110, $p < 0.001$ CGI: 3 RCTs, N = 493, g = -0.418, 95%CI -0.563 to -0.273, $p < 0.0001$ Effect sizes were similar for individual antipsychotic comparisons. All studies were rated as having a low risk of bias.	
Risks	Most weight gain was reported in those receiving olanzapine: mean increase from baseline to endpoint was 4.3kg for olanzapine, 3.2kg for risperidone, and 0.2kg for aripiprazole 30mg, with no increase for

	aripiprazole 10mg. Risperidone showed significant increases in akathisia, dyskinesia, dystonia, parkinsonism and tremor over controls, and aripiprazole 30mg showed significant increases in parkinsonism and tremor with no differences for aripiprazole 10mg. The olanzapine study did not report extrapyramidal side effects.
Consistency in results	Unable to assess, heterogeneity measures are not reported.
Precision in results	Precise
Directness of results	Direct

Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Chaimani A, Leucht S

Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis

European Neuropsychopharmacology 2018; 28: 659-74

View review abstract online

Comparison	**All first generation or second-generation antipsychotics for children and adolescents (7-18 years).**
Summary of evidence	**Moderate quality evidence (large sample, consistent, imprecise, indirect) finds clozapine was more effective and fluphenazine was least effective for symptoms compared to placebo and all other antipsychotics (ziprasidone, loxapine, trifluperazine, asenapine, haloperidol, quetiapine, paliperidone, aripiprazole, risperidone, lurasidone, olanzapine, and molindone). There were few significant differences between other antipsychotics, with only ziprasidone being less effective than olanzapine, molindine and risperidone.** **Haloperidol, loxapine, risperidone and quetiapine showed the most extrapyramidal symptoms. Olanzapine showed the most weight gain, followed by clozapine, quetiapine, paliperidone, risperidone, asenapine and aripiprazole. Clozapine showed the most sedation, followed by paliperidone, asenapine, loxapine, olanzapine, haloperidol, aripiprazole, and risperidone. Risperidone showed the most prolactin increase, followed by haloperidol, olanzapine, paliperidone, and quetiapine.**

Overall efficacy
28 RCTs (N = 3,003) were included in the network analysis
Significant, large effects showed clozapine was more effective than;
Placebo: SMD = -1.60, 95%CI -2.34 to -0.86, $p < 0.05$
Fluphenazine: SMD = -2.53, 95%CI -3.60 to -1.47, $p < 0.05$
Ziprasidone: SMD = -1.46, 95%CI -2.24 to -0.68, $p < 0.05$
Loxapine: SMD = -1.28, 95%CI -2.16 to -0.39, $p < 0.05$
Trifluperazine: SMD = -1.24, 95%CI -2.20 to -0.27, $p < 0.05$
Asenapine: SMD = -1.22, 95%CI -2.00 to -0.43, $p < 0.05$
Haloperidol: SMD = -1.18, 95%CI -1.87 to -0.49, $p < 0.05$
Quetiapine: SMD = -1.18, 95%CI -1.95 to -0.41, $p < 0.05$
Paliperidone: SMD = -1.18, 95%CI -1.96 to -0.41, $p < 0.05$
Aripiprazole: SMD = -1.17, 95%CI -1.93 to -0.41, $p < 0.05$
Lurasidone: SMD = -1.12, 95%CI -1.89 to -0.35, $p < 0.05$
Risperidone: SMD = -0.98, 95%CI -1.70 to -0.27, $p < 0.05$
Olanzapine: SMD = -0.86, 95%CI -1.54 to -0.17, $p < 0.05$
Molindone: SMD = -0.83, 95%CI -1.62 to -0.04, $p < 0.05$
Significant, medium to large effects showed olanzapine was more effective than;
Placebo: SMD = -0.74, 95%CI -1.05 to -0.44, $p < 0.05$
Fluphenazine: SMD = -1.68, 95%CI -2.66 to -0.69, $p < 0.05$
Ziprasidone: SMD = -0.60, 95%CI -1.00 to -0.20, $p < 0.05$
Significant, medium to large effects showed molindone was more effective than;
Placebo: SMD = -0.77, 95%CI -1.23 to -0.31, $p < 0.05$
Fluphenazine: SMD = -1.70, 95%CI -2.75 to -0.65, $p < 0.05$
Ziprasidone: SMD = -0.62, 95%CI -1.15 to -0.10, $p < 0.05$
Significant, medium to large effects showed risperidone was more effective than;
Placebo: SMD = -0.62, 95%CI -0.89 to -0.34, $p < 0.05$
Fluphenazine: SMD = -1.55, 95%CI -2.54 to -0.56, $p < 0.05$
Ziprasidone: SMD = -0.47, 95%CI -0.85 to -0.10, $p < 0.05$
Significant, medium to large effects showed lurasidone was more effective than;
Placebo: SMD = -0.48, 95%CI -0.71 to -0.25, $p < 0.05$

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Fluphenazine: SMD = -1.41, 95%CI -2.45 to -0.38, $p < 0.05$ *Significant, medium to large effects showed aripiprazole was more effective than;* Placebo: SMD = -0.43, 95%CI -0.63 to -0.24, $p < 0.05$ Fluphenazine: SMD = -1.37, 95%CI -2.39 to -0.34, $p < 0.05$ *Significant, medium to large effects showed quetiapine was more effective than;* Placebo: SMD = -0.42, 95%CI -0.65 to -0.19, $p < 0.05$ Fluphenazine: SMD = -1.35, 95%CI -2.38 to -0.32, $p < 0.05$ *Significant, medium to large effects showed paliperidone was more effective than;* Placebo: SMD = -0.42, 95%CI -0.66 to -0.18, $p < 0.05$ Fluphenazine: SMD = -1.35, 95%CI -2.39 to -0.31, $p < 0.05$ *Significant, medium to large effects showed asenapine was more effective than;* Placebo: SMD = -0.38, 95%CI -0.66 to -0.11, $p < 0.05$ Fluphenazine: SMD = -1.32, 95%CI -2.36 to -0.27, $p < 0.05$ *Significant, large effects showed fluphenazine was also less effective than;* Haloperidol: SMD = -1.35, 95%CI -2.16 to -0.55, $p < 0.05$ Trifluperazine: SMD = -1.30, 95%CI -2.35 to -0.24, $p < 0.05$ Loxapine: SMD = -1.26, 95%CI -2.24 to -0.28, $p < 0.05$ Ziprasidone: SMD = -1.08, 95%CI -2.12 to -0.04, $p < 0.05$	
Risks	Compared to placebo, haloperidol, loxapine, risperidone and quetiapine showed the most extrapyramidal symptoms. Olanzapine showed the most weight gain, followed by clozapine, quetiapine, paliperidone, risperidone, asenapine and aripiprazole. Clozapine showed the most sedation, followed by paliperidone, asenapine, loxapine, olanzapine, haloperidol, aripiprazole, and risperidone. Risperidone showed the most prolactin increase, followed by haloperidol, olanzapine, paliperidone, and quetiapine.
Consistency in results	Consistent
Precision in results	Mostly imprecise
Directness of results	Indirect network meta-analysis

Kumar A, Datta SS Wright SD, Furtado VA, Russell PS

Atypical antipsychotics for psychosis in adolescents

Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD009582. DOI: 10.1002/14651858.CD009582.pub2

View review abstract online

Comparison 1	**Second-generation antipsychotics vs. placebo in adolescents (13 to 17 years).**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, some imprecision, direct) suggests a small benefit of olanzapine for relief of symptoms. Moderate quality evidence (small sample) suggests less use of benzodiazepines, less corrected QT and less total bilirubin in adolescents receiving second generation antipsychotics. However, antipsychotic use resulted in more side effects, including weight gain, somnolence, low or high prolactin levels, high triglycerides, high alanine aminotransferase, and high uric acid.**
Global and mental state at ≤12 weeks	
Greater improvement in mental state with olanzapine compared to placebo (small effect); Mental state (BPRS or PANSS): 2 RCTs, N = 304, RR 0.76, 95%CI 0.63 to 0.92, p = 0.0055, I^2 = 0% No differences in global state as measured by the CGI (1 RCT, N = 107)	
Risks	Overall, second generation antipsychotics showed less use of benzodiazepines (1 RCT, N = 107, RR 0.57, 95%CI 0.35 to 0.92, p = 0.021), less corrected QT (1 RCT, N = 107, WMD -6.30, 95%CI -12.57 to -0.09, p = 0.047), less total bilirubin (1 RCT, N = 104, WMD -3.70, 95%CI -6.30 to -1.10, p = 0.0052). However, they showed more somnolence (1 RCT, N = 107, RR 8.26, 95%CI 16.15 to 59.61, p = 0.036), more low prolactin (1 RCT, N = 302, RR 3.77, 95%CI 1.88 to 7.58, p = 0.00019), more high prolactin (1 RCT, N = 107, RR 4.70, 95%CI 2.25 to 9.82, p = 0.000039), more weight gain (1 RCT, N = 107, RR 3.56, 95%CI 1.14 to 11.11, p = 0.028), more high triglycerides (1 RCT, N = 107, RR 2.38, 95%CI 1.31 to 4.30, p = 0.0042), higher alanine aminotransferase (1 RCT, N = 104, WMD 26.60, 95%CI 11.34 to 41.86, p = 0.00064), and uric acid (1 RCT, N = 107, WMD 38.40, 95%CI 18.88 to 57.92, p = 0.00011). No differences were reported for appetite (1 RCT, N = 107), or

	dizziness (1 RCT, N = 107).
Consistency in results	Consistent for mental state.
Precision in results	Precise for mental state and use of benzodiazepines only, imprecise for WMD data.
Directness of results	Direct
Comparison 2	**Second-generation antipsychotics vs. first-generation antipsychotics in adolescents.**
Summary of evidence	**Moderate to high quality evidence (medium to large sample, consistent, precise, direct) suggests a small to medium-sized effect of less risk of inadequate efficiency with second-generation antipsychotics.** **Moderate to low quality evidence (imprecise, small sample) suggests improved mental state with first-generation antipsychotics as measured by PANSS total, although BPRS, PANSS positive or PANSS negative subscales showed no differences.** **Low quality evidence (smaller samples) is unable to determine the differences in global state or side effects between first-generation and second-generation antipsychotics for adolescents.**
Global and mental state at ≤12 weeks	
Less risk of 'inadequate efficiency' with second generation antipsychotics (small to medium effect); 3 RCTs, N = 421, RR 0.59, 95%CI 0.43 to 0.82, *p* = 0.0014, I^2 = 20% *Greater improvement in mental state with first generation antipsychotics measured on PANSS;* Mental state (PANSS total): 1 RCT N = 156, WMD 29.60, 95%CI 20.84 to 38.37, *p* = 0.00001 However, no differences are reported on PANSS positive, or PANSS negative subscales (1 RCT, N = 156) or on the BPRS (5 RCTs, N = 100) *Greater improvement in global state with clozapine (second generation) compared to haloperidol;* Global state (CGAS): 1 RCT, N = 21, WMD 17.00, 95%CI 7.74 to 26.26, *p* = 0.00032 No differences are reported using the CGI.	
Risks	Overall, second generation antipsychotics showed less total side effects (1 RCT, N = 40, RR 0.20, 95%CI 0.05 to 0.80, *p* = 0.023) or extrapyramidal side effects (1 RCT, N = 40, RR 0.37, 95%CI 0.20 to 0.68, *p* = 0.0012).

	No differences in blood pressure or dry mouth (1 RCT, N = 60), dizziness or constipation (2 RCTs, N = 100, I^2 = 0%), hypersalivation (2 RCTs, N = 81, I^2 = 82%), tachycardia (1 RCT, N = 21), restlessness or tremor (2 RCTs, N = 100, I^2 = 0%), AIMS score, neutrophil count, drowsiness (1 RCT, N = 21), weight gain, cholesterol, or prolactin concentration (2 RCTs, N = 156, I^2 = 0% for weight gain and prolactin, I^2 = 73% for cholesterol).
Consistency in results	Consistent where applicable (> 1 RCT), apart from cholesterol.
Precision in results	Precise for 'inadequate efficacy', imprecise for global state, mental state, total side effects and extrapyramidal side effects.
Directness of results	Direct
Comparison 3	**Second-generation antipsychotics vs. second-generation antipsychotics in adolescents.**
Summary of evidence	**Low quality evidence (small samples, imprecise) is unable to determine the differences in efficacy between particular second-generation antipsychotics for adolescents.**
Global and mental state at ≤12 weeks	
Greater improvement in mental state with clozapine compared to olanzapine; Mental state (BPRS): 1 RCT, N = 39, RD -0.44, 95%CI -0.72 to -0.17, *p* = 0.0018 No differences in global state between clozapine and olanzapine (1 RCT, N = 39) No differences in mental state between olanzapine and quetiapine (1 RCT, N = 20), quetiapine and risperidone (1 RCT, N = 22), or risperidone and other second-generation antipsychotics (1 RCT, N = 29). No differences in global state between risperidone and olanzapine (3 RCTs, N = 182, I^2 = 15%).	
Risks	Clozapine vs. olanzapine: olanzapine showed increased salivation (1 RCT, N = 29, OR 6.00, 95%CI 1.09 to 33.02, *p* = 0.039), sweating (1 RCT, N = 29, OR 9.50, 95%CI 1.69 to 53.33, *p* = 0.011) and glucose levels (1 RCT, N = 38, MD 10.10, 95%CI 1.46 to 18.74, *p* = 0.022). No differences in drowsiness, appetite, diabetes, weight gain (1 RCT, N = 29), BMI, cholesterol, triglycerides (1 RCT, N = 38). Risperidone vs. olanzapine: olanzapine showed increased cholesterol (1 RCT, N = 76, MD -27.10, 95%CI -50.13 to -4.07, *p* = 0.021). No differences in muscle stiffness, weight gain (1 RCT, N = 19), prolactin levels (1 RCT, N = 76), or BMI (1 RCT, N = 34). Risperidone vs. quetiapine: risperidone showed greater prolactin elevation (1 RCT, N = 22, OR 10.00, 95%CI 1.53 to 65.41, *p* =

	0.016). No differences in extrapyramidal side effects, or weight gain (2 RCTs, N = 41).
Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Imprecise
Directness of results	Direct
Comparison 4	**Standard dose vs. low-dose antipsychotics in adolescents.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent where applicable, precise, direct) suggests greater improvement in global state with standard dose antipsychotics compared to low dose antipsychotics, however moderate quality evidence (imprecise) shows more side effects with standard doses including extrapyramidal, weight gain, somnolence, and prolactin elevation.**
Global and mental state at ≤12 weeks	
Greater improvement in global state with standard dose compared to low dose of any second-generation antipsychotic; Global state (CGI): 3 RCTs, N = 468, MD -0.34, 95%CI -0.55 to -0.13, *p* = 0.012, I^2 = 55% (NS) *Greater response to treatment with risperidone1.5-6.0mg/day compared to risperidone 0.15-0.6mg/day (small to medium effect);* No response: 1 RCT, N = 255, RR 0.59, 95%CI 0.45 to 0.77, *p* = 0.00016 *Greater improvement in global state with aripiprazole 30 mg/day compared to aripiprazole 10 mg/day;* Global state (CGI-S): 1 RCT, N = 196, MD -0.20, 95%CI -0.23 to -0.17, *p* = 0.00001	
Risks	Low dose of any second generation antipsychotic showed fewer extrapyramidal side effects (1 RCT, N = 254, RR 3.31, 95%CI 1.86 to 5.87, *p* = 0.000043), less weight gain (1 RCT, N = 257, RR 1.24, 95%CI 1.07 to 1.44, *p* = 0.0048), and less somnolence (1 RCT, N = 257, RR 3.17, 95%CI 1.68 to 5.99, *p* = 0.00039). Risperidone 0.15-0.6mg/day showed less prolactin elevation (1 RCT, N = 257, RR 46.46, 95%CI 6.50 to 332.17, *p* = 0.00013) than risperidone1.5-6.0mg/day. Aripiprazole 10 mg showed less somnolence (1 RCT, N = 202, RR 1.96, 95%CI 1.00 to 3.83, *p* = 0.049), less parkinsonism (1 RCT, N = 202, RR 2.03, 95%CI 1.17 to 3.52, *p* = 0.012) than aripiprazole 30 mg.

Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Precise for global and mental state, imprecise for risks.
Directness of results	Direct

Pagsberg AK, Tarp S, Glintborg D, Stenstrom AD, Fink-Jensen A, Correll CU, Christensen R

Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis

Journal of the American Academy of Child and Adolescent Psychiatry 2017; 56(3): 191-202

View review abstract online

Comparison 1	**Antipsychotics vs. placebo in children and adolescents (8 to 19 years).**
Summary of evidence	**For overall symptoms, moderate to high quality evidence (medium-sized samples consistent where applicable, precise, direct) finds medium-sized effects over placebo with olanzapine, risperidone and paliperidone, and small effects with quetiapine, aripiprazole and asenapine, with no effect of ziprasidone. Low quality evidence (indirect and imprecise) is unable to determine the effects of molindone over placebo for overall symptoms.** **For positive symptoms, moderate to high quality evidence suggests medium-sized improvements with olanzapine, risperidone and asenapine, and small improvements with quetiapine, aripiprazole and paliperidone, with no effect of ziprasidone. For negative symptoms, moderate to low quality evidence (indirect, precise) suggests aripiprazole, asenapine, molindone, olanzapine and risperidone may all have small to medium-sized effects over placebo, but only quetiapine is more effective than placebo for depression symptoms. For social functioning, moderate to low quality evidence suggests aripiprazole, asenapine paliperidone and risperidone may have small to medium-sized effects over placebo.** **Moderate to high quality evidence suggests more weight gain with all antipsychotics apart from ziprasidone, with olanzapine and quetiapine resulting in the most weight gain. Moderate to**

	low quality evidence (imprecise or indirect) found large effects of more extrapyramidal side effects with paliperidione, ziprasidone, risperidone, and aripiprazole. Olanzapine and quetiapine resulted in increases in triglycerides (medium-sized effects), and there was a small effect of decreased prolactin with aripiprazole, medium-sized effects of increased prolactin with olanzapine and paliperidione, and a large effect of increased prolactin with risperidone. The data for sedation was of low quality (imprecise and indirect). **Moderate to low quality evidence (imprecise, direct) suggests medium-sized effects of less discontinuation of medication for any reason with olanzapine, risperidone, paliperidone, quetiapine and ziprasidone compared to placebo, with no effects of aripiprazole or asenapine.**
Overall symptoms **Measured on the PANSS**	
Significant, medium-sized effects of improved overall symptoms with the following antipsychotics compared to placebo (direct comparisons); Olanzapine: 1 RCT, N = 106, SMD -0.59, 95%CI -1.00 to -0.18, $p = 0.005$ Risperidone: 2 RCTs, N = 413, SMD -0.57, 95%CI -0.77 to -0.37, $p < 0.00001$, $I^2 = 0\%$ Paliperidone: 1 RCT, N = 146, SMD -0.49, 95%CI -0.84 to -0.15, $p = 0.005$ *Significant, small effects of improved overall symptoms with the following antipsychotics compared to placebo (direct comparisons);* Quetiapine: 1 RCT, N = 220, SMD -0.40, 95%CI -0.68 to -0.12, $p = 0.006$ Aripiprazole: 1 RCT, N = 294, SMD -0.34, 95%CI -0.59 to -0.10, $p = 0.006$ Asenapine: 1 RCT, N = 228, SMD -0.38, 95%CI -0.66 to -0.11, $p = 0.006$ Indirect network meta-analysis comparisons found molindone showed a large significant effect over placebo (unclear sample size, SMD = -0.94, 95%CI -1.57 to -0.31), and no significant effect of asenapine. *No differences with placebo were found in direct comparison for;* Ziprasidone: 1 RCT, N = 269, SMD -0.14, 95%CI -0.40 to 0.12, $p = 0.28$ Indirect network meta-analysis comparisons contained to studies conducted in the United States, Europe, and Eastern European regions showed a significant result favouring ziprasidone, as the placebo response was higher in Asia, and South and Central American regions. Authors state that risk of bias across trials was generally low.	
Positive symptoms	

Significant, medium-sized effects of improved positive symptoms with the following antipsychotics compared to placebo (direct comparisons); Olanzapine: 1 RCT, N = 106, SMD -0.65, 95%CI -1.06 to -0.24, $p = 0.002$ Risperidone: 2 RCTs, N = 413, SMD -0.47, 95%CI -0.67 to -0.27, $p < 0.00001$, $I^2 = 0\%$ Asenapine: 1 RCT, N = 228, SMD -0.43, 95%CI -0.71 to -0.15, $p = 0.002$ *Significant, small effects of improved overall symptoms with the following antipsychotics compared to placebo (direct comparisons);* Aripiprazole: 1 RCT, N = 294, SMD -0.38, 95%CI -0.62 to -0.13, $p = 0.002$ Paliperidone: 1 RCT, N = 146, SMD -0.37, 95%CI -0.71 to -0.02, $p = 0.04$ Quetiapine: 1 RCT, N = 220, SMD -0.38, 95%CI -0.66 to -0.10, $p = 0.008$ *No differences with placebo were found in direct comparison for;* Ziprasidone: 1 RCT, N = 269, SMD -0.24, 95%CI -0.49 to 0.02, $p = 0.07$
Negative symptoms
Significant, small to medium-sized effects of improved negative symptoms with the following antipsychotics compared to placebo (all indirect comparisons); Aripiprazole: unclear sample size, SMD -0.27, 95%CI -0.52 to -0.02, $p < 0.05$ Asenapine: unclear sample size, SMD -0.32, 95%CI -0.63 to 0.00, $p = 0.05$ Molindone: unclear sample size, SMD -0.58, 95%CI -1.06 to -0.09, $p < 0.05$ Olanzapine: unclear sample size, SMD -0.45, 95%CI -0.77 to -0.12, $p < 0.05$ Risperidone: unclear sample size, SMD -0.35, 95%CI -0.55 to -0.15, $p < 0.05$ *No differences with placebo were found in indirect comparisons for;* Paliperidone: unclear sample size, SMD -0.25, 95%CI -0.53 to 0.02, $p > 0.05$ Quetiapine: unclear sample size, SMD -0.26, 95%CI -0.59 to 0.08, $p > 0.05$ Ziprasidone: unclear sample size, SMD 0.08, 95%CI -0.24 to 0.40, $p > 0.05$
Depression symptoms
Only quetiapine improved depression symptoms, with a small to medium-sized effect (indirect comparison); Quetiapine: unclear sample size, SMD -0.37, 95%CI -0.71 to -0.04, $p < 0.05$
Discontinuation of antipsychotic medication

Significant, medium-sized effects of less all cause discontinuation with the following antipsychotics compared to placebo (direct comparisons); Paliperidone: 1 RCT, N = 146, OR 0.26, 95%CI 0.12 to 0.54, $p = 0.0003$ Olanzapine: 1 RCT, N = 107, OR 0.35, 95%CI 0.15 to 0.81, $p = 0.01$ Quetiapine: 1 RCT, N = 222, OR 0.43, 95%CI 0.23 to 0.80, $p = 0.007$ Risperidone: 2 RCTs, N = 413, OR 0.53, 95%CI 0.33 to 0.86, $p = 0.01$, $I^2 = 14\%$ Ziprasidone: 1 RCT, N = 383, OR 0.59, 95%CI 0.35 to 0.99, $p = 0.04$ Indirect network meta-analysis comparisons found no significant differences between placebo and olanzapine, paliperidone, quetiapine or risperidone. *No differences with placebo were found in direct comparisons for;* Aripiprazole: 1 RCT, N = 302, OR 1.82, 95%CI 0.86 to 3.86, $p = 0.12$ Asenapine: 1 RCT, N = 306, OR 0.91, 95%CI 0.50 to 1.65, $p = 0.76$
Social functioning
Significant, small to medium-sized effects of improved social functioning with the following antipsychotics compared to placebo (all indirect comparisons); Paliperidone: unclear sample size, SMD 0.55, 95%CI 0.18 to 0.93, $p < 0.05$ Risperidone: unclear sample size, SMD 0.51, 95%CI 0.14 to 0.89, $p < 0.05$ Asenapine: unclear sample size, SMD 0.42, 95%CI 0.09 to 0.76, $p < 0.05$ Aripiprazole: unclear sample size, SMD 0.30, 95%CI 0.02 to 0.59, $p < 0.05$ *No differences with placebo were found in indirect comparisons for;* Molindone: unclear sample size, SMD 0.23, 95%CI -0.40 to 0.86, $p > 0.05$ Olanzapine: unclear sample size, SMD 0.42, 95%CI -0.18 to 1.02, $p > 0.05$ Quetiapine: unclear sample size, SMD 0.31, 95%CI -0.03 to 0.64, $p > 0.05$ Ziprasidone: unclear sample size, SMD 0.11, 95%CI -0.18 to 0.40, $p > 0.05$

Risks	**Weight gain** Large effects were found in direct comparisons with placebo for olanzapine (SMD = 1.32, 95%CI 0.88 to 1.77) and quetiapine (SMD = 0.80, 95%CI 0.51 to 1.09); medium-sized effects were found for paliperidione (SMD = 0.57, 95%CI 0.23 to 0.92), asenapine (SMD = 0.44, 95%CI 0.20 to 0.69), risperidone (SMD = 0.43, 95%CI 0.23 to 0.62), and aripiprazole (SMD = 0.38, 95%CI 0.14 to 0.63), and no effect was found for ziprasidone (SMD = -0.04, 95%CI -0.36 to 0.28). **Extrapyramidal** Large effects were found in direct comparisons with placebo for

	paliperidone (OR = 29.33, 95%CI 1.74 to 495.11), ziprasidone (OR = 11.45, 95%CI 1.52 to 86.34), risperidone (OR = 4.32, 95%CI 2.31 to 8.06), and aripiprazole (OR = 3.98, 95%CI 1.51 to 10.51), and no effects were found for quetiapine (OR = 2.63, 95%CI 0.86 to 8.05), asenapine (OR = 2.09, 95%CI 0.68 to 6.41), or olanzapine (OR = 0.72, 95%CI 0.11 to 4.50). For akathasia in particular, no effects were found between any antipsychotic and placebo, apart from risperidone which showed a large effect of more frequent akathasia (OR = 5.64, 95%CI 1.45 to 21.96). Note: indirect network meta-analyses showed more akathisia with aripiprazole, olanzapine, and paliperidone than with placebo. **Triglycerides** No effects were found between any antipsychotic and placebo in direct comparisons, apart from olanzapine (SMD = 0.54, 95%CI 0.05 to 1.02) and quetiapine (SMD = 0.36, 95%CI 0.05 to 0.66), which showed medium-sized effects of greater increase in triglycerides. **Sedation** Large effects were found in indirect comparisons with placebo for olanzapine (OR = 6.77, 95%CI 1.86 to 24.60), paliperidone (OR = 4.91, 95%CI 1.42 to 16.99), risperidone (OR = 6.85, 95%CI 2.00 to 23.50), aripiprazole (OR = 2.96, 95%CI 1.05 to 8.34), and molindone (OR = 10.88, 95%CI 2.36 to 50.17). No effect was found for quetiapine or ziprasidone. **Prolactin** A small effect of decreased prolactin in an indirect comparison with placebo vs. aripiprazole (SMD = -0.30, 95%CI -0.59 to -0.01). Medium-sized effects of increased prolactin with olanzapine (SMD = 0.49, 95%CI 0.09 to 0.87) and paliperidone (SMD = 0.70, 95%CI 0.36 to 1.03), and large effects of increased prolactin with risperidone (SMD = 1.19, 95%CI 0.92 to 1.45. No effect was found for quetiapine, ziprasidone, molindone or asenapine.
Consistency in results	Consistent where applicable (risperidone [>1 RCT]).
Precision in results	Precise for SMDs, apart from indirect comparisons for all molindone and olanzapine for social functioning, imprecise for all ORs.
Directness of results	Direct, apart from network analyses.
Comparison 2	**Antipsychotics vs. antipsychotics in children and adolescents (8 to 19 years) with schizophrenia spectrum disorders.**
Summary of evidence	**Low quality evidence (unclear sample sizes and consistency,**

	imprecise, indirect) is unable to determine the benefits or harms of any antipsychotic over any other antipsychotic for children and adolescents with schizophrenia.
Overall symptoms **Measured on the PANSS**	
There were no significant differences in comparisons between antipsychotics apart from the following indirect comparisons with large effects; Molindone over ziprasidone: unclear sample size, SMD -1.02, 95%CI -1.78 to -0.26, $p < 0.05$ Olanzapine over ziprasidone: unclear sample size, SMD -0.85, 95%CI -1.44 to -0.27, $p < 0.05$ Quetiapine over ziprasidone: unclear sample size, SMD -0.81, 95%CI -1.39 to -0.22, $p < 0.05$ *And the following indirect comparisons with medium-sized effects;* Paliperidone over ziprasidone: unclear sample size, SMD -0.63, 95%CI -1.18 to -0.08, $p < 0.05$ Risperidone over ziprasidone: unclear sample size, SMD -0.51, 95%CI -1.01 to -0.01, $p < 0.05$	
Negative symptoms	
There were no significant differences in comparisons between antipsychotics apart from the following indirect comparisons with medium-sized effects; Molindone over ziprasidone: unclear sample size, SMD -0.66, 95%CI -1.24 to -0.07, $p < 0.05$ Olanzapine over ziprasidone: unclear sample size, SMD -0.53, 95%CI -0.99 to -0.07, $p < 0.05$ Risperidone over ziprasidone: unclear sample size, SMD -0.44, 95%CI -0.82 to -0.06, $p < 0.05$	
Other outcomes	
There were no differences between any antipsychotic for positive symptoms, social functioning or all cause discontinuation.	
Risks	**Weight gain** *The following comparisons were significant for less weight gain;* Molindone over olanzapine (direct SMD = -1.77 [large effect], 95%CI -2.31 to -1.23), quetiapine (indirect SMD = -1.23 [large effect], 95%CI -1.79 to -0.68), paliperidone (indirect SMD = -1.07 [large effect], 95%CI -1.61 to -0.53), risperidone (direct SMD = -0.93 [large effect], 95%CI -1.24 to -0.47), asenapine (indirect SMD = 0.83 [large effect], 95%CI 0.29 to 1.36), and aripiprazole (indirect SMD = 0.65 [medium-sized effect], 95%CI 0.13 to 1.17). Ziprasidone over olanzapine (indirect SMD = 1.25 [large effect], 95%CI 0.77 to 1.74), quetiapine (indirect SMD = 0.89 [large effect],

	95%CI 0.46 to 1.32), paliperidone (indirect SMD = 0.73 [medium-large effect], 95%CI 0.33 to 1.14), asenapine (indirect SMD = 0.49 [medium-sized effect], 95%CI 0.09 to 0.89), and risperidone (indirect SMD = 0.46 [medium-sized effect], 95%CI 0.08 to 0.83). Risperidone over olanzapine (direct SMD = 0.60 [medium-sized effect], 95%CI 0.19 to 1.01), and quetiapine (indirect SMD = 0.44 [medium-sized effect], 95%CI 0.08 to 0.79). Aripiprazole over olanzapine (indirect SMD = -0.94 [large effect], 95%CI -1.37 to -0.52), quetiapine (indirect SMD = -0.58 [medium-sized effect], 95%CI -0.94 to -0.22), and paliperidone (direct SMD = -0.50 [medium-sized effect], 95%CI -0.76 to -0.23). Asenapine over olanzapine (indirect SMD = -0.77 [medium-large effect], 95%CI -1.21 to -0.32), and quetiapine (indirect SMD = -0.40 [medium-sized effect], 95%CI -0.78 to -0.03). Paliperidone over olanzapine (indirect SMD = 0.52 [medium-sized effect], 95%CI 0.07 to 0.97). **Extrapyramidal** *The following comparisons were significant for fewer extrapyramidal side effects;* Olanzapine over molindone (direct; all extrapyramidal OR = 4.91, [large effect], 95%CI 1.58 to 15.25). Risperidone over molindone (direct; akathisia OR = 6.84, [large effect], 95%CI 2.04 to 22.86). Asenapine over molindone (indirect all extrapyramidal OR = 0.18, [large effect], 95%CI 0.03 to 0.97). Aripiprazole over molindone (indirect; akathisia OR = 0.13, [large effect], 95%CI 0.03 to 0.60). **Triglycerides** *No significant differences between any antipsychotic.* **Prolactin** *The following comparisons were significant for lower prolactin levels;* Aripiprazole over olanzapine (indirect SMD = -0.78, [large effect], 95%CI -1.27 to -0.29). Aripiprazole over paliperidone (indirect SMD = -1.00, [large effect], 95%CI -1.32 to -0.68). Aripiprazole over risperidone (indirect SMD = -1.49, [large effect], 95%CI -1.88 to -1.09). Molindone over risperidone (indirect SMD = -1.11, [large effect],

	95%CI -1.62 to -1.61). Olanzapine over risperidone (indirect SMD = -0.71, [medium-large effect], 95%CI -1.11 to -0.31). Paliperidone over risperidone (indirect SMD = -0.49, [medium-sized effect], 95%CI -0.92 to -0.06). Quetiapine over paliperidone (indirect SMD = -0.53, [medium-sized effect], 95%CI -0.01 to -1.05). Quetiapine over risperidone (indirect SMD = -1.02, [large effect], 95%CI -1.50 to -0.54).
Consistency in results	Not able to be assessed for network analysis (no consistency measure is reported).
Precision in results	Mostly imprecise
Directness of results	Mostly indirect

Sarkar S, Grover S

Antipsychotics in children and adolescents with schizophrenia: A systematic review and meta-analysis

Indian Journal of Pharmacology 2013; 45(5): 439-446

View review abstract online

Comparison	**First generation vs. second-generation antipsychotics for children and adolescents.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, some inconsistency, precise, direct) suggests second-generation antipsychotics may be more efficacious than first-generation antipsychotics. Extrapyramidal symptoms may be more common with first-generation antipsychotics, while sedation and weight gain may be more common with second-generation antipsychotics.**
Overall efficacy	

A significant, medium-sized effect favouring second-generation antipsychotics over first-generation antipsychotics; N = 243, *d* = -0.363, 95%CI -0.562 to -0.163, $p < 0.05$, $I^2 = 48.2\%$ Authors report that clozapine had highest effect size compared with placebo followed by haloperidol, risperidone, olanzapine, paliperidone (medium dose), aripiprazole, quetiapine (higher dose), aripiprazole (lower dose), paliperidone (high dose), quetiapine (lower dose) and paliperidone (lower dose).	
Risks	Authors report that extrapyramidal symptoms were the most common side effects encountered with first generation antipsychotics, while sedation and weight gain were seen more frequently with second generation antipsychotics.
Consistency in results	Moderate heterogeneity.
Precision in results	Precise
Directness of results	Direct

Seida JC, Schouten JR, Boylan K, Newton AS, Mousavi SS, Beaith A, Vandermeer B, Dryden DM, Carrey N

Antipsychotics for Children and Young Adults: A Comparative Effectiveness Review

Pediatrics 2012; 129: e771

View review abstract online

Comparison	**First generation vs. second generation antipsychotics for children and young adults (up to 24 years).**
Summary of evidence	**Moderate quality evidence (unclear sample size, consistent, unable to assess precision, direct) suggests second-generation antipsychotics may be more efficacious than first-generation antipsychotics for improving global state.**
Global and mental state	
Results favoured second generation antipsychotics over first generation antipsychotics for global improvement; Global state (CGI): 3 RCTs, N not reported, MD = 20.8, 95%CI 21.3 to 20.3, $p < 0.05$, $I^2 = 0\%$	

No differences for positive or negative symptoms, medication adherence or suicide-related behaviours (data not reported).	
Risks	Not reported separately for schizophrenia.
Consistency in results	Consistent
Precision in results	Unable to assess; MDs not standardised.
Directness of results	Direct

Stafford M, Stafford R, Mayo-Wilson E, Loucas CE, James A, Hollis C, Birchwood M, Kendall T

Efficacy and Safety of Pharmacological and Psychological Interventions for the Treatment of Psychosis and Schizophrenia in Children, Adolescents and Young Adults: A Systematic Review and Meta-Analysis

PLOS ONE 2015; 10(2): e0117166. doi:10.1371/journal.pone.0117166

View review abstract online

Comparison	**Antipsychotics (quetiapine, aripiprazole, risperidone, paliperidone, amisulpride, olanzapine and haloperidol) vs. placebo in adolescents 15-20 years old.**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistency, precise, direct) suggests small to medium-sized benefits of antipsychotic medication for global and mental state compared to placebo, although weight gain and discontinuation due to side effects are higher with antipsychotics.**
Global and mental state	
Significant, small to medium-sized effects for improved symptoms with antipsychotics; PANSS total: 4 RCTs, N = 782, g = -0.42, 95%CI -0.58 to -0.26, $p < 0.05$, $I^2 = 0\%$ PANSS positive: 6 RCTs, N = 952, g = -0.42, 95%CI -0.56 to -0.28, $p < 0.05$, $I^2 = 0\%$ PANSS negative: 6 RCTs, N = 845, g = -0.32, 95%CI -0.46 to -0.18, $p < 0.05$, $I^2 = 0\%$ Depression: 3 RCTs, N = 393, g = -0.24, 95%CI -0.45 to -0.03, $p < 0.05$, $I^2 = 0\%$ Psychosocial functioning: 4 RCTs, N = 919, g = -0.37, 95%CI -0.52 to -0.23, $p < 0.05$, $I^2 = 15\%$	

Global state: 3 RCTs, N = 621, *g* = -0.41, 95%CI -0.58 to -0.25, *p* < 0.05, I^2 = 0% Effect sizes were slightly higher in studies with higher dosages. No significant differences were reported between individual antipsychotics, except for a small effect for olanzapine on negative symptoms compared with haloperidol, and a small effect for risperidone compared with quetiapine on positive symptoms in first-episode psychosis patients. Authors report high risk of study and publication bias.	
Risks	A medium effect of antipsychotics having a more adverse effect on mean weight gain (SMD = 0.63, 95%CI 0.32 to 0.93, I^2 = 68%), and there was more discontinuation due to side effects (RR = 2.44, 95% CI, 1.12 to 5.31, *p* < 0.05, I^2 = 0%).
Consistency in results	Consistent for global and mental state and discontinuation, inconsistent for weight gain.
Precision in results	Precise for global and mental state and weight gain, imprecise for discontinuation.
Directness of results	Direct

Explanation of acronyms

AIMS = Abnormal Involuntary Movements Scale, BPRS = Brief Psychiatric Rating Scale, CGAS = Children's Global Assessment Scale, CGI = Clinical Global Improvement scale, CI = confidence interval, *g* = Hedges g (SMD), I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, *p* = statistical probability of obtaining that result (*p* < 0.05 generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, RCT = randomised controlled trial, RD = risk difference, 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[11].

† 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[11].

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[12]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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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[11];

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

§ 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[13].

‖ 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. Kumar A, Datta SS, Wright SD, Furtado VA, Russell PS (2013): Atypical antipsychotics for psychosis in adolescents. *Cochrane Database of Systematic Reviews* 10: CD009582.
4. Ardizzone I, Nardecchia F, Marconi A, Carratelli TI, Ferrara M (2010): Antipsychotic medication in adolescents suffering from schizophrenia: a meta-analysis of randomized controlled trials. *Psychopharmacology Bulletin* 43: 45-66.
5. Sarkar S, Grover S (2013): Antipsychotics in children and adolescents with schizophrenia: A systematic review and meta-analysis. *Indian Journal of Pharmacology* 45: 439-46.
6. Seida JC, Schouten JR, Boylan K, Newton AS, Mousavi SS, Beaith A*, et al.* (2012): Antipsychotics for children and young adults: a comparative effectiveness review. *Pediatrics* 129: e771-84.
7. Stafford MR, Mayo-Wilson E, Loucas CE, James A, Hollis C, Birchwood M*, et al.* (2015): Efficacy and safety of pharmacological and psychological interventions for the treatment of psychosis and schizophrenia in children, adolescents and young adults: A systematic review and meta-analysis. *PLoS ONE* 10.
8. Pagsberg AK, Tarp S, Glintborg D, Stenstrom AD, Fink-Jensen A, Correll CU*, et al.* (2017): Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* 56: 191-202.
9. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Chaimani A*, et al.* (2018): Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. *European Neuropsychopharmacology* 28: 659-74.
10. Arango C, Ng-Mak D, Finn E, Byrne A, Loebel A (2019): Lurasidone compared to other atypical antipsychotic monotherapies for adolescent schizophrenia: a systematic literature review and network meta-analysis. *European Child & Adolescent Psychiatry*: doi.org/10.1007/s00787-019-1425-2.
11. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
12. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
13. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*