[New 2015]

Pharmacological interventions in adolescents with psychotic disorders

SCOPING QUESTION: Is pharmacological intervention effective and safe for treatment of psychotic disorders in adolescents (including schizophrenia and bipolar disorder)?

BACKGROUND

Psychotic disorders (including schizophrenia and bipolar disorders) are severe mental disorders associated with considerable disability, morbidity and mortality and which require a disproportionate share of mental health services (Mueser and McGurk, 2004; Hirschfeld and Vornik, 2005). The onset of psychotic and bipolar disorders is often during adolescence (van Os and Kapur, 2009; Kessler et al., 2005, Ben Amor, 2012) and patients with adolescent onset of psychosis are more likely to present with clinical characteristics that are related to a poorer outcome (Ballageer et al., 2005). Despite clinical studies showing that adolescents may be at higher risk for side-effects (such as weight gain, prolactin changes and extrapyramidal symptoms), the prescription of antipsychotics for the treatment of psychosis and bipolar disorder in adolescence has consistently increased over the last 15 years, while the age of prescription has decreased (Schneider et al., 2014; Ben Amor, 2012). However, evidence from studies on adults generally guides the treatment of schizophrenia and bipolar disorder for adolescents (Datta et al., 2014). Prescribing antipsychotics to adolescents remains controversial due to the uncertainty surrounding medication efficacy and safety. A recommendation on antipsychotic medication use for psychotic and bipolar disorders in adolescents is necessary for clinical practice.

The 2010 WHO mhGAP guidelines do not give specific recommendations for adolescents with psychotic or bipolar disorders. This new scoping question was included in the mhGAP guideline update to recognize the importance of treating early-onset psychosis and it aims at identifying the effectiveness and safety of antipsychotics in adolescents with psychotic and bipolar disorders.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adolescents* with psychotic disorders (including schizophrenia and bipolar disorder)
- **Interventions:** First- and second-generation antipsychotic medications
- **Comparison:** Placebo
- **Outcomes:**
  - **Critical – Symptoms severity, adverse effects of treatment**
  - **Important** – Functioning, school achievement, quality of life, treatment adherence, user and family satisfaction with care

** WHO identifies adolescence as the period in human growth and development that occurs after childhood and before adulthood, aged 10–19 years.*

[New 2015]

Search strategy

The search was conducted in Week 34 of 2014 using the following databases: the Cochrane Database of Systematic Reviews, PubMED (clinical queries), the Campbell Collaboration, LILACS, PsycINFO, Embase and PILOTS. Keywords used included *"antipsychotic*" AND "(adolescent* OR child* OR young adults)" AND "systematic review"*.

In databases that allowed specifically for the selection of systematic reviews and meta-analyses (such as PubMED, PsycINFO and Embase) this option was selected and the only keywords searched were *"antipsychotic*" AND "(adolescent* OR child* OR young adults)"*.

Studies were included if they were systematic reviews of treatment studies with adolescents or young adults and were published from 2010 onwards. Studies including children less than 10 years old were excluded. A search for additional studies was conducted in used the databases PubMED, PsycINFO, Embase and Google Scholar. Keywords used included *"antipsychotic*" AND "(adolescent* OR child* OR young adults)"*.

Studies excluded from systematic reviews were also considered.

Systematic reviews or studies included in GRADE tables or footnotes

- Findling RL, McKenna K, Earley WR, Stankowski J, Pathak S (2012). Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. Journal of Child and Adolescent Psychopharmacoly.22(5):327-42.

- Fraguas D, Correll CU, Merchan-Naranjo J, Rapado-Castro M, Parellada M, Moreno C, Arango C (2011). Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. European Neuropsychopharmacology.21(8): 621-645. doi:10.1016/j.euroneuro.2010.07.002.

- Kumar A, Datta SS, Wright SD, Furtado VA, Russell PS (2013). Atypical antipsychotics for psychosis in adolescents. Cochrane Database of Systematic Reviews.10:CD009582. doi:10.1002/14651858.CD009582.pub2.

- Seida JC, Schouten JR, Boylan K, Newton AS, Mousavi SS, Beaith A, Vandermeer B, Dryden DM, Carrey N (2012). Antipsychotics for children and young adults: a comparative effectiveness review. Pediatrics.129(3):e771-84. doi:10.1542/peds.2011-2158.

Excluded from GRADE tables and footnotes

Sarkar S and Grover S (2013). Antipsychotics in children and adolescents with schizophrenia: A systematic review and meta-analysis. Indian Journal of Pharmacology.45:439-46. doi:10.4103/0253-7613.117720.
REASON FOR EXCLUSION: Wide inclusion criteria (in terms of participant age and study design). Includes analysis of only one efficacy outcome. Confidence intervals (CIs) not reported.

Zuddas A1, Zanni R, Usala T (2011). Second-generation antipsychotics (SGAs) for non-psychotic disorders in children and adolescents: A review of the randomized controlled studies. European Neuropsychopharmacology.21(8):600-620. doi:10.1016/j.euroneuro.2011.04.001.
REASON FOR EXCLUSION: This review examines the wrong population and included studies are not pooled.

PICO Table

Population 1: Adolescents with psychotic disorders (including schizophrenia)					
Intervention	**Comparison**	**Outcome**	**Systematic reviews used for GRADE**	**Justification for systematic review used**	**Relevant GRADE Table(s)**
Second-generation antipsychotics (SGAs)	Placebo	Symptoms severity	Kumar et al. (2013)	This is the most recent Cochrane Review available.	Table 1
		Functioning	No evidence available		
		School achievement	No evidence available		
		Quality of life	Kumar et al. (2013)	This is the most recent Cochrane Review available.	
		Adverse effects of treatment	Kumar et al. (2013)	This is the most recent Cochrane Review available.	
		Treatment adherence	Kumar et al. (2013)	This is the most recent Cochrane Review available.	
		User and family satisfaction with care	No evidence available		
First-generation antipsychotics (FGAs)	Placebo	All outcomes	No evidence available		N/A
SGAs	FGAs	Symptoms severity	Kumar et al. (2013)	This is the most recent Cochrane Review available.	Table 2
		Functioning	No evidence available		
		School achievement	No evidence available		
		Quality of life	No evidence available		
		Adverse effects of treatment	Kumar et al. (2013)	This is the most recent Cochrane Review available.	
		Treatment adherence	Kumar et al. (2013)	This is the most recent Cochrane Review available.	

		Users' and families' satisfaction with care	No evidence available		
Population 2: Adolescents with bipolar disorder					
SGAs	Placebo	Symptoms severity	Seida et al. (2012)	This the most recent and comprehensive systematic review available.	Table 3
		Functioning	No evidence available		
		School achievement	No evidence available		
		Quality of life	No evidence available		
		Adverse effects of treatment	No evidence available		
		Treatment adherence	Seida et al. (2012)	This is the most recent and comprehensive systematic review available.	
		Users' and families' satisfaction with care	No evidence available		
FGAs	Placebo	All outcomes	No evidence available		

Narrative description of the studies that went into the analysis

Kumar et al. (2013) included two 6-week studies comparing SGA medications with placebo in adolescents with DSM-IV schizophrenia, in both inpatient and outpatient settings. In a multi-centre randomized controlled trial (RCT) (in the United States of America [USA], Europe, South America, Asia, the Caribbean and South Africa) Findling et al. (2008) randomized 302 adolescents (with an age range of 13 to 17; mean age 15.4) to aripiprazole 10 mg (N = 100) and aripiprazole 30 mg (N = 102) or placebo (N = 100). In the other 6-week study, Kryzhanovskaya et al. (2009) randomized 107 adolescents (with an age range of 13 to 17; mean age 16) to olanzapine (mean dose 11.1 ± 4.0 mg, N = 72) or placebo (N = 35) in a multi-centre RCT (in USA and Russia). There was no difference between the efficacies of both antipsychotics, but patients receiving aripiprazole had significantly lower blood cholesterol, suggesting that aripiprazole is less associated with weight gain in terms of adverse effects. The authors also included the five RCTs, outlined below in Figure 1, which compared SGA medications with FGA medications.

Figure 1. Summary of RCTs included in the Kryhanovskaya et al. (2009) review

Study reference	Duration	Country or	Diagnosis	N	Mean age	Interventions	High risk of bias

		region					
Huo et al. (2007)	8 weeks	China	Schizophrenia (CCMD-3)	40	14	Risperidone Perphenazine	-
Kumar et al. (1996)	6 weeks	USA	Schizophrenia (DSM-III-R)	21	14	Clozapine Haloperidol	Selective reporting and low sample size
Sikich et al. (2004)	8 weeks	North America	Psychotic disorder (K-SADS-PL,SCID)	51	15	Risperidone Olanzapine Haloperidol	Other bias
Sikich et al. (2008)	8 weeks	North America	Schizophrenia, schizoaffective disorder or schizophreniform disorder (DSM IV)	116	8 to 19	Molindone Risperidone Olanzapine	-
Xiong et al. (2004)	8 weeks	China	Childhood-onset schizophrenia (CCMD-2-R).	60	14	Risperidone Chlorpromazine	Blinding

When the findings of all five trials comparing SGAs with an FGA (such as haloperidol, chlorpromazine, perphenazine, molindone) were collated, with no difference in the mean end-point Brief Psychiatric Rating Scale (BPRS) score noted between the two arms (5 RCTs, n = 236, MD -1.08, 95% CI -3.08 to 0.93). Most adverse effects (including extrapyramidal symptoms (EPS), treatment-emergent hyperprolactinaemia and anticholinergic adverse effects) were similar for FGA- and SGA medications. Less weight gain was reported with some of the typical antipsychotic medications. There were no significant differences in leaving the study because of adverse effects (3 RCTs, n = 187, RR 0.65, 95% CI 0.36 to 1.15) or for any reason (3 RCTs, n = 187, RR 0.62, 95% CI 0.39 to 0.97). The authors concluded that there is no convincing evidence suggesting that SGAs are superior to FGAs for the treatment of adolescents with psychosis.

Findling et al. (2012) published a study after the Kumar et al.'s (2013) review content assessment. Findling et al. (2012) led a 6-week RCT with 220 patients aged 13–17 years, with a DSM-IV-TR diagnosis of schizophrenia randomized to quetiapine 400 mg (N = 73), quetiapine 800 mg (N = 74) or placebo (N = 73). The trial was conducted in 43 centres located in Asia, Central- and Eastern Europe, South Africa, and USA. The primary efficacy measure was the mean change from baseline in Positive and Negative Syndrome Scale (PANSS) total score. Safety and tolerability assessments included the reported incidence and severity of adverse events and withdrawals related to adverse events.

Seida et al. (2012) systematically reviewed the effectiveness and safety of antipsychotics for patients aged less than 24 years, with a variety psychiatric and behavioural conditions. This review included eight RCTs (3–8 weeks each, mainly conducted in USA) comparing SGA medications (aripiprazole N = 2; olanzapine N = 1;quetiapine N = 3; risperidone N = 1; ziprasidone N = 1) with placebo in adolescents (with an age range of 10 to 18 years among both inpatients and outpatients), with DSM-IV diagnostic criteria for bipolar disorder. Seven studies enrolled patients with acute manic or mixed episode and one study included adolescents with a depressive episode. One study included patients with comorbid attention-deficit/hyperactivity disorder (ADHD).

GRADE Tables

Table 1. Antipsychotics vs. placebo for treatment of psychotic disorders in adolescents

Authors: L Tarsitani and C Barbui
Question: Are antipsychotics effective and safe for treatment of psychotic disorders in adolescents compared to placebo?
Bibliography: Kumar A, Datta SS, Wright SD, Furtado VA, Russell PS (2013). Atypical antipsychotics for psychosis in adolescents. Cochrane Database of Systematic Reviews.10:CD009582. doi:10.1002/14651858.CD009582.pub2.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotics	Placebo	Relative (95% CI)	Absolute		
Symptoms severity – No response (follow-up 6 weeks; assessed with BPRS-C, PANSS)												
2	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	46/171 (26.9%)	63/133 (47.4%)	RR 0.76 (0.63 to 0.92)[3]	114 fewer per 1000 (from 38 fewer to 175 fewer)	⊕OOO VERY LOW	CRITICAL
Functioning												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
School achievement												
0	No evidence available					None	-	-	-	-		IMPORTANT
Quality of life (follow-up 6 weeks; assessed with PQ-LES-Q score at 6 weeks)												
0[4]	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Adverse effects of treatment – Sedation (follow-up 6 weeks)												
1[5]	Randomized trials	Very serious[6]	No serious inconsistency	Serious[7]	Serious[8]	None	17/72 (23.6%)	1/35 (2.9%)	RR 8.26 (1.15 to 59.61)[9]	207 more per 1000 (from 4 more to 1000 more)	⊕OOO VERY	CRITICAL

								0%		-	LOW	
Adverse effects of treatment - Weight gain ≥ 7% (follow-up 6 weeks)												
1[5]	Randomized trials	Very serious[6]	No serious inconsistency	Serious[7]	Serious[8]	None	33/72 (45.8%)	5/34 (14.7%)	RR 3.12 (1.34 to 7.27)[10]	312 more per 1000 (from 50 more to 922 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Adverse effects of treatment - Corrected QT, QT/ms (follow-up 6 weeks; measured with corrected QT, QT/ms from baseline to end-point; better indicated by lower values)												
1[5]	Randomized trials	Very serious[6]	No serious inconsistency	Serious[7]	Serious[8]	None	72	35	-	MD 6.30 lower (12.51 to 0.09 lower)[11]	⊕OOO VERY LOW	CRITICAL
Adverse effects of treatment - Prolactin increase (follow-up 6 weeks; measured with prolactin increase from baseline to end-point; better indicated by lower values)												
2	Randomized trials	Very serious[1]	Very serious[12]	Serious[2]	Serious[13]	None	156	126	-	MD 3.30 higher (1.72 lower to 8.31 higher)[11]	⊕OOO VERY LOW	CRITICAL
Adverse effects of treatment - EPS (not reported)[14]												
2	-	-[1]	-[12]	-[2]	-[13]	None	-	-	-[11]	-	⊕OOO VERY LOW	CRITICAL
Treatment adherence - Leaving the study early for any reason, olanzapine vs. placebo (follow-up 6 weeks)												
1[5]	Randomized trials	Very serious[6]	No serious inconsistency	Serious[7]	Serious[8]	None	23/72 (31.9%)	20/35 (57.1%)	RR 0.56 (0.36 to 0.87)[15]	251 fewer per 1000 (from 74 fewer to 366 fewer)	⊕OOO VERY LOW	IMPORTANT
								0%		-		
Treatment adherence - Leaving the study early for any reason, aripirazole vs. placebo (follow-up 6 weeks)												
1[16]	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[7]	Serious[13]	None	18/102 (17.6%)	10/100 (10%)	RR 1.76 (0.86 to 3.63)[15]	76 more per 1000 (from 14 fewer to 263 more)	⊕⊕OO LOW	IMPORTANT
								0%		-		

User and family satisfaction with care												
0	No evidence available					none	-	-	-	-		IMPORTANT
								0%		-		

[1] Dropout rate is >30% in 1 out of 2 studies.
[2] Patients with psychotic disorders other than schizophrenia were excluded.
[3] Estimates < 1 favours SGAs.
[4] Findling et al. (2008). Mean end point PQ-LES-Q score at 6 weeks (data skewed, high score = good): Aripiprazole 30 mg, Mean 50.2 SD 90 N = 98; Placebo, Mean 48.8 SD 94.4 N = 98. Not reported in the meta-analysis because data were highly skewed.
[5] Kryzhanovskaya et al. (2009): olanzapine vs. placebo.
[6] Dropout rate is > 30% in the study.
[7] Only one study contributed to the analysis and patients with psychotic disorders other than schizophrenia were excluded.
[8] Only one study with around 100 patients.
[9] Estimates > 1 more sedation with the intervention.
[10] Estimates > 1 more weight gain with the intervention.
[11] Estimates < 0 favours SGAs.
[12] $I^2$is 93%
[13] 95% CI includes no effect and appreciable harm.
[14] From 36 studies comparing SGAs with placebo in adolescents with psychiatric and behavioral conditions (including the studies on schizophrenia); Seida et al. (2012). EPS: Significant effect in favour of placebo over aripiprazole (RR = 4.2; 95% CI: 2.4 to 7.2) and risperidone (RR = 2.7; 95% CI: 1.4 to 4.9). No significant differences for placebo compared with olanzapine or quetiapine.
[15] Estimates < 1 favours SGAs.
[16] Findling et al. (2008) aripiprazole vs. placebo. In Findling et al. (2012) with 220 adolescents least-squares mean change in PANSS total score from baseline was -27.31 with quetiapine 400 mg/day; 28.44 (p = 0.043 vs placebo) with quetiapine 800 mg/day (p = 0.009 vs placebo); and -19.15 with placebo. Effect sizes calculated by Sarkar and Grover (2013) are 0.34 and 0.44 for quetiapine 400 mg and 800 mg, respectively. CGI-I score supported the primary outcome measure. Mean changes in body weight at end point were 2.2 kg and 1.8 kg for quetiapine 400 mg/day and 800 mg/day, respectively, and -0.4 kg for placebo.

[New 2015]

Table 2. SGAs vs FGAs for treatment of psychotic disorders in adolescents

Authors: L Tarsitani and C Barbui
Question: Are second-generation antipsychotics effective and safe for treatment of psychotic disorders in adolescents compared to first-generation antipsychotics?
Bibliography: Kumar A, Datta SS, Wright SD, Furtado VA, Russell PS (2013). Atypical antipsychotics for psychosis in adolescents. Cochrane Database of Systematic Reviews.10:CD009582. doi:10.1002/14651858.CD009582.pub2.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGAs	FGAs	Relative (95% CI)	Absolute		
Symptoms severity - Mean end-point scores (follow-up 6-8 weeks; measured with BPRS; better indicated by lower values)												
7[1]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	171	171	-	MD 1.34 lower (3.24 lower to 0.56 higher)	⊕⊕OO LOW	CRITICAL
Symptoms severity - No improvement (follow-up 6-8 weeks; assessed with BPRS)												
2	Randomized trials	Serious[2,4]	No serious inconsistency	No serious indirectness	Very serious[5]	None	7/50 (14%)	7/50 (14%)	RR 1.00 (0.38 to 2.62)	0 fewer per 1000 (from 87 fewer to 227 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Functioning												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
School achievement												
0	No evidence available					None	-	-	-	-		IMPORTANT
Quality of life (follow-up 6 weeks)												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		

Adverse effects of treatment - Leaving the study early for adverse effects (follow-up 8 weeks)												
3	Randomized trials	Serious[6]	Serious[7]	No serious indirectness	Serious[8]	None	19/121 (15.7%)	16/66 (24.2%)	RR 0.65 (0.36 to 1.15)	85 fewer per 1000 (from 155 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Adverse effects of treatment - Sedation (follow-up 8 weeks)												
2	Randomized trials	Serious[9]	No serious inconsistency	Serious[10]	Very serious[11]	None	9/40 (22.5%)	8/41 (19.5%)	RR 1.19 (0.55 to 2.55)	37 more per 1000 (from 88 fewer to 302 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Adverse effects of treatment - Body weight (kg) (follow-up 8 weeks; better indicated by lower values)												
2[12]	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[13]	None	76	80	-	MD 1.71 higher (4.69 lower to 8.11 higher)	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects of treatment - Prolactin increase (follow-up 8 weeks; assessed with mean end-point serum prolactin concentration (mcg/L))												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[10]	Very serious[14]	None	2/10 (20%)	0/11 (0%)	RR 5.45 (0.29 to 101.55)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Treatment adherence - Leaving the study early for any reason (follow-up 8 weeks)												
3	Randomized trials	Serious[6]	No serious inconsistency	No serious indirectness	No serious imprecision	None	27/121 (22.3%)	23/66 (34.8%)	RR 0.62 (0.39 to 0.97)	132 fewer per 1000 (from 10 fewer to 213 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Adverse effects of treatment - Extrapyramidal side effects, any (follow-up 8 weeks; measured with AIMS; better indicated by lower values)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[10]	Very serious[14]	None	10	11	-	MD 0.10 lower (3.72 lower to 3.52 higher)	⊕OOO VERY LOW	CRITICAL
User and family satisfaction with care												

0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		

[1] Seven comparisons, five studies.
[2] Dropout rate is 36% in one out of five studies.
[3] 95% CI includes no effect, appreciable benefit and harm.
[4] Blindness is unclear (not described) in both studies.
[5] 95% CI includes no effect, appreciable benefit and harm and sample size is 100.
[6] Dropout rate is 36% in one out of three studies and blindness is unclear (not described) in one study.
[7] I^2 = 57%
[8] 95% CI includes no effect and appreciable benefit.
[9] Blindness is unclear (not described) in one study.
[10] Only one study contributed to the analysis.
[11] 95% CI includes no effect and appreciable harm and sample size is low.
[12] One study, two comparisons.
[13] 95% CI includes no effect, appreciable benefit and harm.
[14] 95% CI includes no effect, appreciable benefit and harm and sample size is very low.

Table 3. Antipsychotics vs. placebo for treatment of bipolar disorder in adolescents

Authors: L Tarsitani and C Barbui
Question: Are antipsychotics effective and safe for treatment of bipolar disorder in adolescents compared to placebo?
Bibliography: Seida JC, Schouten JR, Boylan K, Newton AS, Mousavi SS, Beaith A, Vandermeer B, Dryden DM, Carrey N (2012). Antipsychotics for children and young adults: a comparative effectiveness review. Pediatrics.129(3):e771-84. doi:10.1542/peds.2011-2158.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antipsychotics**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Symptoms severity CGI (follow-up 3-8 weeks; measured with CGI–Bipolar scale[1]; better indicated by lower values)												
6	Randomized trials	No serious risk of bias[2]	no serious inconsistency[3]	Serious[4]	No serious imprecision	None	0[5,6]	-	-	MD 0.7 lower (0.8 to 0.5 lower)[7,8]	⊕⊕⊕O MODERATE	CRITICAL
Symptoms severity - Manic symptoms[8] (follow-up 3-8 weeks; measured with YMRS[8]; better indicated by lower values)												
8	Randomized trials	no serious risk of bias[2]	Very serious[9]	Serious[4]	No serious imprecision	None	0[5]	-	-	MD 0 higher (0 to 0 higher)[7,8,10]	⊕OOO VERY LOW	CRITICAL
Symptoms severity - Depressive symptoms[11] (follow-up 3-8 weeks; better indicated by lower values)												

4	Randomized trials	No serious risk of bias[2]	Very serious[9]	Serious[4]	No serious imprecision	None	0[5]	-	-	MD 0 higher (0 to 0 higher)[7]	⊕OOO VERY LOW	CRITICAL
Functioning												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
School achievement												
0	No evidence available					None	-	-	-	-		IMPORTANT
Quality of life												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Adverse effect of treatment - EPS (not reported)[12]												
0	-	-	-	-	-	None	-	-	-	-		CRITICAL
Adverse effect of treatment - Prolactin increase (not reported)[13]												
0	-	-	-	-	-	None	0	-	-	-		CRITICAL
Adverse effect of treatment - Sedation (not reported)[14]												
0	-	-	-	-	-	None	-	-	-	-		CRITICAL
Adverse effect of treatment - Weight gain (not reported)[15]												
0	-	-	-	-	-	None	0	-	-	-		CRITICAL
Treatment adherence (follow-up 3-8 weeks)												
2	Randomized trials	No serious risk of bias[2]	No serious inconsistency[16]	Serious[17]	Serious[18]	None	-[5,6]	-	RR 2.0 (1 to 4)	-	⊕⊕OO LOW	IMPORTANT
								0%		-		

User and family satisfaction with care												
0	No evidence available[19]					None	-	-	-	-		IMPORTANT
								0%		-		

[1] CGI - Version adapted for manic and depressive symptoms.
[2] Dropout rate not available.
[3] I^2 = 36%.
[4] Only one study included adolescents with a depressive episode. One study included patients with comorbid attention-deficit/hyperactivity disorder. Four studies include patients from 10 years of age.
[5] Not reported.
[6] Seida et al. (2012) included 11 RCTs with antipsychotics in adolescents: N = 1449 (range: 30 to 296).
[7] Estimates < 1 favours SGAs.
[8] "SGAs (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone) had a greater effect on manic symptoms, as assessed by the Young Mania Rating Scale (YMRS), than placebo (Seita et al. 2012).
[9] High heterogeneity, according to Seita et al. (2012).
[10] Studies not pooled due to high heterogeneity.
[11] No significant difference from placebo for depressive symptoms found in aripiprazole, olanzapine and quetiapine (Seita et al., 2012).
[12] From 36 studies comparing SGAs with placebo in adolescents with psychiatric and behavioral conditions (including the GRADed studies on bipolar disorders) (Seida et al., 2012). EPS: Significant effect in favour of placebo over aripiprazole (RR = 4.2; 95% CI: 2.4 to 7.2) and risperidone (RR = 2.7; 95% CI: 1.4 to 4.9). No significant differences for placebo compared with olanzapine or quetiapine.
[13] From 36 studies comparing SGAs with placebo in adolescents with psychiatric and behavioral conditions (including the GRADed studies on bipolar disorders)(Seida et al., 2012). Prolactin increase: Significant effect in favour of aripiprazole over placebo (MD = 24.1 ng/mL; 95% CI: 26.3 to 21.8). Significant effect in favour of placebo over olanzapine (MD = 11.5 ng/mL; 95% CI: 8.8–14.1;). Significant effect in favour of placebo over risperidone (not pooled due to heterogeneity). No significant difference for quetiapine compared with placebo.
[14] From 36 studies comparing SGAs with placebo in adolescents with psychiatric and behavioral conditions (including the GRADed studies on bipolar disorders) (Seida et al., 2012). Sedation: Significant effect in favour of placebo over risperidone (RR = 2.9; 95% CI: 1.5 to 5.5;); ziprasidone (RR = 3.0; 95% CI: 1.7 to 5.2); and significant effect in favour of placebo over aripiprazole (RR = 2.7; 95% CI: 1.1 to 6.5;). No significant difference in placebo comparisons with olanzapine and quetiapine.
[15] From 36 studies comparing SGAs with placebo in adolescents with psychiatric and behavioral conditions (including the GRADed studies on bipolar disorders) (Seida et al., 2012) Weight gain: Significant effect in favour of placebo over aripiprazole (MD = 0.8 kg; 95% CI: 0.4 to 1.2;); olanzapine (MD = 4.6 kg; 95% CI: 3.1 to 6.1); quetiapine (MD = 1.8 kg; 95% CI: 1.1 to 2.5); and risperidone (MD = 1.8 kg; 95% CI: 1.5 to 2.1). No significant difference for ziprasidone compared with placebo.
[16] II^2 = 0%
[17] Only two studies contributed to the analysis.
[18] Low sample size.
[19] Fraguas et al. (2011) reviewed data on efficacy and safety of SGAs in 34 studies with 2719 children and adolescents with psychotic or bipolar disorders. Safety assessments showed that mean weight gain ranged from 3.8 kg to 16.2 kg with olanzapine (n=353); from 0.9 kg to 9.5 kg with clozapine (n=97); from 1.9 kg to 7.2 kg with risperidone (n=571); from 2.3 kg to 6.1 kg with quetiapine (n=133); and from 0 kg to 4.4 kg with aripiprazole (n=451). Prolactin levels increased the most with risperidone (mean change ranging from 8.3 ng/mL to 49.6 ng/mL) and olanzapine (-1.5 ng/mL to +13.7 ng/mL). Aripiprazole, clozapine and quetiapine did not increase prolactin levels. SGA medications were associated with less extrapyramidal side-effects than FGAs, with no significant differences among SGAs.

Additional evidence not mentioned in GRADE tables

First-generation antipsychotic medications

Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, Purgato M, Spineli LM, Goodwin GM, Geddes JR (2011). Comparative efficacy and acceptability of antimanic medications in acute mania: A multiple-treatments meta-analysis. Lancet.378(9799):1306-1315. doi:10.1016/S0140-6736(11)60873-8.

[New 2015]

In this multiple-treatment meta-analysis, the authors systematically reviewed six randomized placebo-controlled trials of haloperidol at therapeutic dose range for the treatment of acute mania in 1285 adults. The overall quality of studies was rated as good, even though some studies did not record details about randomization and allocation concealment and there were only a few RCTs at low risk of bias. Mean change scores on the YMRS and dropout rates (treatment discontinuation) were chosen as primary outcomes to represent, the most sensible and sensitive estimates of acute treatment efficacy and acceptability, respectively. Haloperidol was significantly more effective than placebo (SMD −0.56; 95% CI −0·69 to −0·43). In terms of dropout rate, haloperidol was not significantly superior to placebo (OR 0.85; 95% CI 0.62 to 1.15). Moreover, this review included 14 head-to-head comparisons of haloperidol vs. aripiprazole (N=2 studies, n=679 patients), carbamazepine (N=3, n=70), lithium (N=2, n=44), olanzapine (N=2, n=578), quetiapine (N=1, n=201), risperidone (N=3, n=433), ziprasidone (N=1, n=350). Haloperidol was among the most effective evidence-based options for the treatment of manic episodes.

This was the only evidence found investigating FGAs for the treatment of bipolar disorder. Although these are not studies on adolescents with bipolar disorder, they may be considered as indirect evidence.

Ratzoni G, Gothelf D, Brand-Gothelf A, Reidman J, Kikinzon L, Gal G, Phillip M, Apter A, Weizman R (2002). Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. Journal of the American Academy of Child and Adolescent Psychiatry.41(3):337-43.

This is a prospective study of 50 adolescents with schizophrenia who received treatment with olanzapine (2.5–20 mg/day), risperidone (0.5–6 mg/day) or haloperidol (2.5–10 mg/day) for 12 weeks. The olanzapine and risperidone groups experienced significant weight gain between baseline and endpoint ($p < .01$), whereas the average weight of the haloperidol group did not change.

National Institute for Health and Care Excellence (NICE). 2013. *Psychosis and schizophrenia in children and young people*. [CG155]. [online]. London: NICE. Available from: https://www.nice.org.uk/guidance/cg155 (accessed Autumn 2014).

In the NICE (2013) guidelines, treatment options for first episode psychosis in children and young people include oral antipsychotic medication (see recommendations 1.3.14–1.3.25). Oral antipsychotic medication is also recommended for children and young people with an acute exacerbation or recurrence of psychosis or schizophrenia.

National Institute for Health and Care Excellence (NICE). 2014. *Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care*. [CG185]. London: NICE. Available from: https://www.nice.org.uk/guidance/cg185.

The guidelines make the following recommendations for management of mania in young people:

- "To treat mania or hypomania in young people, see NICE's technology appraisal guidance on aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder and also consider the recommendations for adults in section 1.5," (p. 10).
- "Refer to the BNF for children to modify medication treatments, be aware of the increased potential for a range of side effects, and do not routinely continue antipsychotic treatment for longer than 12 weeks," (p. 42).

- "Do not offer valproate to girls or young women of childbearing potential," (p. 10).

The guidelines also advise that structured psychological intervention (such as individual cognitive-behavioural therapy or interpersonal therapy is offered to young people with bipolar depression.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Quantitative summary of evidence table

Outcomes	**SGAs (adolescents with psychotic disorder) vs. placebo** *(Number of studies, RR or MD [95% CI], quality)*	**SGAs (adolescents with psychotic disorder) vs. FGAs** *(Number of studies, RR or MD [95% CI], quality)*	**SGAs. (adolescents with bipolar disorder) vs placebo** *(Number of studies, RR or MD [95% CI], quality)*
Symptoms severity	2 studies, RR 0.76 (0.63 to 0.92) In favour of SGA, VERY LOW	5 studies, 7 comparisons, MD -1.34 (-3.24 to 0.56), LOW	6 studies, MD 0.7 lower (- 0.8 to - 0.5) In favour of SGA, MODERATE
Functioning	No available evidence		No available evidence
School achievement	No available evidence		No available evidence
Quality of life	No available evidence		No available evidence
Sedation	1 study, RR 8.26 (1.15 to 59.61) In favour of placebo, VERY LOW	2 studies, RR 1.19 (0.55 to 2.55), VERY LOW	No available evidence
Weight gain	1 study RR 3.12 (1.34 to 7.27) In favour of placebo, VERY LOW	2 studies, MD 1.71(-4.69 to 8.11), MODERATE	No available evidence
QT prolongation, QT/ms	1 study, MD -6.30 (-12.51 to -0.09 lower), VERY LOW	No available evidence	No available evidence
Prolactin increase	2 studies, MD 3.30 (-1.72 to 8.31),	1 study, RR 5.45 (0.29 to 101.55),	No available evidence

	VERY LOW	VERY LOW	
Extrapyramidal effects	No available evidence	1 study, MD -0.10 (-3.72 to 3.52), VERY LOW	No available evidence
Adverse effects of treatment - Leaving the study early for adverse effects	No available evidence	3 studies, RR 0.65 (0.36 to 1.15), VERY LOW	No available evidence
Treatment adherence - Leaving the study early for any reason	1 study (olanzapine vs. placebo), RR 0.56 (0.36 to 0.87) In favour of olanzapine, VERY LOW	3 studies, RR 0.62 (0.39 to 0.97) In favour of SGAs, MODERATE	2 studies, RR 2.0 (1.0 to 4.0), LOW
Treatment adherence - Leaving the study early for any reason	1 study (aripiprazole vs. placebo), RR 1.76 (0.86 to 3.63), VERY LOW		
User and family satisfaction with care			

Evidence to recommendation table

Benefits	In adolescents with psychotic disorders including schizophrenia, there is evidence that certain SGAs are more effective than placebo, in terms of the proportion of patients showing a response. In terms of treatment adherence, only olanzapine significantly reduced total dropouts when compared with placebo. In adolescents with bipolar disorder, there is evidence that certain SGAs are more effective than placebo in terms of symptom reduction measured with the CGI–Bipolar scale. However, the evidence is inconclusive in terms of manic symptoms measured with the YMRS. Thus, it is unclear if SGAs are better than placebo. In terms of treatment adherence, antipsychotics did not significantly reduce total dropouts compared with placebo. Most of the evidence is short-term, with adolescents recruited in secondary care settings. Therefore, it is uncertain whether improvements observed in trials translate into clinically-meaningful beneficial effects in primary health care settings.

	The evidence is limited in terms of depressive symptoms and it is unclear if SGAs are better than placebo. There was no evidence available on school achievement, quality of life or user and family satisfaction with care in terms of functioning as it relates to adolescents with psychosis (including schizophrenia) or bipolar disorder. There was also no evidence available for FGA medications in adolescents with psychotic disorders (including schizophrenia) compared with placebo. However, in adolescents with psychotic disorders (including schizophrenia), there is evidence that some FGAs (specifically haloperidol, chlorpromazine, perphenazine and molindone) may be similarly effective, in comparison with some SGAs as they relate to symptom severity. The evidence is inconclusive with regards to the proportion of patients showing a response. In terms of treatment adherence, SGAs significantly reduced total dropouts when compared with FGAs. No evidence is available for FGA medications in adolescents with bipolar disorders. However, indirect evidence from six randomized placebo-controlled trials and 14 head-to-head comparisons for the treatment of acute mania in adults suggests that haloperidol is among the most effective treatments for bipolar disorders in general.
Harms	There is evidence that SGAs significantly increased the risk of sedation and weight gain, as compared to placebo in adolescents with schizophrenia. The evidence is inconclusive on the effect of SGA medications on prolactin increase or Q-T interval prolongation. Some SGAs may put adolescents at higher risk of extrapyramidal symptoms EPS compared to placebo. There is also evidence suggesting that some SGAs significantly increased the risk of EPS, weight gain, prolactin increase and sedations compared to placebo in adolescents with bipolar disorder. No evidence is available for adverse events for FGA medications vs. placebo in adolescents with psychotic disorders (including schizophrenia and bipolar disorder). However, evidence on SGAs compared with FGAs in adolescents with psychotic disorders (including schizophrenia) found no significant differences for the most common side-effects. There were no significant differences in the 'leaving the study' outcome because of adverse effects. The evidence is inconclusive for sedation, weight

	gain, prolactin increase and extrapyramidal side effects. In six randomized placebo-controlled trials and 14 head-to-head comparisons for the treatment of acute mania in adults, haloperidol was not significantly different from placebo with regard to dropout rate. However, this evidence is highlighted as indirect.
Summary of the quality of evidence	The quality of evidence was VERY LOW for all outcomes considered except for treatment adherence for SGA vs. placebo in psychotic disorders including schizophrenia (LOW). The quality of evidence was VERY LOW, LOW or MODERATE for SGAs vs. FGAs. For bipolar disorder, the quality of evidence was MODERATE and LOW for SGA effectiveness on symptoms severity and treatment adherence, respectively. Most of the available evidence on FGAs for treatment of bipolar disorders examines adults only, so this evidence is considered indirect.

Value and preferences	
In favour	The onset of psychosis (including schizophrenia and bipolar disorders) is often during adolescence. Patients with early-onset schizophrenia or bipolar disorder have greater disease severity and a more severe course with a poorer psychosocial outcome.
Against	There are significant concerns about the safety and tolerability associated with antipsychotic medications in adolescents. Adolescents may respond differently to antipsychotics compared to adults. Side-effects may seriously affect development, treatment adherence, school achievement and quality of life in adolescents with psychotic disorders.
Uncertainty or variability?	Variability in the benefits/harms profiles.

Feasibility (including resource use considerations)	In many LAMICs, the continuous availability of antipsychotics in non-specialized health care settings is a challenge. Haloperidol, chlorpromazine and risperidone are included in the WHO Essential Medicine List.
Uncertainty or variability?	There is very limited availability of evidence on the effect of antipsychotic medication in adolescents and most of the available evidence is of low quality. Therefore, there is uncertainty on the possible effects on adolescent development and on treatment adherence.

Recommendation and remarks

Recommendation

In adolescents with psychotic disorders (including schizophrenia and bipolar disorder) certain second-generation antipsychotic medications (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) can be offered as a treatment option under supervision of a specialist.
If treatment with one of the above agents is not feasible, first-generation antipsychotics (haloperidol, chlorpromazine, perphenazine, molindone) may be used under supervision of a specialist.

Rationale: Although the quality of the evidence is very low, the benefits of certain second-generation antipsychotics outweigh their harms with no clinically relevant differences between individual interventions in direct comparisons. Some first-generation antipsychotics may be similarly effective in comparison with second- generation antipsychotics. In the long-term, there are relevant safety and tolerability concerns associated with antipsychotic treatment in this age group. A feasibility issue is the burden of taking medicines that require regular clinical and laboratory monitoring.

Remarks

All studies in adolescents with psychotic disorders (including schizophrenia and bipolar disorder) have investigated the

efficacy and tolerability profile of second generation antipsychotics, while no direct evidence is available for first-generation antipsychotics. However, comparisons of second-generation versus first-generation antipsychotics in adolescents, and indirect evidence collected in adults with psychotic disorders (including schizophrenia and bipolar disorder) demonstrated the efficacy of first-generation antipsychotics.
Antipsychotic medications can give rise to adverse effects.
The evidence for the use of antipsychotics in adolescents is limited to specialist service settings and does not follow patients over long periods of time. It is for these reasons that supervision is required and that patients are monitored regularly for any incidence of unwanted side effects.
As there is no clinically relevant advantage of one antipsychotic over the others, choice should be based on availability, cost, preferences and possible negative consequences associated with each medication, including sedation, metabolic, extrapyramidal, cardiovascular and hormonal side-effects.

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High □ Moderate □ Low **x Very low**
Balance of benefits versus harms	**x Benefits clearly outweigh harms** □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits
Values and preferences	**x No major variability** □ Major variability

[New 2015]

Resource use	□ Less resource-intensive **x More resource-intensive**
Strength	**CONDITIONAL**

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