

Q1: In individuals with psychotic disorders (including schizophrenia), are antipsychotic drugs safe and effective?

Background

Antipsychotic drugs are the mainstay of pharmacological treatment for patients with psychotic disorders, including schizophrenia. The earliest antipsychotics, chlorpromazine and haloperidol have been used for about 5 decades. Many newer antipsychotics have been developed in the last 2 decades. Traditionally, antipsychotics are divided into two classes: the older (including haloperidol and chlorpromazine) first generation, and the newer, more expensive, second generation. The criteria for this separation are not clearly defined. A belief that the second-generation medicines is superior to the first-generation ones is not confirmed by the evidence and the high costs of the former has led to a continuing debate about their real benefits. Despite the introduction of newer antipsychotics, haloperidol and chlorpromazine are still the most frequently prescribed antipsychotic drugs worldwide and they are included in the World Health Organization List of Essential Medicines. A clear recommendation on antipsychotic medication use for psychotic disorders is necessary for clinical practice.

Population/Intervention(s)/Comparator/Outcome(s) (PICO)

Population: adults with psychotic disorders (including schizophrenia)

Interventions: antipsychotics drugs

Comparisons: placebo

Outcomes: symptoms severity

prevention of relapses

disability and functioning

quality of life

adverse effects of treatment

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mortality

treatment adherence

users' and families' satisfaction with care

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Irving CB, Adams CE, Lawrie S (2006). Haloperidol versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews*, (4):CD003082.

Adams CE et al (2007). Chlorpromazine versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews*, (2):CD000284.

Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
I	Haloperidol/ Placebo	Symptoms severity	Irving et al, 2006	
		Prevention of relapses	Irving et al, 2006	
		Disability and functioning	No evidence available	
		Adverse effects of treatment	Irving et al, 2006	
		Quality of life	No evidence available	
		Mortality	No evidence available	

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		Treatment adherence	Irving et al, 2006	
		Users' and families' satisfaction with care	No evidence available.	
II	Chlorpromazine vs placebo	Symptoms severity	Adams et al, 2007	
		Prevention of relapses	Adams et al, 2007	
		Disability and functioning	Adams et al, 2007	
		Adverse effects of treatment	Adams et al, 2007	
		Quality of life	No evidence available.	
		Mortality	Adams et al, 2007	
		Treatment adherence	Adams et al, 2007	
		Users' and families' satisfaction with care	No evidence available.	
III	Second-generation antipsychotic drugs vs placebo (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, zotepine)	Symptoms severity	Leucht et al, 2009	
		Disability and functioning	No evidence available.	
		Adverse effects of treatment	Leucht et al, 2009	
		Treatment acceptability (adherence)	Leucht et al, 2009	
		Quality of life	No evidence available.	
		Users' and families' satisfaction with care	No evidence available.	

Narrative description of the studies that went into the analysis

Irving et al, 2006 included 21 controlled trials randomising 1519 patients with schizophrenia or non affective psychotic disorders to haloperidol or placebo. A wide range of doses of haloperidol was used in the trials. The greatest dose was used in Howard 1974 (doses up to 200 mg/day). Most studies used doses in the range of 4mg/day to 20 mg/day. Sixteen studies used doses or had ranges including doses greater than 7.5 mg/day. All studies included people with schizophrenia. The majority of participants were hospitalised and chronically ill. Four studies specifically stated that participants were currently in acute phase.

Adams et al, 2007 included 50 placebo controlled studies of chlorpromazine in patients with schizophrenia or non affective psychoses, with a mean number of participants of 99 ranging from 21 to 838. Over 4992 people have been included in trials relating to the review, 1625 were given chlorpromazine. The doses of chlorpromazine in these studies ranged from 25mg/day to 2400mg/day. The mean dose was 574 mg/day (SD 446). None of the included studies attempted to quantify quality of life or levels of satisfaction.

Leucht et al, 2009 included 38 studies with 7323 participants: amisulpride (N= 5), aripiprazole (N= 7), clozapine (N= 1), olanzapine (N= 6), quetiapine (N= 5), risperidone (N= 7), sertindole (N= 3), ziprasidone (N= 4), zotepine (N=3; three studies provided results on two SGA drugs). Most of the studies were short-term and examined patients with positive symptoms, while only six studies examined patients with predominantly negative symptoms (four amisulpride studies, one olanzapine and amisulpride study and one zotepine study). Almost all studies were conducted by pharmaceutical companies and usually for registrational purposes. The minimum duration of washout was usually not more than a few days. The median of mean age was 38 years.

GRADE Tables

Table 1

Author(s): Clive E Adams and Lorenzo Tarsitani

Date: 2009-06-08

Question: HALOPERIDOL versus PLACEBO for schizophrenia

Settings: largely in hospital

Bibliography: Irving CB, Adams CE, Lawrie S (2006). Haloperidol versus placebo for schizophrenia. Cochrane Database of Systematic Reviews, (4):CD003082.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	HALOPERIDOL versus PLACEBO	control	Relative (95% CI)	Absolute		

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Symptom severity - Global effect: No marked global improvement (0-24 weeks)												
10	randomised trials	serious ¹	no serious inconsistency	serious ²	no serious imprecision	none	118/250 (47.2%)	173/217 (79.7%)	RR 0.62 (0.52 to 0.75)	303 fewer per 1000 (from 199 fewer to 383 fewer)	⊕⊕OO LOW	CRITICAL
								84.6%		321 fewer per 1000 (from 211 fewer to 406 fewer)		
Relapse or not remaining in remission (<52 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	serious ²	very serious ³	none	32/47 (68.1%)	23/23 (100%)	RR 0.7 (0.57 to 0.87)	300 fewer per 1000 (from 130 fewer to 430 fewer)	⊕OOO VERY LOW	CRITICAL
								100%		300 fewer per 1000 (from 130 fewer to 430 fewer)		
Disability and functioning												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Adverse events: Movement disorders - non-acute - needing antiparkinson medication or parkinsonism												
7	randomised trials	no serious limitations	no serious inconsistency	serious ²	no serious imprecision	none	71/217 (32.7%)	13/192 (6.8%)	RR 4.4 (2.08 to 9.3)	230 more per 1000 (from 73 more to 562 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 more per 1000 (from 0 more to 0 more)		
Adverse events: Weight gain												
1	randomised trials	no serious limitations	no serious inconsistency	serious ⁴	no serious imprecision	none	10/103 (9.7%)	1/104 (1%)	RR 10.1 (1.32 to 77.46)	88 more per 1000 (from 3 more to 735 more)	⊕⊕⊕O MODERATE	CRITICAL
								1%		91 more per 1000 (from 3 more to 765 more)		
All cause mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT

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								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Quality of life												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Treatment adherence - Leaving the study early (0-24 weeks)												
19	randomised trials	no serious limitations	no serious inconsistency	serious ²	no serious imprecision	none	185/615 (30.1%)	236/587 (40.2%)	RR 0.82 (0.72 to 0.93)	72 fewer per 1000 (from 28 fewer to 113 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								16.3%		29 fewer per 1000 (from 11 fewer to 46 fewer)		
User' and family satisfaction												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

¹ Methodological limitations, many studies were published from the sixties.

² The majority of participants were hospitalised and chronically ill.

³ Low overall sample size.

⁴ Only one study contributed to the analysis.

Table 2

Author(s): Clive E Adams and Lorenzo Tarsitani

Date: 2009-06-10

Question: CHLORPROMAZINE versus PLACEBO for schizophrenia

Settings: Largely in Hospital

Bibliography: Adams CE et al (2007). Chlorpromazine versus placebo for schizophrenia. Cochrane Database of Systematic Reviews, (2):CD000284.

Quality assessment	Summary of findings			Importance
	No of patients	Effect	Quality	

Antipsychotic medications for psychotic disorders

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CHLORPROMAZINE versus PLACEBO	control	Relative (95% CI)	Absolute		
Symptom severity - Global impression: No global improvement (0-6 months)												
24	randomised trials	no serious limitations ¹	serious ²	no serious indirectness	no serious imprecision	none	564/921 (61.2%)	595/790 (75.3%)	RR 0.74 (0.69 to 0.79)	196 fewer per 1000 (from 158 fewer to 233 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								78.5%		204 fewer per 1000 (from 165 fewer to 243 fewer)		
Relapse - medium term (0 - 6 months)												
5	randomised trials	very serious ³	very serious ⁴	no serious indirectness	no serious imprecision	none	91/531 (17.1%)	160/352 (45.5%)	RR 0.48 (0.39 to 0.58)	236 fewer per 1000 (from 191 fewer to 277 fewer)	⊕OOO VERY LOW	CRITICAL
								45.1%		235 fewer per 1000 (from 189 fewer to 275 fewer)		
Relapse - long term (6 months - 2 years)												
3	randomised trials	very serious ⁵	serious ⁶	no serious indirectness	no serious imprecision	none	106/264 (40.2%)	176/248 (71%)	RR 0.57 (0.48 to 0.67)	305 fewer per 1000 (from 234 fewer to 369 fewer)	⊕OOO VERY LOW	CRITICAL
								72%		310 fewer per 1000 (from 238 fewer to 374 fewer)		
Disability and functioning												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Adverse effects: 1. Central nervous system - acute movement disorders (dystonia)												
5	randomised trials	serious ⁷	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/560 (5.7%)	5/382 (1.3%)	RR 3.47 (1.5 to 8.03)	32 more per 1000 (from 7 more to 92 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 more per 1000 (from 0 more to 0 more)		
Adverse effects: 1. Central nervous system - parkinsonism (includes EPS)												

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12	randomised trials	no serious limitations	serious ⁸	no serious indirectness	no serious imprecision	none	123/723 (17%)	40/542 (7.4%)	RR 2.01 (1.5 to 2.7)	75 more per 1000 (from 37 more to 125 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
								0%		0 more per 1000 (from 0 more to 0 more)		
Adverse effects: 2. Metabolic - weight increase												
5	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁹	none	31/75 (41.3%)	7/90 (7.8%)	RR 4.92 (2.32 to 10.43)	305 more per 1000 (from 103 more to 733 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
								7.7%		302 more per 1000 (from 102 more to 726 more)		
Quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
All cause mortality												
0	no evidence available					none	0/7 (0%)	0/7 (0%)	not pooled	not pooled		IMPORTANT
								0%		not pooled		
Treatment acceptability (total drop-out 9 weeks to 6 months)												
26 ¹⁰	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	144/1004 (14.3%)	157/775 (20.3%)	RR 0.65 (0.53 to 0.79)	71 fewer per 1000 (from 43 fewer to 95 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment acceptability (total drop-out 0-8 weeks)												
16	randomised trials	no serious limitations	serious ¹¹	no serious indirectness	no serious imprecision	none	78/438 (17.8%)	149/507 (29.4%)	RR 0.72 (0.59 to 0.88)	82 fewer per 1000 (from 35 fewer to 120 fewer)	⊕⊕⊕⊕ MODERATE	CRITICAL
User' and family satisfaction												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

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¹ Only 2 studies (Kurland et al, 1961; Cooper et al, 2000) with dropout rate >30% were included in this analysis.

² I-squared test is between 51% and 69% in the analyses pooled by Adams et al, 2007.

³ This analysis include 2 (Peet et al, 1981, Rappaport et al, 1978) studies out of 5, with more than 30% drop-outs.

⁴ No explanation was provided.

⁵ One (Engelhardt et al, 1960) out of 3 studies has a 37% drop-out rate.

⁶ I-squared test = 72%.

⁷ One study (Kurland et al, 1961) out of five has a drop-out rate >30.

⁸ I-squared test = 59%.

⁹ Small overall sample size.

¹⁰ From analysis 1.14 of Adam 2007.

¹¹ I-squared test is 54%.

Table 3

Author(s): Corrado Barbui

Date: 2009-09-07

Question: Should amisulpride vs placebo be used for schizophrenia?

Settings: Largely in Hospital

Bibliography: Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	amisulpride	placebo	Relative (95% CI)	Absolute		
symptom severity (positive and negative) (Better indicated by lower values)												
1 ¹	randomised trials	serious ²	no serious inconsistency	serious ³	no serious imprecision	reporting bias ⁴	0 ⁵	0 ^{5,6}	-	0.54 lower (0.81 to 0.27 lower)	⊕○○○ VERY LOW	CRITICAL
non-responder rates												
3 ⁷	randomised trials	serious ²	no serious inconsistency ⁵	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{5,8}	0%	RR 0.66 (0.58 to 0.76) ⁹	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	CRITICAL
disability and functioning (Better indicated by lower values)												
0	no evidence					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL

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	available											
adverse effects (antiparkinson medication)												
3 ¹⁰	randomised trials	serious ²	no serious inconsistency ⁵	no serious indirectness	serious ¹¹	reporting bias ⁴	0/0 (0%) ^{5,12}	0%	RR 0.87 (0.24 to 3.2) ⁹	0 fewer per 1000 (from 0 fewer to 0 more)	⊕○○○ VERY LOW	IMPORTANT
adverse effects (sedation)												
0	no evidence available					none	0/0 (0%)	0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
treatment acceptability (total dropouts)												
5 ¹³	randomised trials	no serious limitations	no serious inconsistency ⁵	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{5,14}	0%	RR 0.69 (0.48 to 1) ⁹	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕○ MODERATE	IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

¹ From Figure 1 of Leucht et al, 2009.

² Loss to follow up exceeds 30%.

³ Only one study contributed to the analysis.

⁴ Authors reported that the funnel plot was asymmetrical.

⁵ Not reported.

⁶ The total number of patients included in this analysis was 241.

⁷ From Figure 2 of Leucht et al, 2009.

⁸ The total number of patients included in this analysis was 487.

⁹ Estimates below 1 are in favor of second-generation antipsychotics.

¹⁰ From Figure 3 of Leucht et al, 2009.

¹¹ Confidence interval ranges from appreciable benefit to appreciable harm.

¹² The total number of patients was 514.

¹³ From Table 3 of Leucht et al, 2009.

¹⁴ The total number of included patients was 618.

Table 4

Author(s): Corrado Barbui

Date: 2009-09-07

Question: Should aripiprazole vs placebo be used for schizophrenia?

Settings: Largely in Hospital

Bibliography: Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	aripiprazole	placebo	Relative (95% CI)	Absolute		
symptom severity (positive and negative) (Better indicated by lower values)												
7 ¹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0 ³	0 ^{3,5}	-	0.41 lower (0.51 to 0.31 lower)	⊕⊕○○ LOW	CRITICAL
non-responder rates												
5 ⁶	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,7}	0%	RR 0.81 (0.75 to 0.87) ⁸	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	CRITICAL
disability and functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
adverse effects (antiparkinson medication)												
6 ⁹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,10}	0%	RR 1.07 (0.81 to 1.41) ⁸	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕○○ LOW	IMPORTANT
adverse effects (sedation)												
4 ¹¹	randomised trials	serious ²	no serious	no serious	serious ¹²	reporting bias ⁴	0/0 (0%) ^{3,13}	0%	RR 1.38 (0.82 to	0 more per 1000 (from 0	⊕○○○	IMPORTANT

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			inconsistency ³	indirectness					2.34) ⁸	fewer to 0 more)	VERY LOW	
treatment acceptability (total dropouts)												
7 ¹⁴	randomised trials	no serious limitations	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,15}	0%	RR 0.80 (0.72 to 0.89) ⁸	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

¹ From Figure 1 of Leucht et al, 2009.

² Loss to follow-up exceeds 30%.

³ Not reported.

⁴ Authors reported that the funnel plot was asymmetrical.

⁵ The total number of included patients was 1556.

⁶ From Figure 2 of Leucht et al, 2009.

⁷ The total number of included patients was 1123.

⁸ Estimates below 1 favor second-generation antipsychotic drugs.

⁹ From Figure 9 of Leucht et al, 2009.

¹⁰ The total number of included patients was 1310.

¹¹ From Figure 11 of Leucht et al, 2009.

¹² Confidence interval ranges from appreciable benefit to appreciable harm.

¹³ The total number of included patients was 1107.

¹⁴ From Table 3 of Leucht et al, 2009.

¹⁵ The total number of included patients was 1615.

Table 5

Author(s): Corrado Barbui

Date: 2009-09-07

Question: Should clozapine vs placebo be used for schizophrenia?

Settings: Largely in Hospital

Bibliography: Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

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Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	clozapine	placebo	Relative (95% CI)	Absolute		
symptom severity (positive and negative) (Better indicated by lower values)												
1 ¹	randomised trials	serious ²	no serious inconsistency ³	serious ⁴	very serious ⁵	reporting bias ⁶	0 ³	0 ^{3,7}	-	1.64 lower (2.61 to 0.68 lower)	⊕○○○ VERY LOW	CRITICAL
non-responder rates												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
disability and functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
adverse effects (antiparkinson medication)												
0	no evidence available					none	0/0 (0%)	0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
adverse effects (sedation)												
0	no evidence available					none	0/0 (0%)	0%	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
treatment acceptability (total dropout)												
1 ⁸	randomised trials	no serious limitations	no serious inconsistency ³	serious ⁴	very serious ⁹	reporting bias ⁶	0/0 (0%) ^{3,10}	0%	RR 0.40 (0.22 to 0.76) ¹¹	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	IMPORTANT

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quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

¹ From Figure 1 of Leucht et al, 2009.

² Loss to follow-up exceeds 30%.

³ Not reported.

⁴ Only one study contributed to the analysis.

⁵ Only 22 patients were included.

⁶ Authors reported that the funnel plot was asymmetrical.

⁷ The total number of included patients was 22.

⁸ From Table 3 of Leucht et al, 2009.

⁹ The total number of included patients was 24.

¹⁰ The total number of included patients was 24.

¹¹ Estimates below 1 favor second-generation antipsychotic drugs.

Table 6

Author(s): Corrado Barbui

Date: 2009-09-07

Question: Should olanzapine vs placebo be used for schizophrenia?

Settings: Largely in Hospital

Bibliography: Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	olanzapine	placebo	Relative (95% CI)	Absolute		
symptom severity (positive and negative) (Better indicated by lower values)												

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6 ¹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0 ³	0 ^{3,5}	-	0.59 lower (0.83 to 0.35 lower)	⊕⊕⊕⊕ LOW	CRITICAL
non-responder rates												
4 ⁶	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,7}	0%	RR 0.82 (0.73 to 0.92) ⁸	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
disability and functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
adverse effects (antiparkinson medication)												
3 ⁹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	serious ¹⁰	reporting bias ⁴	0/0 (0%) ^{3,11}	0%	RR 1.23 (0.52 to 2.93) ⁸	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
adverse effects (sedation)												
3 ¹²	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	serious ¹⁰	reporting bias ⁴	0/0 (0%) ^{3,13}	0%	RR 1.93 (0.76 to 4.9) ⁸	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
treatment acceptability (total dropouts)												
6 ¹⁴	randomised trials	no serious limitations	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,15}	0%	RR 0.70 (0.46 to 1.05) ⁸	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕⊕ MODERATE	IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		

¹ From Figure 1 of Leucht et al, 2009.

² Loss to follow-up exceeds 30%.

³ Not reported.

Antipsychotic medications for psychotic disorders

- ⁴ Authors reported that the funnel plot was asymmetrical.
⁵ The total number of included patients was 992.
⁶ From Figure 2 of Leucht et al, 2009.
⁷ The total number of included patients was 582.
⁸ Estimates below 1 favor second-generation antipsychotic drugs.
⁹ From Figure 9 of Leucht et al, 2009.
¹⁰ Confidence interval ranges from appreciable benefit to appreciable harm.
¹¹ The total number of included patients was 481.
¹² From Figure 11 of Leucht et al, 2009.
¹³ The total number of included patients was 408.
¹⁴ From Table 3 of Leucht et al, 2009.
¹⁵ The total number of included patients was 1088.

Table 7

Author(s): Corrado Barbui

Date: 2009-09-07

Question: Should quetiapine vs placebo be used for schizophrenia?

Settings: Largely in Hospital

Bibliography: Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	quetiapine	placebo	Relative (95% CI)	Absolute		
symptom severity (positive and negative) (Better indicated by lower values)												
5 ¹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0 ³	0 ^{3,5}	-	0.42 lower (0.72 to 0.13 lower)	⊕⊕○○ LOW	CRITICAL
non-responder rates												
5 ⁶	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,7}	0%	RR 0.88 (0.75 to 1.04) ⁸	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕○○ LOW	CRITICAL
disability and functioning (Better indicated by lower values)												

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0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
adverse effects (antiparkinson medication)												
3 ⁹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	serious ¹⁰	reporting bias ⁴	0/0 (0%) ^{3,11}	0%	RR 0.79 (0.46 to 1.35) ⁸	0 fewer per 1000 (from 0 fewer to 0 more)	⊕○○○ VERY LOW	IMPORTANT
adverse effects (sedation)												
5 ¹²	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,13}	0%	RR 2.02 (1.18 to 3.47) ⁸	0 more per 1000 (from 0 more to 0 more)	⊕⊕○○ LOW	IMPORTANT
treatment acceptability (total dropouts)												
5 ¹⁴	randomised trials	no serious limitations	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,15}	0%	RR 0.79 (0.68 to 0.92) ⁸	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

¹ From Figure 1 of Leucht et al, 2009.

² Loss to follow-up exceeds 30%.

³ Not reported.

⁴ Authors reported that the funnel plot was asymmetrical.

⁵ The total number of included patients was 735.

⁶ From Figure 2 of Leucht et al, 2009.

⁷ The total number of included patients was 750.

⁸ Estimates below 1 favor second-generation antipsychotic drugs.

⁹ From Figure 9 of Leucht et al, 2009.

¹⁰ Confidence interval ranges from appreciable benefit to appreciable harm.

¹¹ The total number of included patients was 521.

¹² From Figure 11 of Leucht et al, 2009.

¹³ The total number of included patients was 750.

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¹⁴ From Table 3 of Leucht et al, 2009.

¹⁵ The total number of included patients was 750.

Table 8

Author(s): Corrado Barbui

Date: 2009-09-07

Question: Should risperidone vs placebo be used for schizophrenia?

Settings: Largely in Hospital

Bibliography: Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	risperidone	placebo	Relative (95% CI)	Absolute		
symptom severity (positive and negative) (Better indicated by lower values)												
7 ¹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0 ³	0 ^{3,5}	-	0.59 lower (0.78 to 0.39 lower)	⊕⊕○○ LOW	CRITICAL
non-responder rates												
7 ⁶	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,7}	0%	RR 0.62 (0.51 to 0.75) ⁸	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	CRITICAL
disability and functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
adverse effects (antiparkinson medication)												
4 ⁹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,10}	0%	RR 1.24 (0.89 to 1.71) ⁸	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕○○ LOW	IMPORTANT

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adverse effects (sedation)												
4 ¹¹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,12}	0%	RR 1.29 (0.73 to 2.29) ⁸	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕⊕ LOW	IMPORTANT
treatment acceptability (total dropouts)												
6 ¹³	randomised trials	no serious limitations	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,14}	0%	RR 0.70 (0.57 to 0.86) ⁸	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ MODERATE	IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

¹ From Figure 1 of Leucht et al, 2009.

² Loss to follow-up exceeds 30%.

³ Not reported.

⁴ Authors reported that the funnel plot was asymmetrical.

⁵ The total number of patients was 977.

⁶ From Figure 2 of Leucht et al, 2009.

⁷ The total number of included patients was 997.

⁸ Estimates below 1 favor second-generation antipsychotics.

⁹ From Figure 9 of Leucht et al, 2009.

¹⁰ The total number of included patients was 323.

¹¹ From Figure 11 of Leucht et al, 2009.

¹² The total number of included patients was 665.

¹³ From Table 3 of Leucht et al, 2009.

¹⁴ The total number of included patients was 955.

Table 9

Author(s): Corrado Barbui

Date: 2009-09-07

Question: Should sertindole vs placebo be used for schizophrenia?

Settings: Largely in Hospital

Bibliography: Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

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Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations						
symptom severity (positive and negative) (Better indicated by lower values)												
3 ¹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0 ³	0 ^{3,5}	-	0.42 lower (0.58 to 0.25 lower)	⊕⊕○○ LOW	CRITICAL
non-response rates												
3 ⁶	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,7}	0%	RR 0.91 (0.81 to 1.02) ⁸	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕○○ LOW	CRITICAL
disability and functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
adverse effects (antiparkinson medication)												
3 ⁹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	serious ¹⁰	reporting bias ⁴	0/0 (0%) ^{3,11}	0%	RR 0.79 (0.51 to 1.23) ⁸	0 fewer per 1000 (from 0 fewer to 0 more)	⊕○○○ VERY LOW	IMPORTANT
adverse effects (sedation)												
2 ¹²	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	serious ¹³	reporting bias ⁴	0/0 (0%) ^{3,14}	0%	RR 1.23 (0.53 to 2.87) ⁸	0 more per 1000 (from 0 fewer to 0 more)	⊕○○○ VERY LOW	IMPORTANT
treatment acceptability (total dropouts)												
3 ¹⁵	randomised trials	no serious limitations	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,16}	0%	RR 0.96 (0.83 to 1.1) ⁸	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕○ MODERATE	IMPORTANT

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quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

¹ From Figure 1 of Leucht et al, 2009.

² Loss to follow-up exceeds 30%.

³ Not reported.

⁴ Authors reported that the funnel plot was asymmetrical.

⁵ The total number of included patients was 629.

⁶ From Figure 2 of Leucht et al, 2009.

⁷ The total number of included patients was 661.

⁸ Estimates below 1 favor second-generation antipsychotic drugs.

⁹ From Figure 9 of Leucht et al, 2009.

¹⁰ Confidence interval ranges from appreciable benefit to no difference.

¹¹ The total number of included patients was 661.

¹² From Figure 11 of Leucht et al, 2009.

¹³ Confidence interval ranges from appreciable benefit to appreciable harm.

¹⁴ The total number of included patients was 315.

¹⁵ From Table 3 of Leucht et al, 2009.

¹⁶ The total number of included patients was 661.

Table 10

Author(s): Corrado Barbui

Date: 2009-09-07

Question: Should ziprasidone vs placebo be used for schizophrenia?

Settings: Largely in Hospital

Bibliography: Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

Quality assessment	Summary of findings			Importance
	No of patients	Effect	Quality	

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No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ziprasidone	placebo	Relative (95% CI)	Absolute		
symptom severity (positive and negative) (Better indicated by lower values)												
4 ¹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0 ³	0 ^{3,5}	-	0.48 lower (0.65 to 0.32 lower)	⊕⊕⊕⊕ LOW	CRITICAL
non-response rates												
2 ⁶	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,7}	0%	RR 0.82 (0.71 to 0.94) ⁸	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
disability and functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
adverse effects (antiparkinson medication)												
4 ⁹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	serious ¹⁰	reporting bias ⁴	0/0 (0%) ^{3,11}	0%	RR 1.33 (0.7 to 2.51) ⁸	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
adverse effects (sedation)												
2 ¹²	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	serious ¹⁰	reporting bias ⁴	0/0 (0%) ^{3,13}	0%	RR 2.08 (0.62 to 6.95) ⁸	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
treatment acceptability (total dropouts)												
4 ¹⁴	randomised trials	no serious limitations	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,15}	0%	RR 0.73 (0.63 to 0.84) ⁸	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ MODERATE	IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												

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0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
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¹ From Figure 1 of Leucht et al, 2009.

² Loss to follow-up exceeds 30%.

³ Not reported.

⁴ Authors reported that the funnel plot was asymmetrical.

⁵ The total number of patients was 584.

⁶ From Figure 2 of Leucht et al, 2009.

⁷ The total number of included patients was 291.

⁸ Estimates below 1 favor second-generation antipsychotic drugs.

⁹ From Figure 9 of Leucht et al, 2009.

¹⁰ Confidence interval ranges from appreciable benefit to appreciable harm.

¹¹ The total number of included patients was 598.

¹² From Figure 11 of Leucht et al, 2009.

¹³ The total number of included patients was 291.

¹⁴ From Table 3 of Leucht et al, 2009.

¹⁵ The total number of included patients was 598.

Table 11

Author(s): Corrado Barbui

Date: 2009-09-07

Question: Should zotepine vs placebo be used for schizophrenia?

Settings: Largely in hospital

Bibliography: Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zotepine	placebo	Relative (95% CI)	Absolute		
symptom severity (positive and negative) (Better indicated by lower values)												
3 ¹	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0 ^{3,5}	0 ³	-	0.55 lower (0.89 to 0.21 lower)	⊕⊕⊕⊕ LOW	CRITICAL

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non-response rates												
2 ⁶	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	serious ⁷	reporting bias ⁴	0/0 (0%) ^{3,8}	0%	RR 0.65 (0.32 to 1.33) ⁹	0 fewer per 1000 (from 0 fewer to 0 more)	⊕○○○ VERY LOW	CRITICAL
disability and functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
adverse effects (antiparkinson medication)												
2 ¹⁰	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	serious ⁷	reporting bias ⁴	0/0 (0%) ^{3,11}	0%	RR 1.49 (0.6 to 3.72) ⁹	0 more per 1000 (from 0 fewer to 0 more)	⊕○○○ VERY LOW	IMPORTANT
adverse effects (sedation)												
3 ¹²	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	reporting bias ⁴	0/0 (0%) ^{3,13}	0%	RR 4.60 (1.21 to 17.5) ⁹	0 more per 1000 (from 0 more to 0 more)	⊕⊕○○ LOW	IMPORTANT
treatment acceptability (total dropouts)												
3 ¹⁴	randomised trials	no serious limitations	no serious inconsistency ³	no serious indirectness	serious ⁷	reporting bias ⁴	0/0 (0%) ^{3,15}	0%	RR 0.94 (0.64 to 1.38) ⁹	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕○○ LOW	IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
user's and family's satisfaction (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

¹ From Figure 1 of Leucht et al, 2009.

² Loss to follow-up exceeds 30%.

³ Not reported.

⁴ Authors reported that the funnel plot was asymmetrical.

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⁵ The total number of included patients was 304.

⁶ From Figure 2 of Leucht et al, 2009.

⁷ Confidence interval ranges from appreciable benefit to appreciable harm.

⁸ The total number of included patients was 227.

⁹ Estimates below 1 favor second-generation antipsychotic drugs.

¹⁰ From Figure 9 of Leucht et al, 2009.

¹¹ The total number of included patients was 227.

¹² From Figure 11 of Leucht et al, 2009.

¹³ The total number of included patients was 312.

¹⁴ From Table 3 of Leucht et al, 2009.

¹⁵ The total number of included patients was 312.

Additional information that was not GRADED

COST

Rosenheck et al 2008a; 2008b: The cost of second-generation antipsychotics in the treatment of schizophrenia is about \$10 per day, more than ten times the cost of generic first-generation antipsychotics

DOSE

Waraich et al, 2002: This review selected studies with people being treated for acute schizophrenia, randomised to two or more dose ranges of haloperidol. Using low doses (>3-7.5mg/day) did not clearly result in loss of efficacy (no clinically important improvement in global state, versus >7.5-15mg/day n=48, 1 RCT, RR 1.09 CI 0.7 to 1.8; versus >15-35mg/day n=81, 2 RCTs, 0.95 CI 0.8 to 1.2). Doses of haloperidol in the range of >3-7.5 mg/day had a lower rate of development of clinically significant extrapyramidal adverse effects than higher doses (clinically significant extrapyramidal adverse effects, versus >7.5-15mg/day n=64, 2 RCTs, RR 0.12 CI 0.01 to 2.1; versus >15-35mg/day n=144, 3 RCTs RR 0.59 CI 0.5 to 0.8, NNH 3 CI 2 to 6; versus >35mg/day n=86, 2 RCTs, RR 0.70 CI 0.5 to 1.1).

Liu & De Haan, 2009: This review shows, in the short term, that when low dose chlorpromazine (≤ 400 mg/day) was compared with medium dose (401-800 mg/day), all measured extrapyramidal adverse effects tended to be lower in the low dose group (n=70, 2 RCTs, RR dystonia 0.20 CI 0.04 to 0.97). When low dose was compared with high (>800mg/day) data were taken from only one study and a significantly greater number of people in the high dose group left early due to disabling adverse effects (n=416, RR 0.10 CI 0.04 to 0.27). Significantly less dystonia and unspecified extrapyramidal adverse effects were reported in the low dose group (n=416, dystonia RR 0.11 CI 0.02 to 0.45, extrapyramidal adverse effects RR 0.43 CI 0.32 to 0.59). People in both groups experienced akathisia (n=416, RR 1.00 CI 0.55 to 1.83).

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CLOZAPINE SAFETY

Miller 2000: Clozapine has demonstrated superior efficacy in relieving positive and negative symptoms in treatment-resistant schizophrenic patients. The use of clozapine has been limited because of infrequent but serious side effects, the most notable being agranulocytosis. In recent years, however, mandatory blood monitoring has significantly reduced both the incidence of agranulocytosis and its associated mortality.

USE DURING PREGNANCY AND LACTATION

NCCMH 2007: Women with schizophrenia who are planning a pregnancy or pregnant or breastfeeding should be treated with low-dose oral typical antipsychotics, such as haloperidol, chlorpromazine.

Reference List

Adams CE et al (2007). Chlorpromazine versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews*, (2):CD000284.

Cooper SJ et al (2000). A placebo controlled comparison of zotepine versus chlorpromazine in patients with acute exacerbation of schizophrenia. *Acta Psychiatrica Scandinavica*, 101:218-5.

Engelhardt DM et al (1969). Prevention of psychiatric hospitalization with use of psychopharmacological agents. *Journal of the American Medical Association*, 173:147–9.

Irving CB, Adams CE, Lawrie S (2006). Haloperidol versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews*, (4):CD003082.

Kurland AA et al (1961). The comparative effectiveness of six phenothiazine compounds, phenobarbital and inert placebo in the treatment of acutely ill patients: global measures of severity of illness. *Journal of Nervous and Mental Disease*, 133:1–18.

Leucht S et al (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14:429-47.

Liu X, De Haan S (2009). Chlorpromazine dose for people with schizophrenia. *Cochrane Database of Systematic Reviews*, (2):CD007778.

Miller DD. (2000). Review and management of clozapine side effects. *Journal of Clinical Psychiatry*, 61(Suppl 8):14-7.

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National Collaborating Centre for Mental Health (NCCMH) (2007). Antenatal and Postnatal Mental Health: The NICE guideline on Clinical Management and Service Guidance. London: British Psychological Society & Royal College of Psychiatrists.

Peet M et al (1981). Propranolol in schizophrenia. I. Comparison of propranolol, chlorpromazine and placebo. *British Journal of Psychiatry*, 139:105-11.

Rappaport M et al (1978). Are there schizophrenics for whom drugs may be unnecessary or contraindicated? *International Pharmacopsychiatry*, 13:100-11.

Rosenheck RA, Leslie DL, Doshi JA. (2008a). Second-generation antipsychotics: cost-effectiveness, policy options, and political decision making. *Psychiatric Services*, 59:515-20.

Rosenheck RA et al (2008b). Rethinking antipsychotic formulary policy. *Schizophr Bulletin*, 34:375-80.

Waraich PS et al (2002). Haloperidol dose for the acute phase of schizophrenia. *Cochrane Database of Systematic Reviews*, (3):CD001951.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	In terms of proportion of patients showing a response, there is evidence that both haloperidol (Responders: 52.8 versus 20.3; RR 0.62, 0.52 to 0.75, absolute risk difference 30.3 %) and chlorpromazine (Responders: 38.8 versus 25.9; RR 0.74, 0.69 to 0.79 absolute risk difference 19.6%) were significantly more effective than placebo in psychotic disorders including schizophrenia. In terms of relapse, there is evidence that haloperidol (RR 0.70, 0.57 to 0.87, absolute risk difference 30%) and chlorpromazine (RR 0.48, 0.39 to 0.58 up to six-months; RR 0.56, 0.48 to 0.67 up to two years) are significantly more effective than placebo. In terms of disability and functioning no evidence was available. There is consistent evidence that both haloperidol (RR 4.40, 2.08 to 9.30) and

	chlorpromazine (RR 2.01, 1.50 to 2.70) significantly increased the risk of movement disorders. There is limited evidence that both haloperidol (RR 10.1, 1.32 to 77.46) and chlorpromazine (RR 4.92, 2.32 to 10.43) significantly increased the risk of weight gain. In terms of proportion of patients showing a response, all second-generation antipsychotic drugs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, zotepine) were more effective than placebo (see GRADE tables), but the pooled effect size for overall symptoms (primary outcome) was moderate. Overall, the absolute difference in responder rates was at 17% (41% responded to drug compared with 24% to placebo, number needed to treat = 6). There was no difference in terms of EPS between any second-generation antipsychotic drugs and placebo.
Summary of the quality of evidence	For haloperidol, the quality of evidence was LOW and VERY LOW for symptom reduction and relapse prevention respectively. The quality of evidence was MODERATE for adverse events. For chlorpromazine, the quality of evidence was MODERATE and VERY LOW for symptom reduction and relapse prevention respectively. The quality of evidence was MODERATE for adverse events. For second-generation antipsychotic drugs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, zotepine), the quality of evidence was LOW/VERY LOW for symptom reduction and treatment response. The quality of evidence was MODERATE for treatment discontinuation.
Balance of benefits versus harms	In studies carried out in individuals with psychotic disorders, including

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	schizophrenia, antipsychotics are associated with a beneficial effect. In terms of tolerability, both haloperidol and chlorpromazine are associated with a large increase in the risk of movement disorders. This risk is dose related. Low doses of haloperidol (3 to 7.5 mg/day) and chlorpromazine (≤ 400mg/day) have a lower rate of development of clinically significant extrapyramidal adverse effects than higher doses. Both haloperidol and chlorpromazine are associated with an increase in the risk of weight gain. Clozapine treatment is associated with an increased risk of development of agranulocytosis.
Values and preferences including any variability and human rights issues	Important issues are the short and long term consequences of disability, lack of functioning, discrimination and stigma associated with psychotic symptoms and psychotic relapses. However, there are significant concerns about safety and tolerability associated with antipsychotic medications. A further important issue is the burden of taking medication daily with negative consequences in terms of treatment adherence. Additionally, extrapyramidal symptoms may lead to easy identification of people treated for a mental disorder.
Costs and resource use and any other relevant feasibility issues	Haloperidol, chlorpromazine and other first generation antipsychotics are associated with low acquisition costs. The cost of second generation antipsychotics in the treatment of schizophrenia may be more than ten times the cost of generic first-generation antipsychotics. In many LAMICs continuous availability of antipsychotic in non specialized health care is a challenge.

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	Haloperidol and chlorpromazine are available in WHO Essential Medicine List as antipsychotic medicines.
Recommendation(s) Haloperidol or chlorpromazine should be routinely offered to individuals with psychotic disorders (including schizophrenia). Strength of recommendation: STRONG Second-generation antipsychotics (with the exception of clozapine) may be considered in individuals with psychotic disorders (including schizophrenia) as an alternative to haloperidol or chlorpromazine if availability can be assured and cost is not a constraint. Strength of recommendation: STANDARD For individuals with psychotic disorders (including schizophrenia) who do not respond to adequate dose and duration of other antipsychotic medicines, clozapine may be considered by non-specialist health care providers, preferably under the supervision of mental health professionals, only if routine laboratory monitoring is available. Strength of recommendation: STANDARD In individuals with psychotic disorders (including schizophrenia), minimal effective dose of antipsychotics should be used, paying attention to minimizing adverse effects. Strength of recommendation: STRONG In women with psychotic disorders (including schizophrenia) who are planning a pregnancy or pregnant or breastfeeding, low-dose oral haloperidol or chlorpromazine may be considered. Strength of recommendation: STANDARD	
Any additional remarks Generating more evidence on outcomes like disability and functioning, quality of life, users' and families' satisfaction with care with use of these medicines is necessary. Relative advantages and disadvantages of use of first generation versus second generation antipsychotics in non specialized health care settings.	

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic reviews were found to be relevant without changing the recommendation:

Leucht C, Kitzmantel M, Kane J, Leucht S, Chua WLLC. Haloperidol versus chlorpromazine for schizophrenia. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD004278. DOI: 10.1002/14651858.CD004278.pub2.

Lobos AC, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Leucht S. Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD006633. DOI: 10.1002/14651858. CD006633.pub2.