[New 2015]

Second-generation antipsychotic medications for psychotic disorders (including schizophrenia)

SCOPING QUESTION: In adults with psychotic disorders (including schizophrenia), what is the comparative effectiveness and safety of second-generation antipsychotic medications?

BACKGROUND

Many newer antipsychotics have been developed in the last two decades. Traditionally, antipsychotics are divided into two classes, with older first-generation medicines in one class and newer, more expensive second-generation medicines in the other (Abou-Setta et al., 2012). Currently, most guidelines recommend second-generation antipsychotics as first-choice treatment in patients with psychotic disorders (National Institute for Health and Care Excellence (NICE), 2014). Among second-generation medicines, the question of which antipsychotic should be preferred for treatment of psychotic disorders is controversial (Abou-Setta et al., 2012). Clear evidence-based hierarchies of the comparative efficacy, safety, risk of discontinuation and side-effects of second-generation antipsychotic (SGA) medications are necessary in order to recommend an antipsychotic medication in clinical practice.

This evidence profile is an update of the evidence profile originally produced in 2009 for the mhGAP (2010) intervention guidelines. The update is necessary because new evidence has emerged on the comparative efficacy of new generation antipsychotics. This question does not address the comparative efficacy and safety of first-generation antipsychotics vs. SGA. All recommendations outlined in the 2010 version of the mhGAP intervention guidelines are still valid.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults with psychotic disorders (including schizophrenia)
- **Interventions:** Second-generation antipsychotics medications
- **Comparison:** Placebo or second-generation antipsychotic (head-to-head comparisons)
- **Outcomes:**
  - **Critical** – Symptoms severity, adverse effect of treatment
  - **Important** – Treatment adherence, disability and functioning

Search strategy

The search was conducted in Week 28 of 2014. We used the search strategy developed by the McMaster University[i] to locate relevant systematic reviews. Databases searched included the Cochrane Database of Systematic Reviews, PubMED (clinical queries), the Campbell Collaboration, LILACS, PsycINFO, Embase and PILOTS. Keywords used included *"antipsychotic*" AND "systematic review"*.

In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g., PubMED, PsycINFO and Embase) this option, and was selected and the only keyword used was *"antipsychotic*"*. Studies were included if they were systematic reviews comprised of treatment studies with adults (>18 years) and published from 2010 onwards.

Systematic reviews included in grade tables or footnotes

- Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3.

PICO Table*

<table>
<tr><td colspan="6">Population: Adults with psychotic disorders (including schizophrenia)</td></tr>
<tr><td>Intervention</td><td>Comparison</td><td>Outcome</td><td>Systematic reviews used</td><td>Justification for systematic review used</td><td>Relevant GRADE Table(s)</td></tr>
<tr><td rowspan="2">Second-generation antipsychotic medications (aripiprazole, asenapine,</td><td rowspan="2">Placebo</td><td>Symptoms severity</td><td>Leucht et al. (2013)</td><td>This is the most recent and comprehensive high-quality systematic review available.</td><td rowspan="2">Table 1 – Aripiprazole
Table 2 – Asenapine
Table 3 – Clozapine
Table 4 – Iloperidone
Table 5 –Lurasidone</td></tr>
<tr><td>Disability and functioning</td><td>No evidence available</td><td></td></tr>
</table>

clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine)		Adverse effects of treatment	Leucht et al. (2013)	This is the most recent and comprehensive high-quality systematic review available.	Table 6 –Olanzapine Table 7 – Paliperidone Table 8 – Quetiapine Table 9 –Risperidone Table 10 – Sertindole Table 11 – Ziprasidone Table 12 – Zotepine
		Treatment adherence	Leucht et al. (2013)	This is the most recent and comprehensive high-quality systematic review available.	
Second-generation antipsychotic medications (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine)	other second-generation antipsychotic medications (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine)	Symptoms severity	Leucht et al. (2013)	This is the most recent and comprehensive high-quality systematic review available.	See Figures X-X in the Appendix for SUCRA curves of head-to-head comparisons.
		Disability and functioning	No evidence available		
		Adverse effects of treatment	Leucht et al. (2013)	This is the most recent and comprehensive high-quality systematic review available.	
		Treatment adherence	Leucht et al. (2013)	This is the most recent and comprehensive high-quality systematic review available.	

Narrative description of the studies that went into analysis

Leucht et al. (2013) included 65 studies randomizing 14874 patients with schizophrenia or non-affective psychotic disorders to an SGA or placebo, specifically: aripiprazole (N=6), asenapine (N=4), clozapine (N=1), Iloperidone (N=4), lurasidone (N=6), olanzapine (N=11), paliperidone (N=7),

quetiapine (N=6), risperidone (N=11), sertindole (N=3), ziprasidone (N=4) and zotepine (N=2). There were 52 studies comprised of head-to-head comparisons of SGAs that included 11 230 patients with schizophrenia or other psychotic disorders. Most of the studies were short-term and examined patients with acute schizophrenia. Trials done in patients with predominant negative symptoms, concomitant medical illness or treatment resistance and those done in stable patients were excluded. The majority of studies were conducted by pharmaceutical companies and usually for registration purposes. The mean duration of illness was 12 years (SD = 7) and the mean age of trial participants was 38 years (SD = 7).

GRADE Tables

For feasibility reasons, GRADE was carried out only for studies that included placebo (51 studies, 97 comparisons). For head-to-head studies, please see the 'summary of evidence table' on p. 190.

Table 1. Aripoprazole vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should aripiprazole be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aripiprazole	Placebo	Relative (95% CI)	Absolute		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
6[1]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,5]	0[3,21]	-	-	SMD 0.43 lower (0.52 to 0.34 lower)	⊕⊕OO LOW	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

Adverse effects - Antiparkinson medication												
5[6]	Randomized trials	S	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	-[3,10]	0%	OR 1.20 (0.73 to 1.85)[11]	-	⊕⊕OO LOW	CRITICAL
Adverse effects – Sedation												
5[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	-[3,10]	0%	OR 1.84 (1.05 to 3.05)[12]	-	⊕⊕OO LOW	CRITICAL
Adverse effects – Weight gain (Better indicated by lower values)												
3[6]	Randomized trials	Serious[13]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	0[3,14]	-	-	SMD 0.17 higher (0.05 to 0.28 higher)[15]	⊕⊕OO LOW	CRITICAL
Adverse effects – Prolactin increase (Better indicated by lower values)												
5[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	0[3,10]	-	-	SMD 0.22 lower (0.46 lower to 0.03 higher)[16]	⊕⊕OO LOW	CRITICAL
Adverse effects – QT prolongation)												
5[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	-[3,10]	0%	OR 0.01 (-0.13 to 0.15)[17]	-	⊕⊕OO LOW	CRITICAL
Treatment acceptability – Total dropouts												
6[6]	Randomized trials	Serious[18]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	-[3,19]	0%	OR 0.61 (0.51 to 0.72)[20]	-	⊕⊕OO LOW	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013).
[2] High risk of attrition bias in all six studies, according to Leucht et al. (2013).
[3] Not reported.
[4] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons."
[5] High risk of reporting bias in 4 out of 6 studies according to Leucht et al. (2013).
[6] Additional information provided by the authors of Leucht et al. (2013).
[7] High risk of attrition bias in all five studies, according to Leucht et al. (2013).
[8] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[9] High risk of reporting bias in some studies, according to Leucht et al. (2013)
[10] The total number of included patients was 1000.

[11] Estimates >1 = more extrapyramidal side-effects with active medication.
[12] Estimates >1 = more sedation with active medication.
[13] High risk of attrition bias in all three studies, according to Leucht et al. (2013).
[14] The total number of included patients was 922.
[15] Estimates > 0 = more weight gain with active medication.
[16] Estimates > 0 = more prolactin increase with active medication.
[17] Estimates > 0 = more QT prolongation with active medication.
[18] High risk of attrition bias in all six studies, according to Leucht et al. (2013).
[19] The total number of included patients was 1305.
[20] Estimates below 1 favour SGAs.
[21] The total number of included patients was 1314.

Table 2. Asenapine vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should asenapine be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Asenapine	Placebo	Relative (95% CI)	Absolute		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
4[1]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4,5]	0[3,19]	-	-	SMD 0.38 lower (0.51 to 0.25 lower)	⊕⊕⊕O MODERATE	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-			IMPORTANT
Adverse effects – Antiparkinson medication												
2[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	Serious[8]	None[9]	-[3,10]	0%	OR 1.17 (0.59 to 2.33)[11]	-	⊕⊕OO LOW	CRITICAL

Adverse effects – Sedation												
2[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	Serious[8]	None[9]	-[3,10]	0%	OR 1.78 (0.88 to 3.61)[12]	-	⊕⊕OO LOW	CRITICAL
Adverse effects – Weight gain (Better indicated by lower values)												
2[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[9]	0[3,13]	-	-	SMD 0.23 higher (0.07 to 0.39 higher)[14]	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects – Prolactin increase (Better indicated by lower values)												
2[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[9]	0[3,10]	-	-	SMD 0.12 higher (0 to 0.37 higher)[15]	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects – QT prolongation												
2[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	Serious[8]	None[9]	-[3,10]	0%	OR 0.3 (-0.04 to 0.65)[16]	-	⊕⊕OO LOW	CRITICAL
Treatment acceptability – All-cause discontinuation												
4[6]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[5,9]	-[3,17]	0%	OR 0.69 (0.54 to 0.86)[18]	-	⊕⊕⊕O MODERATE	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013).
[2] High risk of attrition bias in all four studies, according to Leucht et al. (2013).
[3] Not reported.
[4] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons," (p. 961).
[5] High risk of reporting bias only in 1 out of 4 studies, according to Leucht et al. (2013).
[6] Additional information is provided by the authors of Leucht et al. (2013).
[7] High risk of attrition bias in the two studies, according to Leucht et al. (2013).
[8] Confidence interval includes no effect and appreciable harm.
[9] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[10] The total number of included patients was 465.
[11] Estimates > 1 = more extrapyramidal side-effects with active medication.
[12] Estimates > 1 = more sedation with active medication.

[13] The total number of included patients was 436.
[14] Estimates > 0 = more weight gain with active medication.
[15] Estimates > 0 = more prolactin increase with active medication.
[16] Estimates > 0 = more QT prolongation with active medication.
[17] The total number of included patients was 963.
[18] Estimates below 1 favour SGAs.
[18] The total number of included patients was 942.

Table 3. Clozapine vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should clozapine be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Clozapine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
1[1,2]	Randomized trials	Serious[3]	No serious inconsistency[4]	Serious[5]	Serious[6]	Reporting bias[7]	0[4,12]	-	-	SMD 0.88 lower (1.03 to 0.73 lower)	⊕OOO VERY LOW	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects – Antiparkinson medication (not reported)												
0	-	-	-	-	-	None	-	-	-	-		CRITICAL
								0%		-		
Adverse effects – Sedation (not reported)												

0	-	-	-	-	-	None	-	-	-	-		CRITICAL
Adverse effects – Weight gain (not reported)												
0	-	-	-	-	-	None	0	-	-	-		CRITICAL
Adverse effects – Prolactin increase (not reported)												
0	-	-	-	-	-	None	0	-	-	-		CRITICAL
Adverse effects – QT prolongation - not reported												
0	-	-	-	-	-	None	0	-	-	-		CRITICAL
Treatment acceptability – All-cause discontinuation												
1[8]	Randomized trials	Serious[9]	No serious inconsistency[4]	Serious[10]	Serious[11]	Reporting bias[7]	-[4,12]	0%	OR 0.46 (0.32 to 0.65)[13]	-	⊕OOO VERY LOW	CRITICAL

[1] From Appendix 8 of Leucht et al. (2013).
[2] Trials done in patients with treatment resistance or predominant negative symptoms were excluded.
[3] High risk of attrition bias, according to Leucht et al. (2013).
[4] Not reported.
[5] Only one study contributed to the analysis.
[6] Only 22 patients contributed to the analysis.
[7] High risk of reporting bias, according to Leucht et al. (2013).
[8] Additional information was provided by the authors of Leucht et al. (2013).
[9] High risk of attrition bias in all four studies, according to Leucht et al. (2013).
[10] Only one study contributed to the analysis.
[11] Only 24 patients contributed to the analysis.
[12] The total number of included patients was 24.
[13] Estimates below 1 favour SGAs.

[New 2015]

Table 4. Iloperidone vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Is iloperidone effective for treatment of schizophrenia compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Iloperidone**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
4[1]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4]	0[3,13]	-	-	SMD 0.33 lower (0.43 to 0.22 lower)	⊕⊕⊕O MODERATE	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-			IMPORTANT
Adverse effects - Antiparkinson medication												
1[5]	Randomized trials	Serious[6]	No serious inconsistency[3]	Serious[7]	Serious[8,9]	None[10]	-[3,11]	0%	OR 1.58 (0.55 to 3.65)[12]	-	⊕OOO VERY LOW	CRITICAL
Adverse effects – Sedation												
4[5]	Randomized	Serious[6]	No serious	No serious	Serious[9]	None[10]	-[3,13]	0%	OR 1.71 (0.63	-	⊕⊕OO	CRITICAL

	trials		inconsistency[3]	indirectness					to 3.77)[14]		LOW	
Adverse effects - Weight gain (better indicated by lower values)												
4[5]	Randomized trials	Serious[6]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[10]	0[3,13]	-	-	SMD 0.62 higher (0.49 to 0.74 higher)[15]	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects - Prolactin increase (better indicated by lower values)												
4[5]	Randomized trials	Serious[6]	No serious inconsistency[3]	No serious indirectness	Serious[9]	None[10]	0[3,13]	-	-	SMD 0.21 higher (0.09 lower to 0.51 higher)[16]	⊕⊕OO LOW	CRITICAL
Adverse effects - QT prolongation												
4[5]	Randomized trials	Serious[6]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[10]	-[3,13]	0%	OR 0.34 (0.22 to 0.46)[17]	-	⊕⊕⊕O MODERATE	CRITICAL
Treatment acceptability - All-cause discontinuation												
4[5]	Randomized trials	Serious[18]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[10]	-[3,19]	0%	OR 0.69 (0.56 to 0.84)[20]	-	⊕⊕⊕O MODERATE	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013)
[2] High risk of attrition bias in 3 out of 4 studies according to Leucht et al. (2013)
[3] Not reported
[4] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[5] Additional information provided by the authors of Leucht et al. (2013)
[6] High risk of attrition bias in 3 out of 4 studies according to Leucht et al. (2013)
[7] Only 1 study contributed to the analisys
[8] Confidence interval ranges from appreciable benefit to appreciable harm
[9] Confidence interval includes no effect and appreciable harm
[10] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[11] The total number of included patients was 455
[12] Estimates > 1 = more extrapyramidal side-effects with active medication
[13] The total number of included patients was 1515
[14] Estimates > 1 = more sedation with active medication
[15] Estimates > 0 = more weight gain with active medication
[16] Estimates > 0 = more prolactin increase with active medication
[17] Estimates > 0 = more QTc prolongation with active medication
[18] High risk of attrition bias in 3 out of 4 studies according to Leucht et al. (2013)
[19] The total number of included patients was 1565
[20] Estimates below 1 favour SGAs.

Table 5. Lurasidone vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should lurasidone be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lurasidone**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
6[1]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4]	0[3,11]	-	-	SMD 0.33 lower (0.45 to 0.21 lower)	⊕⊕⊕O MODERATE	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects - Antiparkinson medication												
6[5]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	-[3,7]	0%	OR 2.46 (1.55 to 3.72)[8]	-	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects - Weight gain (better indicated by lower values)												
6[5]	Randomized	Serious[2]	no serious	No serious	No serious	None[6]	0[3,9]	-	-	SMD 0.10 higher (0.02	⊕⊕⊕O	CRITICAL

	trials		inconsistency[3]	indirectness	imprecision					to 0.21 higher)[10]	MODERATE	
Adverse effects – Sedation												
6[5]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	-[3,11]	0%	OR 2.45 (1.31 to 4.24)[12]	-	⊕⊕⊕O MODERATE	IMPORTANT
Adverse effects - Prolactin increase (better indicated by lower values)												
6[5]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	0[3,9]	-	-	SMD 0.34 higher (0.11 to 0.57 higher)[13]	⊕⊕⊕O MODERATE	IMPORTANT
Adverse effects - QT prolongation												
6[5]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	-[3,11]	0%	-[14]	-	⊕⊕⊕O MODERATE	IMPORTANT
Treatment acceptability - All-cause discontinuation												
6[5]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	-[3,15]	0%	OR 0.77 (0.61 to 0.96)[16]	-	⊕⊕⊕O MODERATE	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013).
[2] High risk of attrition bias in at least two studies, according to Leucht et al. (2013) .
[3] Not reported.
[4] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[5] Additional information was provided by the authors of Leucht et al. (2013).
[6] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons"(p. 961).
[7] The total number of included patients was 1764.
[8] Estimates > 1 = more extrapyramidal side-effects with active medication.
[9] The total number of included patients was 1715.
[10] Estimates > 0 = more weight gain with active medication.
[11] The total number of included patients was 1733.
[12] Estimates > 1 = more sedation with active medication.
[13] Estimates > 0 = more prolactin increase with active medication.
[14] Estimates > 0 = more QTc prolongation with active medication.
[15] The total number of included patients was 1764.
[16] Estimates below 1 favour SGAs.

[New 2015]

Table 6. Olanzapine vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should olanzapine be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Olanzapine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
14[1]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,5]	0[3,6]	-	-	SMD 0.59 lower (0.65 to 0.53 lower)[7]	⊕⊕OO LOW	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects - Antiparkinson medication												
7[8]	Randomized trials	Serious[9,10]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[5,11]	-[3,12]	0%	OR 1 (0.73 to 1.33)[13]	-	⊕⊕OO LOW	CRITICAL
Adverse effects – Sedation												

3[14,15]	Randomized trials	Serious[9]	No serious inconsistency[3]	No serious indirectness	Serious[16]	Reporting bias[11,17]	-[3,18]	0%	OR 1.93 (0.76 to 4.9)[13]	-	⊕OOO VERY LOW	CRITICAL
Adverse effects - Weight gain (better indicated by lower values)												
9[8,15]	Randomized trials	Serious[10]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[5,11]	0[3,19]	-	-	SMD 0.74 higher (0.81 to 0.67 higher)[20]	⊕⊕OO LOW	CRITICAL
Adverse effects - Prolactin increase (better indicated by lower values)												
9[8,15]	Randomized trials	Serious[10]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[5,11]	0[3,19]	-	-	SMD 0.14 higher (0 to 0.28 higher)[21]	⊕⊕OO LOW	CRITICAL
Adverse effects - QT prolongation												
3[14,15]	Randomized trials	Serious[9]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[11,17]	-[3,18]	0%	OR 0.22 (0.11 to 0.31)[22]	-	⊕⊕OO LOW	CRITICAL
Treatment acceptability - All-cause discontinuation												
14[8]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,17]	-[3,23]	0%	OR 0.46 (0.41 to 0.52)[13]	-	⊕⊕OO LOW	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013).
[2] High risk of attrition bias in 10 out of 14 studies, according to Leucht et al. (2013).
[3] Not reported.
[4] High risk of reporting bias in 4 out of 14 studies, according to Leucht et al. (2013).
[5] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons"(p. 961).
[6] The total number of included patients was 2182.
[7] From Figure 2 of Leucht et al. (2013).
[8] Additional information was provided by the authors of Leucht et al. (2013).
[9] Loss to follow-up exceeds 30%.
[10] High risk of attrition bias in many studies, according to Leucht et al. (2013).
[11] High risk of reporting bias in some studies, according to Leucht et al. (2013).
[12] The total number of included patients was 1380.
[13] Estimates below 1 favour SGA medications.
[14] From Figure 11 of Leucht et al. (2013).
[15] From Leucht et al. (2013).
[16] Confidence interval includes no effect ad appreciable harm.
[17] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[18] The total number of included patients was 408.
[19] The total number of included patients was 1738.

[20] Estimates > 0 = more weight gain with active medication.
[21] Estimates > 0 = more prolactin increase with active medication.
[22] Estimates > 0 = more QT prologation with active medication.
[23] The total number of included patients was 2670.

Table 7. Paliperidone vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should paliperidone be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paliperidone	Placebo	Relative (95% CI)	Absolute		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
7[1]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4]	0[3,17]	-	-	SMD 0.50 lower (0.6 to 0.39 lower)	⊕⊕⊕O MODERATE	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects - Antiparkinson medication												
7[5]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	-[3,7]	0%	OR 1.81 (1.17 to 2.69)[8]	-	⊕⊕⊕O MODERATE	CRITICAL

Adverse effects - Weight gain (better indicated by lower values)												
8[5]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	0[3,9]	-	-	SMD 0.38 higher (0.27 to 0.48 higher)[10]	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects – Sedation												
8[5]	Randomized trials	Serious[2]	no serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	-[3,11]	0%	OR 1.40 (0.85 to 2.19)[12]	-	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects - Prolactin increase (better indicated by lower values)												
8[5]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	0[3,9]	-	-	SMD 1.30 higher (1.08 to 1.51 higher)[13]	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects – QT prolongation												
8[5]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	-[3,11]	0%	OR 0 (-0.18 to 0.26)[14]	-	⊕⊕⊕O MODERATE	CRITICAL
Treatment acceptability - All-cause discontinuation												
8[5]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[6]	-[3,15]	0%	OR 0.77 (0.61 to 0.96)[16]	-	⊕⊕⊕O MODERATE	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013).
[2] High risk of attrition bias in at least three studies, according to Leucht et al. (2013).
[3] Not reported.
[4] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[5] Additional information was provided by the authors of Leucht et al. (2013).
[6] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[7] The total number of included patients was 2120.
[8] Estimates > 1 = more extrapyramidal side-effects with active medication.
[9] The total number of included patients was 2116.
[10] Estimates > 0 = more weight gain with active medication.
[11] The total number of included patients was 2116.
[12] Estimates > 1 = more sedation with active medication.
[13] Estimates > 0 = more prolactin increase with active medication.
[14] Estimates > 0 = more QT prolongation with active medication.

[15] The total number of included patients was 2234.
[16] Estimates below 1 favour SGAs.
[17] The total number of included patients was 1931.

[New 2015]

Table 8. Quetiapine vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should quetiapine be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quetiapine	Placebo	Relative (95% CI)	Absolute		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
6[1]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4,5]	0[3,18]	-	-	SMD 0.44 lower (0.52 to 0.35 lower)	⊕⊕⊕O MODERATE	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects - Antiparkinson medication												
7[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4,8]	-[3,9]	0%	OR 1.01 (0.68 to 1.44)[10]	-	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects – Sedation												
6[11]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4,5]	-[3,12]	0%	OR 2.76 (2.68 to 5.19)[13]	-	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects - Weight gain (better indicated by lower values)												
6[11]	Randomized	Serious[2]	No serious	No serious	No serious	None[4,5]	0[3,12]	-	-	SMD 0.43 higher (0.34 to	⊕⊕⊕O	CRITICAL

	trials		inconsistency[3]	indirectness	imprecision					0.53 higher)[14]	MODERATE	
Adverse effects - Prolactin increase (better indicated by lower values)												
6[11]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4,5]	0[3,12]	-	-	SMD 0.05 lower (0.23 lower to 0.13 higher)[15]	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects - QT prolongation												
6[11]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4,5]	-[3,12]	0%	OR 0.17 (0.06 to 0.29)[16]	-	⊕⊕⊕O MODERATE	CRITICAL
Treatment acceptability - All-cause discontinuation												
7[11]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4,8]	-[3,17]	0%	OR 0.61 (0.52 to 0.71)[13]	-	⊕⊕⊕O MODERATE	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013).
[2] High risk of attrition bias in 5 out of 6 studies, according to Leucht et al. (2013).
[3] Not reported.
[4] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[5] High risk of reporting bias in only 1 out of 6 studies, according to Leucht et al. (2013).
[6] Additional information was provided by the authors of Leucht et al. (2013)
[7] High risk of attrition bias in 5 out of 7 studies, according to Leucht et al. (2013)
[8] High risk of reporting bias in only 1 out of 7 studies, according to Leucht et al. (2013).
[9] The total number of included patients was 2203.
[10] Estimates > 1 = more extrapyramidal side-effects with active medication.
[11] Additional information was provided by the authors of Leucht et al. (2013).
[12] The total number of included patients was 1951.
[13] Estimates below 1 favour SGA medications.
[14] Estimates > 0 = more weight gain with active medication.
[15] Estimates > 0 = more prolactin increase with active medication.
[16] Estimates > 0 = more QT prolongation with active medication.
[17] The total number of included patients was 2203.
[18] The total number of included patients was 1354.

[New 2015]

Table 9. Risperidone vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should risperidone be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone	Placebo	Relative (95% CI)	Absolute		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
12[1]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,5]	0[3,21]	-	-	SMD 0.56 lower (0.63 to 0.5 lower)	⊕⊕OO LOW	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects - Antiparkinson medication												
6[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	-[3,10]	0%	OR 2.09 (1.54 to 2.78)[11]	-	⊕⊕OO LOW	CRITICAL
Adverse effects - Weight gain (better indicated by lower values)												
7[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	0[3,12]	-	-	SMD 0.42 higher (0.33 to 0.5 higher)[13]	⊕⊕OO LOW	CRITICAL

[New 2015]

Adverse effects – Sedation												
6[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	-[3,10]	0%	OR 2.45 (1.76 to 3.35)[14]	-	⊕⊕OO LOW	CRITICAL
Adverse effects - Prolactin increase (better indicated by lower values)												
7[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	0[3,12]	-	-	SMD 1.23 higher (1.06 to 1.4 higher)[15]	⊕⊕OO LOW	CRITICAL
Adverse effects - QT prolongation (better indicated by lower values)												
7[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,9]	0[3,12]	-	-	SMD 0.25 higher (0.15 to 0.36 higher)[16]	⊕⊕OO LOW	CRITICAL
Treatment acceptability - All-cause discontinuation												
11[6]	Randomized trials	Serious[2,17]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[8,18]	-[3,19]	0%	OR 0.53 (0.46 to 0.6)[20]	-	⊕⊕OO LOW	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013).
[2] High risk of attrition bias in 11 out of 12 studies, according to Leucht et al. (2013).
[3] Not reported.
[4] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[5] High risk of reporting bias in 6 out of 12 studies, according to Leucht et al. (2013).
[6] Additional information was provided by the authors of Leucht et al. (2013).
[7] High risk of attrition bias in the majority of studies, according to Leucht et al. (2013).
[8] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[9] High risk of reporting bias in many studies, according to Leucht et al. (2013).
[10] The total number of included patients was 826.
[11] Estimates > 1 = more extrapyramidal side-effects with active medication.
[12] The total number of included patients was 1537.
[13] Estimates > 0 = more weight gain with active medication.
[14] Estimates > 1 = more sedation with active medication.
[15] Estimates > 0 = more prolactin increase with active medication.
[16] Estimates > 0 = more QT prologation with active medication.
[17] High risk of attrition bias in the majority of studies, according to Leucht et al. (2013).
[18] High risk of reporting bias in 6 out of 11 studies, according to Leucht et al. (2013).
[19] The total number of included patients was 2203.
[20] Estimates below 1 favour SGAs.
[21] The total number of patients was 2108.

[New 2015]

Table 10. Sertindole vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should sertindole be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sertindole**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
3[1]	Randomized trials	serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,5]	0[3,21]	-	-	SMD 0.39 lower (0.52 to 0.26 lower)	⊕⊕OO LOW	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects - Antiparkinson medication												
3[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[5,8]	-[3,9]	0%	OR 0.81 (0.47 to 1.3)[10]	-	⊕⊕OO LOW	CRITICAL
Adverse effects - Weight gain (better indicated by lower values)												
2[6]	Randomized	Serious[2]	No serious	No serious	No serious	Reporting bias[5,8]	0[3,11,12]	-	-	SMD 0.53 higher (0.38	⊕⊕OO	CRITICAL

	trials		inconsistency[3]	indirectness	imprecision					to 0.68 higher)[13]	LOW	
Adverse effects – Sedation												
2[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	Serious[14]	Reporting bias[5,8]	-[3,12]	0%	OR 1.53 (0.82 to 2.62)[15]	-	⊕OOO VERY LOW	CRITICAL
Adverse effects - Prolactin increase (better indicated by lower values)												
2[6]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[5,8]	0[3,11,12]	-	-	SMD 0.45 higher (0.16 to 0.44 higher)[16]	⊕⊕OO LOW	CRITICAL
Adverse effects - QT prolongation												
2[6]	Randomized trials	Serious[7]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[5,8]	-[3,12]	0%	OR 0.90 (0.76 to 1.02)[17]	-	⊕⊕OO LOW	CRITICAL
Treatment acceptability - All-cause discontinuation												
3[6]	Randomized trials	Serious[7,18]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[5,8]	-[3,19]	0%	OR 0.78 (0.61 to 0.98)[20]	-	⊕⊕OO LOW	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013).
[2] High risk of attrition bias in all three studies, according to Leucht et al. (2013).
[3] Not reported.
[4] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[5] High risk of reporting bias in 1 out of 3 studies, according to Leucht et al. (2013).
[6] Additional information was provided by the authors of Leucht et al. (2013).
[7] High risk of attrition bias in all 3 studies, according to Leucht et al. (2013).
[8] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[9] The total number of patients was 545.
[10] Estimates > 1 = more extrapyramidal side-effects with active medication.
[11] The total number of included patients was 1537.
[12] The total number of included patients was 325.
[13] Estimates > 0 = more weight gain with active medication.
[14] Confidence interval ranges from no difference to appreciable harm.
[15] Estimates > 1 = more sedation with active medication.
[16] Estimates > 0 = more prolactin increase with active medication.
[17] Estimates > 0 = more QT prolongation with active medication.

[18] High risk of attrition bias in the majority of studies, according to Leucht et al. (2013).
[19] The total number of included patients was 675.
[20] Estimates below 1 favour SGAs.
[21] The total number of patients was 545.

Table 11. Ziprasidone vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should ziprasidone be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ziprasidone	Placebo	Relative (95% CI)	Absolute		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
4[1]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,5]	0[3,13]	-	-	SMD 0.39 lower (0.49 to 0.3 lower)	⊕⊕OO LOW	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects - Antiparkinson medication												
4[6]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,5]	-[3,7]	0%	OR 1.61 (1.05 to 2.37)[8]	-	⊕⊕OO LOW	CRITICAL

[New 2015]

Adverse effects - Weight gain (better indicated by lower values)												
3[6]	Randomized trials	Serious[9]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,10]	0[3,11]	-	-	SMD 0.10 higher (0.02 to 0.22 higher)[12]	⊕⊕OO LOW	CRITICAL
Adverse effects – Sedation												
3[6]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,5]	-[3,13]	0%	OR 3.80 (2.58 to 5.42)[14]	-	⊕⊕OO LOW	CRITICAL
Adverse effects - Prolactin increase (better indicated by lower values)												
3[6]	Randomized trials	Serious[9]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,10]	0[3,11]	-	-	SMD 0.25 higher (0.01 to 0.49 higher)[15]	⊕⊕OO LOW	CRITICAL
Adverse effects - QT prolongation												
3[6]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,5]	-[3,13]	0%	OR 0.41 (0.31 to 0.51)[16]	-	⊕⊕OO LOW	CRITICAL
Treatment acceptability - All-cause discontinuation												
4[6]	Randomized trials	Serious[2,17]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	Reporting bias[4,5]	-[3,7]	0%	OR 0.72 (0.59 to 0.86)[18]	-	⊕⊕OO LOW	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013).
[2] High risk of attrition bias in all four studies, according to Leucht et al. (2013) .
[3] Not reported.
[4] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[5] High risk of reporting bias in 1 out of 4 studies and unclear risk in two studies, according to Leucht et al. (2013).
[6] Additional information was provided by the authors of Leucht et al. (2013).
[7] The total number of included patients was 841.
[8] Estimates > 1 = more extrapyramidal side-effects with active medication.
[9] High risk of attrition bias in all three studies, according to Leucht et al. (2013).
[10] High risk of reporting bias in 1 out of 3 studies and unclear risk in two studies, according to Leucht et al. (2013).
[11] The total number of included patients was 854.
[12] Estimates > 0 = more weight gain with active medication.
[13] The total number of patients was 584.
[14] Estimates > 1 = more sedation with active medication.

[15] Estimates > 0 = more prolactin increase with active medication.
[16] Estimates > 0 = more QT prolongation with active medication.
[17] High risk of attrition bias in the majority of studies, according to Leucht et al. (2013).
[18] Estimates below 1 favour SGAs.

Table 12. Zotepine vs. placebo for treatment of schizophrenia

Authors: L Tarsitani and C Barbui
Question: Should zotepine be considered for treatment of schizophrenia when compared to placebo?
Bibliography: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zotepine	Placebo	Relative (95% CI)	Absolute		
Symptom severity (measured with PANSS, BPRS total score; better indicated by lower values)												
2[1]	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision	None[4]	0[3,14]	-	-	SMD 0.49 lower (0.66 to 0.31 lower)	⊕⊕⊕O MODERATE	CRITICAL
Disability and functioning (better indicated by lower values)												
0	No evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects - Antiparkinson medication												
1[5]	Randomized trials	Serious[2,6]	No serious inconsistency[3]	Serious[7]	No serious imprecision	None[4]	-[3,8]	0%	OR 3.01 (1.38 to 5.77)[9]	-	⊕⊕OO LOW	CRITICAL

[New 2015]

Adverse effects - Weight gain (better indicated by lower values)												
1[5]	Randomized trials	Serious[6]	No serious inconsistency[3]	Serious[7]	No serious imprecision	None[4]	0[3,8]	-	-	SMD 0.71 higher (0.47 to 0.96 higher)[10]	⊕⊕OO LOW	CRITICAL
Adverse effects – Sedation												
1[5]	Randomized trials	Serious[6]	No serious inconsistency[3]	Serious[7]	No serious imprecision	None[4]	-[3,8]	-	Not estimable[11]	-	⊕⊕OO LOW	CRITICAL
Adverse effects - Prolactin increase (not reported)												
0[5]	-	-[6]	-[3]	-[7]	-	None[4]	0[3,8]	-	-	-[10]		CRITICAL
Adverse effects - QT prolongation (not reported)												
0[5]	-	-[6]	-[3]	-[7]	-	None[4]	-[3,8]	-	-[11]	-		CRITICAL
Treatment acceptability - All-cause discontinuation												
1[5]	Randomized trials	Serious[2,6]	No serious inconsistency[3]	Serious[7]	Serious[12]	None[4]	-[3,8]	0%	OR 0.69 (0.41 to 1.07)[13]	-	⊕OOO VERY LOW	IMPORTANT

[1] From Appendix 8 of Leucht et al. (2013).
[2] High risk of attrition bias in 1 out of 2 study, according to Leucht et al. (2013).
[3] Not reported.
[4] Authors reported that the funnel plot was asymmetrical, "which is not necessarily the expression of publication bias, but rather of higher efficacy in small trials than in larger ones, for various reasons" (p. 961).
[5] Additional information was provided by the authors of Leucht et al. (2013).
[6] High risk of attrition bias in the study, according to Leucht et al. (2013).
[7] Only one study contributed to the analysis.
[8] The total number of included patients was 106.
[9] Estimates > 1 = more extrapyramidal side-effects with active medication
[10] Estimates > 0 = more weight gain with active medication.
[11] Estimates > 1 = more sedation with active medication.
[12] Confidence interval ranges from no effect to appreciable benefit.
[13] Estimates below 1 favour SGAs.
[14] The total number of included patients was 30

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

Ranking of efficacy and tolerability of SGAs compared to placebo

Table 13. Summary of evidence: symptom severity

SGA	SMD (95% CrI)	Quality of evidence
Clozapine	−0.88 (−1.03 to −0.73)	VERY LOW
Amisulpride	−0.66 (−0.78 to −0.53)	-
Olanzapine	−0.59 (−0.65 to −0.53)	LOW
Risperidone	−0.56 (−0.63 to −0.50)	LOW
Paliperidone	−0.50 (−0.60 to −0.39)	MODERATE
Zotepine	−0.49 (−0.66 to −0.31)	MODERATE
Quetiapine	−0.44 (−0.52 to −0.35)	MODERATE
Aripiprazole	−0.43 (−0.52 to −0.34)	LOW
Sertindole	−0.39 (−0.52 to −0.26)	LOW
Ziprasidone	−0.39 (−0.49 to −0.30)	LOW
Asenapine	−0.38 (−0.51 to −0.25)	MODERATE
Lurasidone	−0.33 (−0.45 to −0.21)	MODERATE
Iloperidone	−0.33 (−0.43 to −0.22)	MODERATE

Table 14. Summary of evidence: Antiparkinson medication

SGA	OR (95% Crl)	Quality of evidence
Clozapine	0.3 (0.12 to 0.62)	VERY LOW
Sertindole	0.81 (0.47 to 1.3)	LOW
Olanzapine	1.00 (0.73 to 1.33)	LOW
Quetiapine	1.01 (0.68 to 1.44)	MODERATE
Aripiprazole	1.20 (0.73 to 1.85)	LOW
Iloperidone	1.58 (0.55 to 3.65)	VERY LOW
Amisulpride	1.60 (0.88 to 2.65)	-
Ziprasidone	1.61 (1.05 to 2.37)	LOW
Asenapine	1.66 (0.85 to 2.93)	LOW
Paliperidone	1.81 (1.17 to 2.69)	MODERATE
Risperidone	2.09 (1.54 to 2.78)	LOW
Lurasidone	2.46 (1.55 to 3.72)	MODERATE
Zotepine	3.01 (1.38 to 5.77)	LOW

Table 15. Summary of evidence: Weight gain

SGA	SMD (95% Crl)	Quality of evidence
Ziprasidone	0.10 (–0.02 to 0.22)	LOW
Lurasidone	0.10 (–0.02 to 0.21)	MODERATE
Aripiprazole	0.17 (0.05 to 0.28)	LOW
Amisulpride	0.20 (0.05 to 0.35)	-
Asenapine	0.23 (0.07 to 0.39)	MODERATE
Paliperidone	0.38 (0.27 to 0.48)	MODERATE
Risperidone	0.42 (0.33 to 0.50)	LOW
Quetiapine	0.43 (0.34 to 0.53)	MODERATE
Sertindole	0.53 (0.38 to 0.68)	LOW
Iloperidone	0.62 (0.49 to 0.74)	MODERATE
Clozapine	0.65 (0.31 to 0.99)	VERY LOW
Zotepine	0.71 (0.47 to 0.96)	LOW
Olanzapine	0.74 (0.67 to 0.81)	LOW

Table 16. Summary of evidence: Sedation

SGA	OR (95% Crl)	Quality of evidence
Amisulpride	1.42 (0.72 to 2.51)	-
Paliperidone	1.40 (0.85 to 2.19)	MODERATE
Sertindole	1.53 (0.82 to 2.62)	VERY LOW
Iloperidone	1.71 (0.63 to 3.77)	LOW
Aripiprazole	1.84 (1.05 to 3.05)	LOW
Lurasidone	2.45 (1.31 to 4.24)	MODERATE
Risperidone	2.45 (1.76 to 3.35)	LOW
Asenapine	3.28 (1.37 to 6.69)	LOW
Olanzapine	3.34 (2.46 to 4.50)	VERY LOW
Quetiapine	3.76 (2.68 to 5.19)	MODERATE
Ziprasidone	3.80 (2.58 to 5.42)	LOW
Zotepine	8.15 (3.91 to 15.33)	LOW
Clozapine	8.82 (4.72 to 15.06)	VERY LOW

Table 19. Adverse effects - All-cause discontinuation

SGA	OR (95% Crl)	Quality of evidence
Amisulpride	0.43 (0.32 to 0.57)	
Olanzapine	0.46 (0.41 to 0.52)	LOW
Clozapine	0.46 (0.32 to 0.65)	VERY LOW
Paliperidone	0.48 (0.39 to 0.58)	MODERATE
Risperidone	0.53 (0.46 to 0.60)	LOW
Aripiprazole	0.61 (0.51 to 0.72)	LOW
Quetiapine	0.61 (0.52 to 0.71)	MODERATE
Zotepine	0.69 (0.41 to 1.07)	VERY LOW
Asenapine	0.69 (0.54 to 0.86)	MODERATE
Iloperidone	0.69 (0.56 to 0.84)	MODERATE
Ziprasidone	0.72 (0.59 to 0.86)	LOW
Lurasidone	0.77 (0.61 to 0.96)	MODERATE
Sertindole	0.78 (0.61 to 0.98)	LOW

Table 18. QT prolongation

SGA	OR (95% Crl)	Quality of evidence
Lurasidone	–0.10 (–0.21 to 0.01)	MODERATE
Aripirazole	0.01 (–0.13 to 0.15)	LOW
Paliperidone	0.05 (–0.18 to 0.26)	MODERATE

Table 19. Summary of evidence: Prolactin increase

SGA	SMD (95% Crl)	Quality of evidence
Aripiprazole	–0.22 (–0.46 to 0.03)	LOW
Quetiapine	–0.05 (–0.23 to 0.13)	MODERATE
Asenapine	0.12 (–0.12 to 0.37)	MODERATE

Quetiapine	0.17 (0.06 to 0.29)	MODERATE
Olanzapine	0.22 (0.11 to 0.31)	LOW
Risperidone	0.25 (0.15 to 0.36)	LOW
Asenapine	0.30 (–0.04 to 0.65)	LOW
Iloperidone	0.34 (0.22 to 0.46)	MODERATE
Ziprasidone	0.41 (0.31 to 0.51)	LOW
Amisulpride	0.66 (0.39 to 0.91)	-
Sertindole	0.90 (0.76 to 1.02)	LOW

Olanzapine	0.14 (+0.00 to 0.28)	LOW
Iloperidone	0.21 (–0.09 to 0.51)	LOW
Ziprasidone	0.25 (0.01 to 0.49)	LOW
Lurasidone	0.34 (0·11 to 0.57)	MODERATE
Sertindole	0.45 (0.16 to 0.74)	LOW
Risperidone	1.23 (1.06 to 1.40)	LOW
Paliperidone	1.30 (1.08 to 1.51)	MODERATE

Summary of evidence not mentioned in GRADE tables

For feasibility reasons, GRADE was not carried out for the head-to-head comparisons that are summarized below. Additional evidence on the head-to-head comparisons can be found in Appendix 1 where Figures 3-8 detail surface under the cumulative ranking curve (SUCRA) estimates for each outcome.

Figure 1. Comparative effectiveness of SGAs: head-to-head comparisons

CLO						
–0·22 (–0·41 to –0·04)	**AMI**					
–0·29 (–0·44 to –0·14)	–0·07 (–0·19 to 0·05)	**OLA**				
–0·32 (–0·47 to –0·16)	–0·09 (–0·21 to 0·03)	–0·03 (–0·10 to 0·04)	**RIS**			
–0·38 (–0·57 to –0·20)	**–0·16 (–0·32 to –0·00)**	–0·09 (–0·21 to 0·02)	–0·07 (–0·19 to 0·06)	**PAL**		
–0·39 (–0·60 to –0·19)	–0·17 (–0·38 to 0·04)	–0·10 (–0·29 to 0·08)	–0·08 (–0·26 to 0·11)	0·01 (–0·22 to 0·20)	**ZOT**	
–0·44 (–0·61 to –0·28)	**–0·22 (–0·36 to –0·08)**	**–0·15 (–0·25 to –0·06)**	**–0·13 (–0·22 to –0·03)**	–0·06 (–0·19 to 0·08)	–0·05 (–0·24 to 0·14)	**QUE**

–0·45 (–0·62 to –0·28)	**–0·23 (–0·37 to –0·08)**	**–0·16 (–0·25 to –0·07)**	**–0·13 (–0·23 to –0·03)**	–0·07 (–0·20 to 0·08)	–0·06 (–0·25 to 0·14)	–0·01 (–0·12 to 0·11)	**ARI**					
–0·49 (–0·68 to –0·30)	**–0·27 (–0·43 to –0·10)**	**–0·20 (–0·33 to –0·06)**	**–0·17 (–0·31 to –0·04)**	–0·10 (–0·27 to 0·07)	–0·09 (–0·31 to 0·12)	–0·04 (–0·19 to 0·10)	–0·04 (–0·19 to 0·11)	**SER**				
–0·49 (–0·66 to –0·31)	**–0·26 (–0·41 to –0·12)**	**–0·20 (–0·29 to –0·10)**	**–0·17 (–0·27 to 0·07)**	–0·10 (–0·24 to 0·04)	–0·09 (–0·29 to 0·11)	–0·04 (–0·16 to 0·08)	–0·04 (–0·16 to 0·09)	0·00 (–0·15 to 0·16)	**ZIP**			
–0·50 (–0·69 to –0·30)	**–0·27 (–0·45 to –0·10)**	**–0·21 (–0·34 to –0·08)**	**–0·18 (–0·32 to –0·04)**	–0·11 (–0·28 to 0·05)	–0·10 (–0·32 to 0·11)	–0·05 (–0·20 to 0·09)	–0·05 (–0·20 to 0·10)	–0·01 (–0·19 to 0·17)	–0·01 (–0·17 to 0·14)	**ASE**		
–0·55 (–0·74 to –0·36)	**–0·33 (–0·50 to –0·16**)	**–0·26 (–0·39 to –0·13)**	**–0·23 (–0·37 to –0·10)**	**–0·17 (–0·33 to –0·00)**	–0·16 (–0·37 to 0·06)	–0·11 (–0·25 to 0·03)	–0·10 (–0·25 to 0·05)	–0·06 (–0·24 to 0·11)	–0·07 (–0·22 to 0·09)	–0·05 (–0·23 to 0·12)	**LUR**	
–0·55 (–0·73 to –0·38)	**–0·33 (–0·48 to –0·18**)	**–0·26 (–0·38 to –0·15)**	**–0·24 (–0·35 to –0·12)**	**–0·17 (–0·32 to –0·02)**	–0·16 (–0·36 to 0·04)	–0·11 (–0·24 to 0·02)	–0·10 (–0·24 to 0·03)	–0·07 (–0·23 to 0·10)	–0·07 (–0·20 to 0·06)	–0·06 (–0·22 to 0·11)	0·00 (–0·16 to 0·16)	**ILO**

NOTES: Medications are reported in order of efficacy ranking. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. SMDs lower than 0 favour the column-defining treatment. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa. Significant results are in bold. CLO=clozapine. AMI=amisulpride. OLA=olanzapine. RIS=risperidone. PAL=paliperidone. ZOT=zotepine. QUE=quetiapine. ARI=aripiprazole. SER=sertindole. ZIP=ziprasidone. ASE=asenapine. LUR=lurasidone. ILO=iloperidone. Modified from: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet.382(9896):951-962.

Figure 2. Treatment acceptability, all-cause discontinuation of SGAs: head-to-head comparisons

CLO				
1·10 (0·69 to 1·69)	**AMI**			
1·00 (0·68 to 1·43)	0·93 (0·69 to 1·22)	**OLA**		
0·87 (0·59 to 1·22)	0·81 (0·60 to 1·08)	0·87 (0·76 to 1·01)	**RIS**	
0·97 (0·63 to 1·42)	0·90 (0·62 to 1·24)	0·97 (0·78 to 1·20)	1·12 (0·88 to 1·40)	**PAL**

0·70 (0·39 to 1·16)	0·66 (0·37 to 1·10)	0·71 (0·43 to 1·13)	0·82 (0·49 to 1·29)	0·74 (0·43 to 1·20)	**ZOT**							
0·76 (0·50 to 1·10)	**0·70 (0·51 to 0·95)**	**0·76 (0·63 to 0·91)**	0·87 (0·73 to 1·04)	0·79 (0·61 to 1·01)	1·13 (0·66 to 1·78)	**QUE**						
0·76 (0·51 to 1·09)	**0·71 (0·51 to 0·96)**	**0·76 (0·64 to 0·90)**	0·88 (0·72 to 1·06)	0·79 (0·61 to 1·02)	1·14 (0·67 to 1·81)	1·01 (0·80 to 1·25)	**ARI**					
0·60 (0·38 to 0·89)	**0·56 (0·38 to 0·78)**	**0·60 (0·47 to 0·76)**	**0·69 (0·53 to 0·88)**	**0·63 (0·46 to 0·85)**	0·90 (0·51 to 1·46)	0·80 (0·60 to 1·04)	0·80 (0·59 to 1·04)	**SER**				
0·65 (0·43 to 0·95)	**0·60 (0·43 to 0·83)**	**0·65 (0·53 to 0·79)**	**0·75 (0·61 to 0·91)**	**0·68 (0·52 to 0·88)**	0·97 (0·56 to 1·55)	0·86 (0·68 to 1·07)	0·86 (0·68 to 1·07)	1·09 (0·81 to 1·45)	**ZIP**			
0·68 (0·43 to 1·01)	**0·63 (0·43 to 0·89)**	**0·68 (0·53 to 0·86)**	0·78 (0·60 to 1·01)	**0·71 (0·52 to 0·95)**	1·02 (0·58 to 1·65)	0·90 (0·68 to 1·19)	0·90 (0·68 to 1·18)	1·14 (0·81 to 1·56)	1·06 (0·78 to 1·41)	**ASE**		
0·61 (0·39 to 0·90)	**0·56 (0·39 to 0·79)**	**0·61 (0·47 to 0·77)**	**0·70 (0·53 to 0·89)**	**0·63 (0·47 to 0·85)**	0·91 (0·51 to 1·47)	0·81 (0·61 to 1·03)	0·80 (0·6 to 1·05)	1·02 (0·73 to 1·39)	0·94 (0·70 to 1·24)	0·91 (0·64 to 1·22)	**LUR**	
0·67 (0·45 to 0·99)	**0·63 (0·44 to 0·87)**	**0·68 (0·54 to 0·84)**	**0·78 (0·62 to 0·96)**	**0·70 (0·53 to 0·93)**	1·01 (0·58 to 1·61)	0·89 (0·70 to 1·13)	0·89 (0·69 to 1·14)	1·13 (0·83 to 1·52)	1·05 (0·81 to 1·33)	1·01 (0·73 to 1·36)	1·12 (0·83 to 1·50)	**ILO**

Medications are reported in order of efficacy ranking. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Odds ratios (ORs) higher than 1 favour the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold. CLO=clozapine. AMI=amisulpride. OLA=olanzapine. RIS=risperidone. PAL=paliperidone. ZOT=zotepine. QUE=quetiapine. ARI=aripiprazole. SER=sertindole. ZIP=ziprasidone. ASE=asenapine. LUR=lurasidone. ILO=iloperidone.
Modified from: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013;382:951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3.

Evidence to recommendation table

Benefits	The most effective SGA is clozapine and the least effective is iloperidone (see Table 13). In terms of causing less treatment discontinuation, the most effective SGA is amisulpride, while sertindole is the least effective is (see Table 19). Hierarchies of effect size on the basis of placebo-controlled and head-to-head comparisons (with direct plus indirect meta-analysis) show that most of the differences between medications are gradual rather than discrete. Clozapine was significantly more effective than all of the other medications, followed by amisulpride, olanzapine and risperidone, which were significantly more effective than the other

	medications apart from paliperidone and zotepine. However, the differences between individual medications were small. Therefore, the clinical meaning of these differences is uncertain. In terms of the proportion of patients discontinuing treatment, amisulpride, olanzapine, clozapine, paliperidone and risperidone had significantly lower all-cause discontinuation than several other medications (see Figures 2 and 4). In terms of disability, functioning, quality of life or satisfaction with care, there was no evidence available.
Harms	The OR between individual SGAs and for extrapyramidal side-effects ranged from 0.3 for the most effective medication (clozapine) to 3.01 for the least effective (zotepine) (see Table 14). The OR for sedation ranged from 1.42 (amisulpride) to 8.82 (clozapine) (see Table 16). The OR for QT prolongation ranged from -0.10 (lurasidone) to 0.90 (sertindole) (see Table 16). In terms of weight gain, the SMD between individual SGAs and placebo ranged from 0.10 for the most effective medication (ziprasidone) to 0.74 for the least effective (olanzapine) (see Table 15). The SMD for prolactin increase ranged from -0.22 (aripiprazole) to 1.30 (paliperidone) (see Table 17). Clozapine treatment is associated with an increased risk of development of agranulocytosis. In terms of mortality, there was no evidence available.
Summary of the quality of evidence	The quality of the available evidence was MODERATE (6 medications), LOW (5 medications) and VERY LOW (1 medication) for symptom reduction. For adverse events, it was MODERATE (5 medications), LOW (5 medications) and VERY LOW (2 medications). The quality of evidence was MODERATE (5 medications), LOW (5 medications) and VERY LOW (2 medications) for all-cause discontinuation.

Value and preferences	
In favour	The interventions address important issues faced by people with schizophrenia, including the short- and long-term consequences of disability, lack of functioning, discrimination and stigma associated with

	psychotic symptoms and psychotic relapses.
Against	There are significant concerns about tolerability associated with SGAs. A further important issue is the burden of taking medication daily, with negative consequences in terms of treatment adherence. Additionally, sedation is unpleasant for patients, while weight gain, other metabolic abnormalities and cardiovascular and hormonal problems increase the risk for several health conditions.
Uncertainty or variability?	Tolerability varies greatly between patients.

Feasibility (including resource use considerations)	The cost of SGAs 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 settings, which is a challenge. Risperidone is included in the WHO Essential Medicine List for the treatment of psychotic disorders. Clozapine is included in WHO Essential Medicine List only for treatment of resistant psychosis. Regular blood tests that are required during clozapine treatment may not be feasible in most LAMICs.
Uncertainty or variability?	SGA-related procurement costs are higher than those for first-generation.

[New 2015]

Recommendation and remarks

Recommendation

Second-generation antipsychotics (with the exception of clozapine which is indicated for treatment resistant psychosis) can be offered for the treatment of psychotic disorders (including schizophrenia). There is no clinically relevant advantage of one second-generation antipsychotic over others and choice should be based on availability, cost, patient preferences and possible adverse effects associated with each medication.

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

Remarks

Although clozapine is more effective than other second-generation antipsychotics, its use is limited to patients that have not responded to other antipsychotics, as it may cause agranulocytosis. Regular blood tests during treatment are required to decrease this risk. Without monitoring, agranulocytosis occurs in about 1% of patients who take clozapine during the first few months of treatment.
The second generation antipsychotics considered in this evidence profile are aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine. Possible adverse effects include sedation, metabolic, extrapyramidal, cardiovascular and hormonal side-effects.

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High □ Moderate **X Low** □ 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	□ No major variability **X Major variability**
Resource use	□ Less resource-intensive **X More resource-intensive**
• **Strength**	**CONDITIONAL**

OTHER REFERENCES

Abou-Setta AA, Mousavi SS, Sooner C, Schouten JR, Pasichnyk D, et al. First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness. Rockville: Agency for Healthcare Research and Quality (US); 2012.

McMaster University search strategy: http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx.

National Institute for Health and Care Excellent (NICE). 2014. *Psychosis and schizophrenia in adults: treatment and management* [CG178]. London: NICE. Available from: https://www.nice.org.uk/guidance/cg178/ifp/chapter/Treatment-options (accessed Autumn 2014).

APPENDIX 1

Figure 3. Head-to-head comparisons: cumulative SUCRA estimates for the outcome overall efficacy

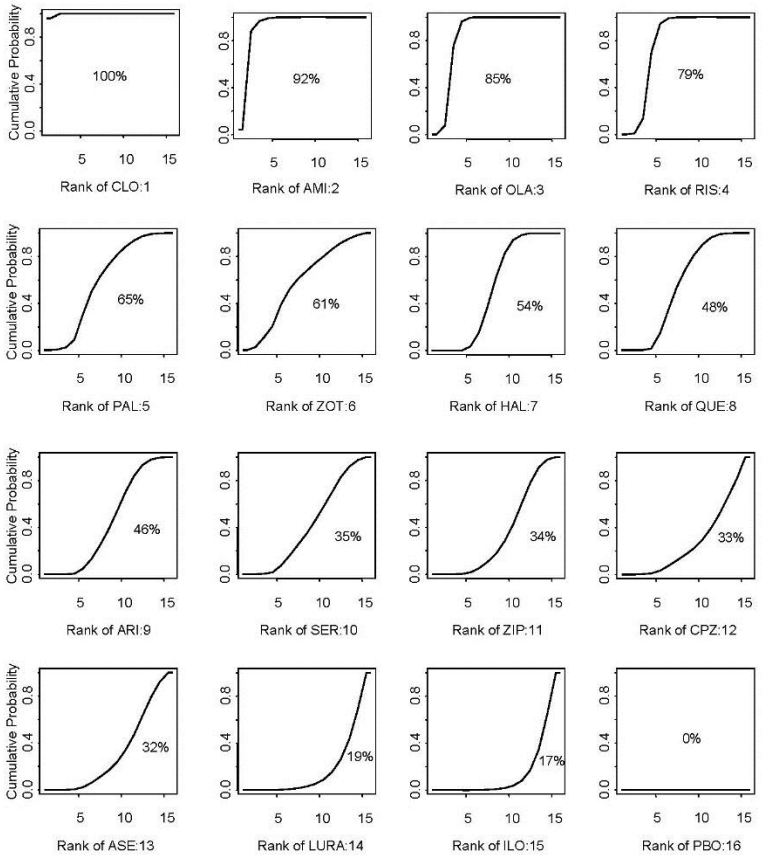
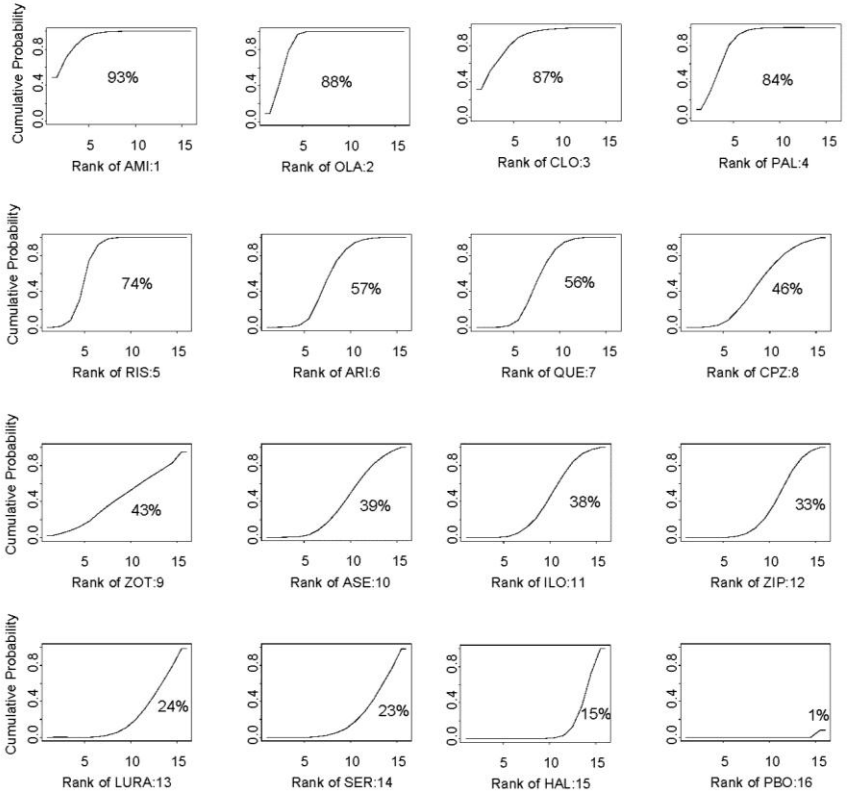


Figure 4. Head-to-head comparisons: SUCRA estimates for the outcome all-cause discontinuation



SUCRA: surface under the cumulative ranking curve. SUCRAs expressed as percentages compare each intervention to an imaginary intervention that is always the best without uncertainty. A SUCRA of x% means that the medication achieves x% of the effectiveness of this imaginary medication, thus larger SUCRAs denote more effective interventions.
AMI = amisulpride, ARI = aripiprazole, ASE = asenapine, CLO = clozapine, CPZ = chlorpromazine, HAL = haloperidol, ILO = iloperidone, LURA = lurasidone, OLA = olanzapine, PAL = paliperidone, PBO = placebo QUE = quetiapine, RIS = risperidone, SER = sertindole, ZIP = ziprasidone, ZOT = zotepine.

[New 2015]

Modified from: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3.

Figure 5. Head-to-head comparisons: SUCRA estimates for the outcome weight gain

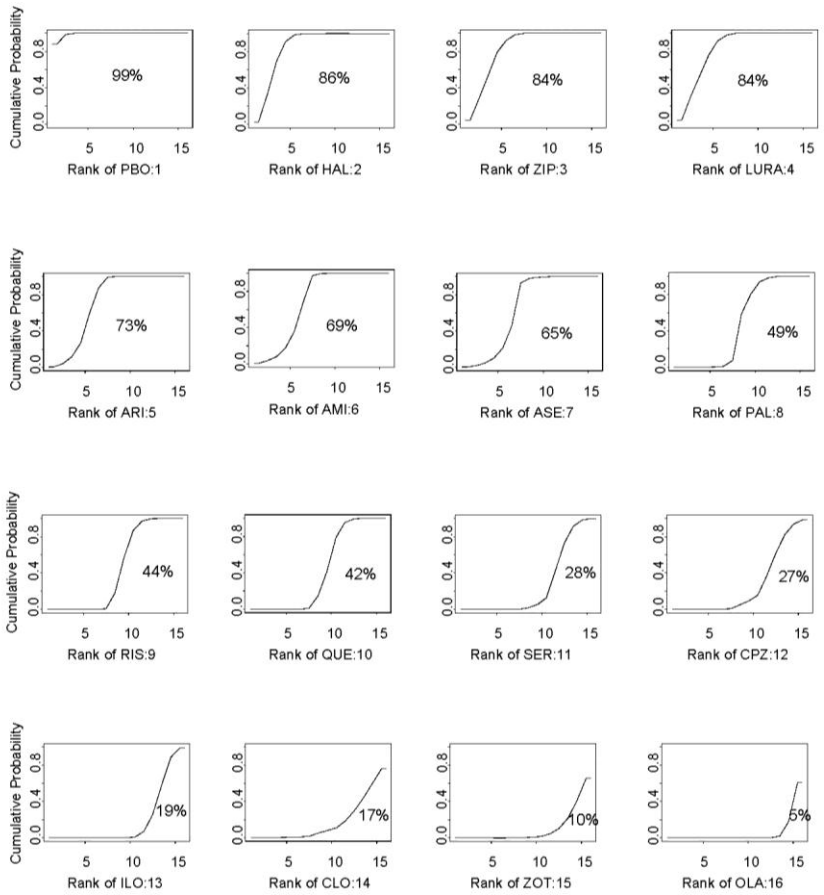
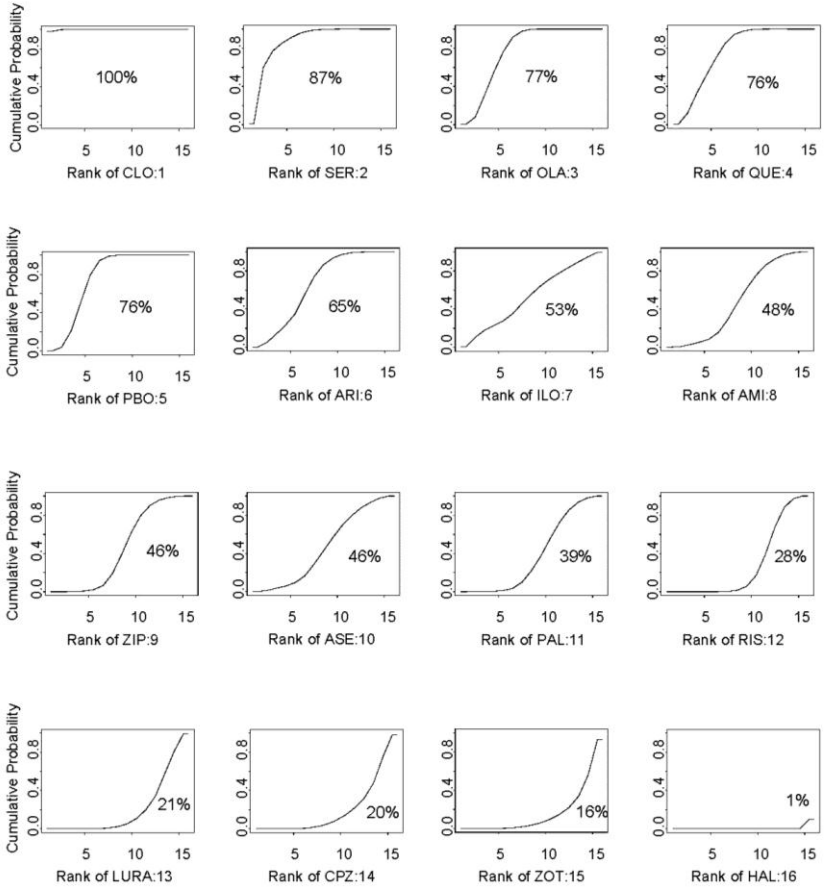


Figure 6. Head-to-head comparisons: SUCRA estimates for the outcome movement disorders



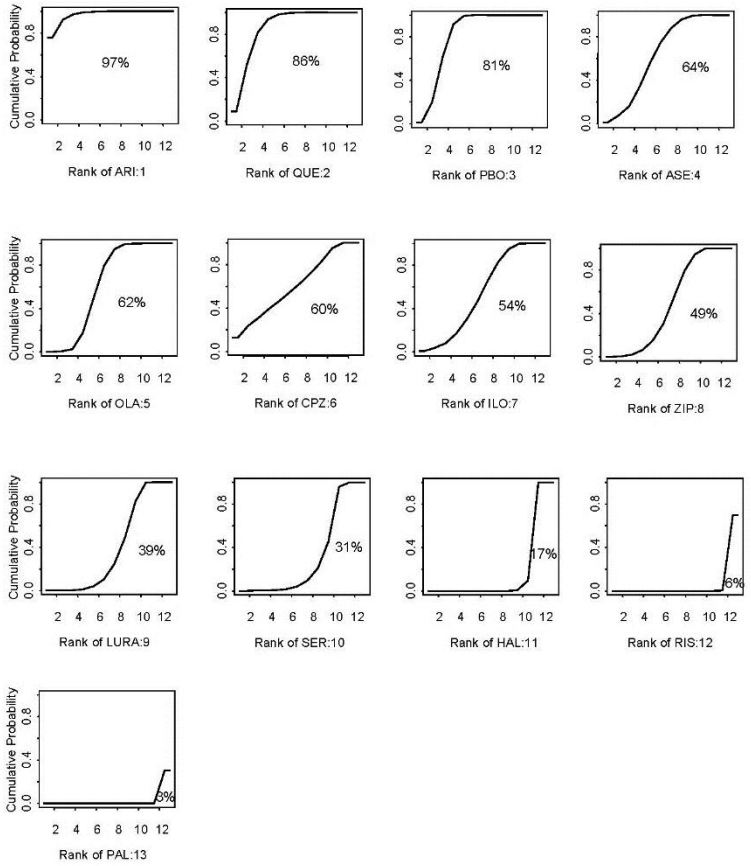
SUCRA: surface under the cumulative ranking curve. SUCRAs expressed as percentages compare each intervention to an imaginary intervention that is always the best without uncertainty. A SUCRA of x% means that the medication achieves x% of the effectiveness of this imaginary medication, thus larger SUCRAs denote more effective interventions.

AMI = amisulpride, ARI = aripiprazole, ASE = asenapine, CLO = clozapine, CPZ = chlorpromazine, HAL = haloperidol, ILO = iloperidone, LURA = lurasidone, OLA = olanzapine, PAL = paliperidone, PBO = placebo QUE = quetiapine, RIS = risperidone, SER = sertindole, ZIP = ziprasidone, ZOT = zotepine.

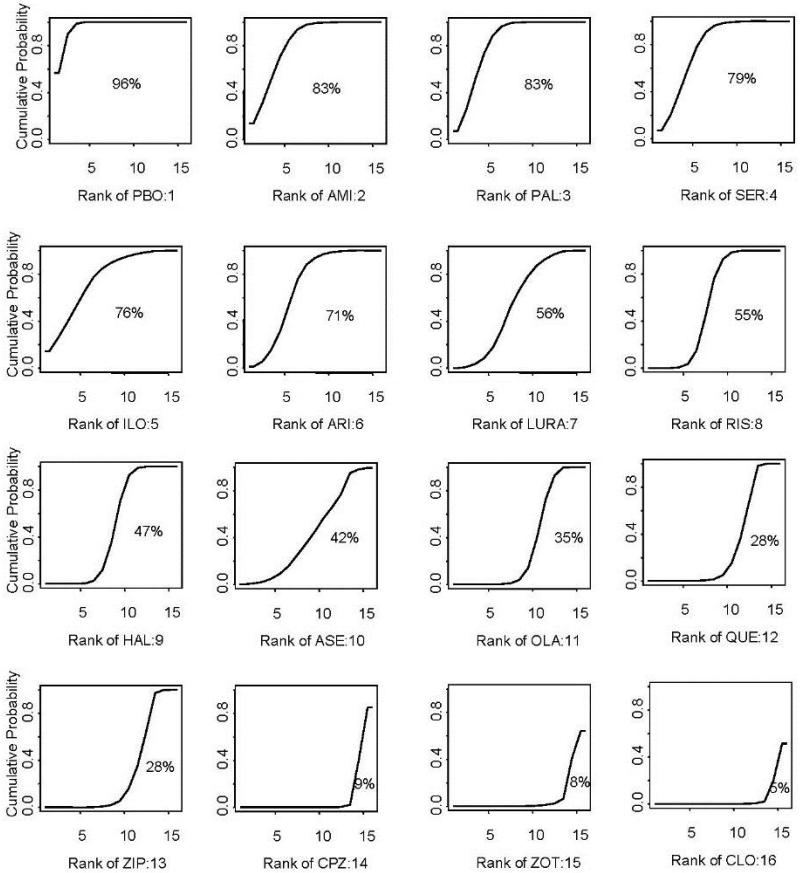
Modified from: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3.

Figure 7. Head-to-head comparisons: SUCRA estimates for the outcome sedation

Figure 8. Head-to-head comparisons: SUCRA estimates for the outcome prolactin increase



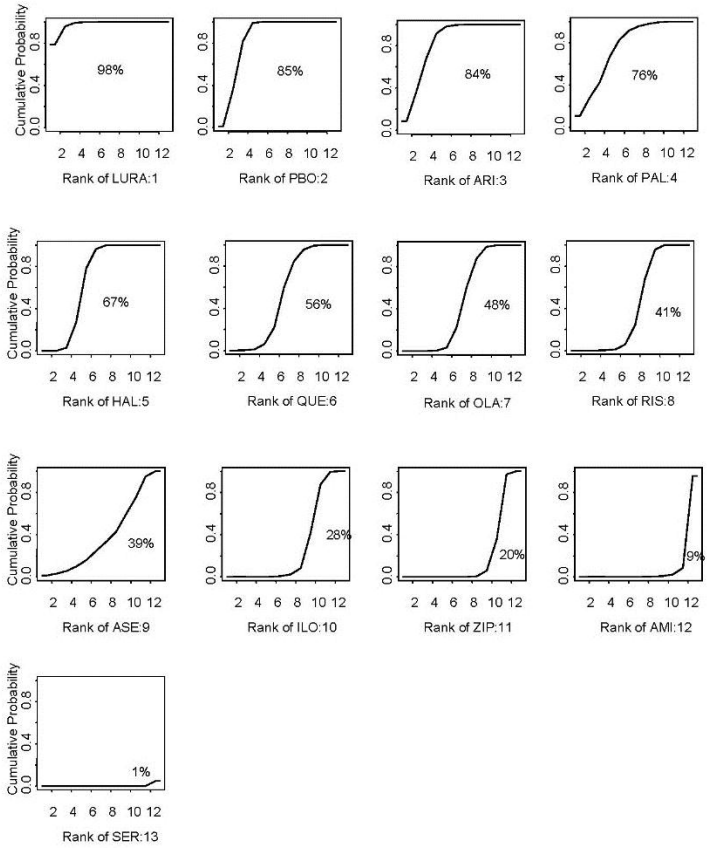
[New 2015]



SUCRA: surface under the cumulative ranking curve. SUCRAs expressed as percentages compare each intervention to an imaginary intervention that is always the best without uncertainty. A SUCRA of x% means that the medication achieves x% of the effectiveness of this imaginary medication, thus larger SUCRAs denote more effective interventions.
AMI = amisulpride, ARI = aripiprazole, ASE = asenapine, CLO = clozapine, CPZ = chlorpromazine, HAL = haloperidol, ILO = iloperidone, LURA = lurasidone, OLA = olanzapine, PAL = paliperidone, PBO = placebo QUE = quetiapine, RIS = risperidone, SER = sertindole, ZIP = ziprasidone, ZOT = zotepine.
Modified from: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic medications in schizophrenia: A multiple-treatments meta-analysis. Lancet 382(9896):951-62. doi:http://dx.doi.org/10.1016/S0140-6736(13)60733-3.

[New 2015]

Figure 9: Head-to-head comparisons: SUCRA estimates for the outcome QT prolongation.



SUCRA: surface under the cumulative ranking curve. SUCRAs expressed as percentages compare each intervention to an imaginary intervention that is always the best without uncertainty. A SUCRA of x% means that the medication achieves x% of the effectiveness of this imaginary medication, thus larger SUCRAs denote more effective interventions.
AMI = amisulpride, ARI = aripiprazole, ASE = asenapine, CLO = clozapine, CPZ = chlorpromazine, HAL = haloperidol, ILO = iloperidone, LURA = lurasidone, OLA = olanzapine, PAL = paliperidone, PBO = placebo QUE = quetiapine, RIS = risperidone, SER = sertindole, ZIP = ziprasidone, ZOT = zotepine.