APPENDIX 17C: CLINICAL EVIDENCE PROFILES: PHARMACOLOGICAL INTERVENTIONS

APPENDIX 17C (I): INITIAL TREATMENT WITH ANTIPSYCHOTIC MEDICATION FOR FIRST EPISODE PSYCHOSIS4
Pharmacological interventions in children and young people 18 years and younger combined with those aged 25 years and younger4
Olanzapine versus quetiapine: post-treatment efficacy outcomes4
Olanzapine versus quetiapine: post-treatment side effect outcomes5
Pharmacological interventions in children and young people 25 years and younger
Risperidone versus quetiapine: post-treatment efficacy outcomes
Risperidone versus quetiapine: post-treatment side effect outcomes9
Olanzapine versus haloperidol: efficacy outcomes at the end of acute treatment (12 weeks)11
Olanzapine versus haloperidol: side effect outcomes at the end of acute treatment (at 12 weeks)12
Haloperidol versus risperidone: efficacy outcomes post-treatment (time point unclear)15
Haloperidol versus risperidone: side effect outcomes post-treatment (time point unclear)16
Risperidone versus olanzapine: post-treatment efficacy outcomes
Risperidone versus olanzapine: post-treatment side effect outcomes
Quetiapine (200 mg per day) versus quetiapine (400 mg per day): post-treatment efficacy outcomes
Quetiapine (200 mg per day) versus quetiapine (400 mg per day): post-treatment side effect outcomes
APPENDIX 17C (II): ANTIPSYCHOTICS IN THE TREATMENT OF SUBSEQUENT ACUTE EPISODES OF PSYCHOSIS AND SCHIZOPHRENIA26
'Lower dose' antipsychotic versus placebo: post-treatment efficacy outcomes26
'Lower dose' antipsychotic versus placebo: post-treatment side effect outcomes
'Higher dose' antipsychotic versus placebo: post-treatment efficacy outcomes.33
Additional (high) dose paliperidone versus placebo: post-treatment efficacy outcomes
'Higher dose' antipsychotic versus placebo: post-treatment side effect outcomes

Additional (high) dose paliperidone versus placebo: post-treatment side effect outcomes40
Risperidone versus olanzapine: post-treatment efficacy outcomes42
Risperidone versus olanzapine: post-treatment side effect outcomes43
Risperidone versus haloperidol: post-treatment efficacy outcomes45
Risperidone versus haloperidol: post-treatment side effect outcomes46
Risperidone versus chlorpromazine: post-treatment efficacy outcomes48
Risperidone versus chlorpromazine: post-treatment side effect outcomes48
Olanzapine versus quetiapine: post-treatment efficacy outcomes
Olanzapine versus quetiapine: post-treatment side effect outcomes51
Olanzapine versus haloperidol: post-treatment efficacy outcomes52
Olanzapine versus haloperidol: post-treatment side effect outcomes53
Quetiapine 400 mg per day versus quetiapine 800 mg per day: post-treatment efficacy outcomes
Quetiapine 400 mg per day versus quetiapine 800 mg: post-treatment side effect outcomes
Aripiprazole 10 mg per day versus aripiprazole 30 mg per day: post-treatment efficacy outcomes
Aripiprazole 10 mg per day versus aripiprazole 30 mg per day: post-treatment
side effect outcomes
side effect outcomes
Risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day: post-
Risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day: post- treatment efficacy outcomes
Risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day: post- treatment efficacy outcomes
Risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day: post- treatment efficacy outcomes
Risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day: post- treatment efficacy outcomes
Risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day: post- treatment efficacy outcomes
Risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day: post- treatment efficacy outcomes

APPENDIX 14C (IV): OBSERVATIONAL STUDIES - SIDE EFFECTS	76
Extractable metabolic side effect outcomes	76
Extractable neurological side effect outcomes	78

Abbreviations

AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
EPS	extrapyramidal symptoms
ITT	intention to treat
LOCF	last observation carried forward
ODT	orally disintegrating tablet
OIS	optimal information size
OS	observational study
QT	the interval between Q and T waves in the electrocardiogram
RCT	randomised controlled trial
RR	relative risk
SAS	Simpson-Angus Extrapyramidal Side Effects Scale
SMD	standardised mean difference
SOT	standard oral tablet

APPENDIX 17C (I): INITIAL TREATMENT WITH ANTIPSYCHOTIC MEDICATION FOR FIRST EPISODE PSYCHOSIS

PHARMACOLOGICAL INTERVENTIONS IN CHILDREN AND YOUNG PEOPLE 18 YEARS AND YOUNGER COMBINED WITH THOSE AGED 25 YEARS AND YOUNGER

Olanzapine versus quetiapine: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirect- ness	Imprec- ision	Other considera- tions	Number of studies/ participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Total symptoms (SMD)	ARANGO2009 McEVOY2007	RCT	Serious ¹	Serious ⁴	Serious ⁵	Serious ²	Reporting bias ³	K = 2; N = 131	-0.04 [-0.54, 0.46]	Very low ^{1,2,3,4,5}	Appendix 14c (i) (1.1)
Positive symptoms (SMD)	ARANGO2009 McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 2; N = 131	-0.42 [-0.77, -0.08]*	Very low ^{1,2,3,5}	Appendix 14c (i) (1.2)
Negative symptoms (SMD)	ARANGO2009 McEVOY2007	RCT	Serious ¹	Serious ⁴	Serious ⁵	Serious ²	Reporting bias ³	K = 2; N = 131	-0.53 [-1.22, 0.15]	Very low ^{1,2,3,4,5}	Appendix 14c (i) (1.3)
Global state (severity) (SMD)	ARANGO2009 McEVOY2007	RCT	Serious ¹	Serious ⁴	Serious ⁵	Serious ²	Reporting bias ³	K = 2; N = 131	0.11 [-0.44, 0.66]	Very low ^{1,2,3,4,5}	Appendix 14c (i) (1.4)
Depression (SMD)	ARANGO2009 McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 2; N = 124	0.31 [-0.04, 0.67]	Very low ^{1,2,3,5}	Appendix 14c (i) (1.5)
Mania (SMD)	ARANGO2009	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 1; N = 60	0.10 [-0.45, 0.66]	Very low ^{1,2,3,5}	Appendix 14c (i) (1.6)
Quality of life (SMD)	McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 1; N = 81	-0.18 [-0.36, -0.00]	Very low ^{1,2,3,5}	Appendix 14c (i) (1.7)
Psychosocial functioning	ARANGO2009	RCT	Serious ¹	No serious inconsistency	No serious indirect- ness	Serious ²	Reporting bias ³	K = 1; N = 50	-0.35 [-0.91, 0.20]	- Very low ^{1,2,3}	Appendix 14c (i) (1.8)
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail. *Favours olanzapine.

¹Serious risk of bias (including unclear sequence generation and/or allocation concealment; one open-label trial (no blinding) or unclear rater blinding; errors in reporting of number of included participants; errors in reporting of outcome data across publications; one analysis of a modified intention-to-treat [ITT] population; last-observation carried forward [LOCF] reported but high dropout).

² Optimal information size (OIS) (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

³Serious risk of reporting bias.

⁴ I²≥50%, p <.05.

⁵Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young people).

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirect- ness	I	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Metabolic: weight (RR)	ARANGO2009 McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 2; N = 131	2.05 [1.41, 2.97]**	Very low ^{1,2,3,4}	Appendix 14c (i) (2.1)
Metabolic: weight lbs (SMD)	McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 81	1.06 [0.59, 1.53]**	Very low ^{1,2,3,4}	Appendix 14c (i) (2.2)
Metabolic: BMI (SMD)	McEVOY2007	RCT	Serious ¹	No serious inconsistency	Low	Serious ²	Reporting bias ³	K = 1; N = 81	1.08 [0.61, 1.54]**	Very low ^{1,2,3}	Appendix 14c (i) (2.3)
Metabolic: fasting serum glucose level mg per dl (SMD)	McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 81	0.23 [-0.21, 0.67]	Very low ^{1,2,3,4}	Appendix 14c (i) (2.4)
Metabolic: fasting total cholesterol mg per dl (SMD)	McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 81	-0.34 [-0.78, 0.11]	Very low ^{1,2,3,4}	Appendix 14c (i) (2.5)
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	No serious inconsistency	-	-	-	-	-	-	-
Metabolic: fasting high- density lipoprotein cholesterol mg per dl (SMD)	McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 81	-0.48 [-0.93, -0.04]*	Very low ^{1,2,3,4}	Appendix 14c (i) (2.6)

Olanzapine versus quetiapine: post-treatment side effect outcomes

Metabolic: fasting low- density lipoprotein cholesterol mg per dl (SMD)	McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 81	-0.02 [-0.46, 0.42]	Very low ^{1,2,3,4}	Appendix 14c (i) (2.7)
Metabolic: fasting triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
<i>Cardio: systolic BP</i> (SMD)	McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 81	0.13 [-0.31, 0.57]	Very low ^{1,2,3,4}	Appendix 14c (i) (2.8)
Cardio: diastolic BP (SMD)	McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 81	0.13 [-0.31, 0.57]	Very low ^{1,2,3,4}	Appendix 14c (i) (2.9)
Cardio: tachycardia (RR)	ARANGO2009	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 60		Very low ^{1,2,3,4}	Appendix 14c (i) (2.10)
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 81	0.17 [-0.27, 0.60]	Very low ^{1,2,3,4}	Appendix 14c (i) (2.11)
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Abnormal Involuntary Movement Scale (AIMS)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Simpson- Angus Extrapyramidal Side Effects Scale (SAS)	-	-	-	-	-	-	-	-	-	-	-
Neurological:Barnes Akathisia Rating Scale (BARS)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Udvalg for Kliniske Undersøgelser (UKU)	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	ARANGO2009	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 60	0.92 [0.26, 3.29]	Very low ^{1,2,3,4}	Appendix 14c (i) (2.12)

Neurological: akathisia	ARANGO2009	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 1; N = 60	6.48	Very	Appendix 14c (i)
(RR)				inconsistency			bias ³		[0.35, 119.32]	low ^{1,2,3,4}	(2.13)
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	ARANGO2009 McEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 2; N = 317	0.97 [0.83, 1.13]	Very low ^{1,2,3,4}	Appendix 14c (i) (2.14)

Note.^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

*Favours olanzapine.

**Favours quetiapine.

¹Serious risk of bias (including unclear sequence generation and/or allocation concealment; one open-label trial [no blinding] or unclear rater blinding; errors in reporting of number of included participants; errors in reporting of outcome data across publications; one analysis of a modified ITT population; LOCF reported but high dropout). ²OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

³Serious risk of reporting bias.

⁴Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young people).

PHARMACOLOGICAL INTERVENTIONS IN CHILDREN AND YOUNG PEOPLE 25 YEARS AND YOUNGER

Outcome or	Study ID	Design	Risk of	Inconsistency	Indirectness	Imprec-	Other	Number of	Effect	Quality of	Forest plot
subgroup		0	bias			ision	considera- tions	studies / participants	estimate (SMD or RR)	evidence (GRADE) ^a	
Total symptoms	MCEVOY2007	RCT	Serious ¹	No serious	No serious	Serious ²	Reporting	K = 2;	-0.28	Very	Appendix 14c (i)
(SMD)	SWADI2010			inconsistency	indirectness		bias ³	N = 103	[-0.67, 0.11]	low ^{1,2,3,4}	(3.1)
<i>Total symptoms (RR:</i>	SWADI2010	RCT	Serious ¹	No serious	No serious	Serious ²	Reporting	K = 1;	1.25	Very	Appendix 14c (i)
response)				inconsistency	indirectness		bias ³	N = 22	[0.45, 3.45]	low ^{1,2,3}	(3.2)
Positive symptoms	MCEVOY2007	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 2;	-0.43	Very	Appendix 14c (i)
	SWADI2007			inconsistency			bias ³	N = 103	[-0.82, -0.03]	low ^{1,2,3,4}	(3.3)
Negative symptoms	MCEVOY2007	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 2;	-0.22	Very	Appendix 14c (i)
	SWADI2007			inconsistency			bias ³	N = 103	[-0.61, 0.17]	low ^{1,2,3,4}	(3.4)
Global state (severity)	MCEVOY2007	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 2;	-0.14	Very	Appendix 14c (i)
(SMD)	SWADI2007			inconsistency			bias ³	N = 103	[-0.53, 0.25]	low ^{1,2,3,4}	(3.5)
Global state (severity)	SWADI2010	RCT	Serious ¹	No serious	No serious	Serious ²	Reporting	K = 1;	0.83	Very	Appendix 14c (i)
(RR: response)				inconsistency	indirectness		bias ³	N = 22	[0.36, 1.94]	low ^{1,2,3}	(3.6)
Depression (SMD)	MCEVOY2007	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 1;	0.38	Very	Appendix 14c (i)
				inconsistency			bias ³	N = 81	[-0.07, 0.82]	low ^{1,2,3,4}	(3.7)
Depression (RR:	SWADI2010	RCT	Serious ¹	No serious	No serious	Serious ²	Reporting	K = 1;	0.71	Very	Appendix 14c (i)
response)				inconsistency	indirectness		bias ³	N = 22	[0.33, 1.57]	low ^{1,2,3}	(3.8)
Mania (RR: response)	SWADI2010	RCT	Serious ¹	No serious	No serious	Serious ²	Reporting	K = 1;	0.70	Very	Appendix 14c (i)
				inconsistency	indirectness		bias ³	N = 22	[0.43, 1.14]	low ^{1,2,3}	(3.9)
Quality of life	MCEVOY2007	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 1;	-0.30	Very	Appendix 14c (i)
				inconsistency			bias ³	N = 81	[-0.60, -0.00]*	low ^{1,2,3,4}	(3.10)
Psychosocial	-	-	-	-	-	-	-	-	-	-	-
functioning											
Social functioning	-	-	-	-	-	-	-	-	-	-	-

Risperidone versus quetiapine: post-treatment efficacy outcomes

Response	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note.^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

*Favours risperidone.

¹Downgraded due to risk of bias (including: unclear sequence and/or allocation concealment; one open-label trial [no blinding] or unclear blinding; one analysis of a modified ITT population; LOCF reported but high dropout).

² OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

³Serious risk of reporting bias.

⁴Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young.

Risperidone versus quetiapine: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec- ision	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Metabolic: weight (RR)	MCEVOY2007 SWADI2010	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 2; N = 103	1.88 [1.22, 2.89]**	Very low 1,2,3,5	Appendix 14c (i) (4.1)
Metabolic: weight kg (SMD)	MCEVOY2007 SWADI2010	RCT	Serious ¹	Serious ⁴	Serious ⁵	Serious ²	Reporting bias ³	K = 2; N = 103	0.13 [-0.26, 0.52]	Very low 1,2,3,4,5	Appendix 14c (i) (4.2)
Metabolic: BMI (SMD)	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 1; N = 81	0.24 [-0.20, 0.67]	Very low 1,2,3,5	Appendix 14c (i) (4.3)
Metabolic: fasting serum glucose level mg per dl (SMD)	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 1; N = 81	-0.13 [-0.57, 0.31]	Very low 1,2,3,5	Appendix 14c (i) (4.4)
Metabolic: fasting total cholesterol mg per dl (SMD)	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 1; N = 81	-0.47 [-0.91, -0.03]*	Very low 1,2,3,5	Appendix 14c (i) (4.5)
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 1; N = 81	0.16 [-0.28, 0.60]	Very low 1,2,3,5	Appendix 14c (i) (4.6)

Metabolic: fasting low-density lipoprotein cholesterol	-	-	-	-	-	-	-	-	-	-	-
mg per dl											
Metabolic: fasting triglycerides	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 1; N = 81	-0.56 [-1.00, -0.11]	Very low 1,2,3,5	Appendix 14c (i) (4.7)
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP (SMD)	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 1; N = 81	-0.60 [-1.05, -0.15]	Very low 1,2,3,5	Appendix 14c (i) (4.8)
<i>Cardio: diastolic BP</i> <i>(SMD)</i>	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 1; N = 81	-0.43 [-0.87, 0.02]	Very low 1,2,3,5	Appendix 14c (i) (4.9)
Cardio: tachycardia	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin (SMD)	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁵	Serious ²	Reporting bias ³	K = 1; N = 81	1.81 [1.29, 2.33]**	Very low 1,2,3,5	Appendix 14c (i) (4.10)
Hormonal: prolactin (RR)	SWADI2010	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 22	10.00 [1.53, 65.41]**	Very low 1,2,3	Appendix 14c (i) (4.11)
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS (RR)	SWADI2010	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 22	3.00 [0.37, 24.58]	Very low ^{1,2,3}	Appendix 14c (i) (4.12)
Neurological: SAS (RR)	SWADI2010	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 22	2.00 [0.66, 6.04]	Very low ^{1,2,3}	Appendix 14c (i) (4.13)
Neurological: BARS (RR)	SWADI2010	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 22	1.00 [0.40, 2.50]	Very low ^{1,2,3,}	Appendix 14c (i) (4.14)
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-

Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological:	-	-	-	-	-	-	-	-	-	-	-
dyskinesia (RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
extrapyramidal											
disorder (RR)											
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study	MCEVOY2007	RCT	Serious ¹	Serious ⁴	No serious	Serious ²	Reporting	K = 2; N = 289	0.51	Very	Appendix 14c (i)
early for any reason	SWADI2010				indirectness		bias ³		[0.06, 4.08]	low ^{1,2,3,4}	(4.15)
(RR)									_		

Note.^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

* Favours risperidone.

**Favours quetiapine.

¹Serious risk of bias (including: unclear sequence and/or allocation concealment; one open-label trial [no blinding] or unclear blinding; one analysis of a modified ITT population; LOCF reported but high dropout).

²OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

³Serious risk of reporting bias.

⁴ I² = ≥ 50%, p<.05.

⁵Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young people).

Olanzapine versus haloperidol: efficacy outcomes at the end of acute treatment (12 weeks)

Outcome or	Study ID	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Number of	Effect estimate	Quality of	Forest plot
subgroup			bias				considerat	studies /	(SMD or RR)	evidence	
							ions	participants		(GRADE) ^a	
Total symptoms	LIEBERMAN	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 1; N =	-0.21 [-0.46,	Very	Appendix 14c (i)
(SMD)	2003			inconsistency			bias ³	251	0.04]	low ^{1,2,3,4}	(5.1)
Positive symptoms	LIEBERMAN 2003	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 252	-0.04 [-0.29, 0.20]	Very low ^{1,2,3,4}	Appendix 14c (i) (5.2)
Negative symptoms	LIEBERMAN	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 1; N =	-0.25 [-0.50, -	Very	Appendix 14c (i)
	2003			inconsistency			bias ³	252		low ^{1,2,3,4}	(5.3)

									0.00]*		
Global state (severity) (SMD)	LIEBERMAN 2003	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 254	-0.16 [-0.41, 0.08]	Very low ^{1,2,3,4}	Appendix 14c (i) (5.4)
Depression (SMD)	LIEBERMAN 2003	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 251	-0.19 [-0.43, 0.06]	Very low ^{1,2,3,4}	Appendix 14c (i) (5.5)
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning	-	-	-	-	-	-	-	-	-	-	-
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

*Favours olanzapine.

¹Serious risk of bias (including: unclear sequence generation & allocation concealment; unclear rater blinding, trial registration couldn't be found, LOCF reported but dropout high). ²OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

³Serious risk of reporting bias.

⁴Serious risk of indirectness (upper age range was 40).

Olanzapine versus haloperidol: side effect outcomes at the end of acute treatment (at 12 weeks)

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	-	consider-		· /	Quality of evidence (GRADE)ª	Forest plot
Metabolic: weight	LIEBERMAN	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 1; N =	0.70	Very	Appendix 14c (i)
(SMD)	2003			inconsistency			bias ³	263	[0.45, 0.95]**	low ^{1,2,3,4}	(6.1)
Metabolic: BMI	-	-	-	-	-	-	-	-	-	-	-
(SMD)											
Metabolic: fasting	-	-	-	-	-	-	-	-	-	-	-
serum glucose level											
mg per dl (SMD)											

Metabolic: fasting	-	_	_	-	-	-	-	_	_	_	_
total cholesterol mg											
per dl (SMD)											
Metabolic: lipid	_	-	-	_	_	_	-	_	_	_	-
level change in total											
cholesterol mg per											
dl											
Metabolic: fasting	-	-	-	-	-	_	-	-	-	-	-
high-density											
lipoprotein											
cholesterol mg per											
dl (SMD)											
Metabolic: fasting	-	-	-	-	-	-	-	-	-	-	-
low-density											
lipoprotein											
cholesterol mg per											
dl (SMD)											
Metabolic: fasting	-	-	-	-	-	-	-	-	-	-	-
triglycerides											
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP	-	-	-	-	-	-	-	-	-	-	-
(SMD)											
Cardio: diastolic BP	-	-	-	-	-	-	-	-	-	-	-
(SMD)											
Cardio: tachycardia	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting	-	-	-	-	-	-	-	-	-	-	-
pulse											
Cardio: standing	-	-	-	-	-	-	-	-	-	-	-
pulse											
Hormonal:	-	-	-	-	-	-	-	-	-	-	-
prolactin (SMD)											
	LIEBERMAN	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 1;	-0.34	Very	Appendix 14c (i)
	2003			inconsistency			bias ³	N = 263	[-0.59, -0.10]*	low ^{1,2,3,4}	(6.2)
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS	-	-	-	-	-	-	-	-	-	-	-
(RR)											

Neurological:	-	-	-	-	-	-	-	-	-	-	-
AIMS (RR)											
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
(RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
BARS (RR)											
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological:	-	-	-	-	-	-	-	-	-	-	-
parkinsonism (RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
tremor (RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
akathisia (RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
dystonia (RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
dyskinesia (RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
extrapyramidal											
disorder (RR)											
<i>Mortality (RR)</i>	-	-	-	-	-	-	-	-	-	-	-
Leaving the study		RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting		0.87	Very	Appendix 14c (i)
early for any reason	2003			inconsistency			bias ³	N = 263	[0.77, 0.97]*	low ^{1,2,3,4}	(6.3)
(RR)											

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

*Favours olanzapine.

**Favours haloperidol.

¹Serious risk of bias (including: unclear sequence generation and allocation concealment; unclear rater blinding, trial registration could not be found, LOCF reported but dropout high). ²OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

³Serious risk of reporting bias.

⁴Serious risk of indirectness (inclusion upper age range was 40. May not be representative of children and young people).

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considera	Number of studies /	Effect estimate (SMD or RR)	Quality of evidence	Forest plot
Succioup			DIas				tions	participants		(GRADE) ^a	
Total symptoms	SCHOOLER	RCT	Serious ¹	No serious	Serious ²	No serious	Reporting	K = 1;	-0.02	Very low ^{1,2,3}	Appendix 14c (i)
(SMD)	2005			inconsistency		imprecision	bias ³	N = 528	[-0.19, 0.15]	-	(7.1)
Positive symptoms	SCHOOLER	RCT	Serious ¹	No serious	Serious2	No serious	Reporting	K = 1;	0.05	Very low ^{1,2,3}	Appendix 14c (i)
	2005			inconsistency		imprecision	bias ³	N = 528	[-0.12, 0.22]	-	(7.2)
Negative symptoms	SCHOOLER	RCT	Serious ¹	No serious	Serious2	No serious	Reporting	K = 1;	-0.08	Very low ^{1,2,3}	Appendix 14c (i)
	2005			inconsistency		imprecision	bias ³	N = 528	[-0.25, 0.09]	-	(7.3)
Global state	SCHOOLER	RCT	Serious ¹	No serious	Serious2	No serious	Reporting	K = 1;	0.06	Very low ^{1,2,3}	Appendix 14c (i)
(severity) (SMD)	2005			inconsistency		imprecision	bias ³	N = 528	[-0.11, 0.23]	-	(7.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life	-	-	-	-	-	-	-	-	-	-	-
Psychosocial	-	-	-	-	-	-	-	-	-	-	-
functioning											
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Haloperidol versus risperidone: efficacy outcomes post-treatment (time point unclear)

Note.^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

¹Serious risk of bias (including unclear sequence generation and allocation concealment, unclear rater blinding, unable to find trial registration; unclear at what time point data was taken; high dropout).

²Serious risk of indirectness (48% population had bipolar disorder).

³Serious risk of reporting bias.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirect- ness	Imprecision	Other consider- ations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Metabolic: weight	SCHOOLER	RCT	Serious ¹	No serious	Serious ³	No serious	Reporting	K = 1;	0.11	Very	Appendix 14c (i)
(SMD)	2005			inconsistency		imprecision	bias ⁴	N = 415	[-0.08, 0.30]	Low ^{1,3,4}	(8.1)
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting serum	-	-	-	-	-	-	-	-	-	-	-
glucose level mg per dl (SMD)											
Metabolic: fasting total	-	-	-	-	-	-	-	-	-	-	-
cholesterol mg per dl											
(SMD)											
Metabolic: lipid level	-	-	-	-	-	-	-	-	-	-	-
change in total											
cholesterol mg per dl											
Metabolic: fasting high-	-	-	-	-	-	-	-	-	-	-	-
density lipoprotein											
cholesterol mg per dl											
(SMD)											
Metabolic: fasting low-	-	-	-	-	-	-	-	-	-	-	-
density lipoprotein cholesterol mg per dl											
(SMD)											
Metabolic: fasting		_		_	_					_	_
triglycerides											
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
\sim <i>Cardio: systolic BP</i>	-	-	-	-	-	-	-	-	-	-	-
(SMD)											
Cardio: diastolic BP	-	-	-	-	-	-	-	-	-	-	-
(SMD)											
Cardio: tachycardia	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-

Haloperidol versus risperidone: side effect outcomes post-treatment (time point unclear)

Hormonal: prolactin (SMD)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	SCHOOLER 2005	RCT	Serious ¹	No serious inconsistency	Serious ³	No serious imprecision	Reporting bias ⁴	K = 1; N = 507	0.51 [0.33, 069]*	Very Low ^{1,3,4}	Appendix 14c (i) (8.2)
Hormonal: insulin	_	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS (RR)	_	-	-	-	-	-	-	-	-	-	-
Neurological: BARS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	_	-	-	-	-	-	-	-	-	-	-
	SCHOOLER 2005	RCT	Serious ¹	No serious inconsistency	Serious ³	Serious ²	Reporting bias ⁴	K = 1; N = 218	1.15 [0.94, 1.42]	Very Low ^{1,2,3,4}	Appendix 14c (i) (8.3)

¹Serious risk of bias (including unclear sequence generation and allocation concealment, unclear rater blinding, unable to find trial registration; unclear at what time point data was taken; high dropout).

²OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

³ Serious risk of indirectness (48% population had bipolar disorder).

⁴Serious risk of reporting bias.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirect- ness	Imprecision	Other considerati ons	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Total symptoms (SMD)	MCEVOY2007 SIKICH2008 VANBRUGGEN2003	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 3; N = 150	-0.09 [-0.41, 0.24]	Very low ^{1,2,3,4}	Appendix 14c (i) (9.1)
Positive symptoms	MCEVOY2007 SIKICH2008 VANBRUGGEN2003	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 3; N = 150	-0.72 [-1.87, 0.43]	Very low ^{1,2,3,4,5}	Appendix 14c (i) (9.2)
Negative symptoms	MCEVOY2007 SIKICH2008 VANBRUGGEN2003	RCT	Serious ¹	Serious ⁵	Serious ⁴	Serious ²	Reporting bias ³	K = 3; N = 150	0.22 [-0.53, 0.98]	Very low ^{1,2,3,4,5}	Appendix 14c (i) (9.3)
Global state (severity) (SMD)	MCEVOY2007 SIKICH2008	RCT	Serious ¹	No serious inconsistency	No serious indirect- ness	Serious ²	Reporting bias ³	K = 2; N = 108	-0.06 [-0.44, 0.32]	Very low ^{1,2,3}	Appendix 14c (i) (9.4)
Depression (SMD)	MCEVOY2007 VANBRUGGEN2003	RCT	Serious ¹	No serious inconsistency	No serious indirect- ness	Serious ²	Reporting bias ³	K = 2; N = 116	-0.60 [-1.74, 0.53]	Very low ^{1,2,3}	Appendix 14c (i) (9.5)
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	No serious indirect- ness	Serious ²	Reporting bias ³	K = 1; N = 74	-0.13 [-0.45, 0.19]	Very low ^{1,2,3}	Appendix 14c (i) (9.6)
Psychosocial functioning	-	-	-	-	-	-	-	-	-	-	-
Social functioning	-	-	-	-	-	-	-	-	-	-	-

Risperidone versus olanzapine: post-treatment efficacy outcomes

Response	ROBINSON2006	RCT	Serious ¹	No serious	No	Serious ²	None	K = 1;	1.25	Very low ^{1,2}	Appendix 14c (i)
				inconsistency	serious			N = 120	[0.84, 1.86]		(9.7)
					indirect-						
					ness						
Remission	VANBRUGGEN2003	RCT	Serious ¹	No serious	No	Serious ²	Reporting	K = 1; N = 44	0.55	Very	Appendix 14c (i)
				inconsistency	serious		bias ³		[0.17 <i>,</i> 1.78]	low ^{1,2,3}	(9.8)
				-	indirect-						
					ness						

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

¹ Serious risk of bias (including serious or unclear sequence generation and allocation concealment, unclear rater blinding trial registration couldn't be found; analysis included modified ITT population; large discrepancies in length of untreated psychosis in each treatment group and antipsychotic use; unclear treatment of participants considered to be in remission and actively symptomatic during treatment, LOCF reported but high dropout)

²OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

³ Serious risk of reporting bias

⁴ Serious risk of indirectness (upper age limit includes adults over 40 years and may not therefore be representative of a CYP population)

 ${}^{5}\mathrm{I}^{2} \geq 50\%$, p<.05

Risperidone versus olanzapine: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirect- ness	Imprecis- ion	Other considera- tions	studies /	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Metabolic: weight (SMD)	MCEVOY2007 SIKICH2008 VANBRUGGEN 2003	RCT	Serious ¹	Serious⁵	Serious ⁴	Serious ²	Reporting bias ³	K = 3; N = 139	-0.29 [-1.02, 0.45]	Very low ^{1,2,3,4,5}	Appendix 14c (i) (10.1)
Metabolic: weight (RR) (N = patients with >7% gain)	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³		0.68 [0.47, 0.98]*	Very low ^{1,2,3,4}	Appendix 14c (i) (10.2)
Metabolic: BMI (SMD)	MCEVOY2007 ROBINSON2006	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 2; N = 186	-0.66 [-0.98, -0.33]*	Very low ^{1,2,3,4}	Appendix 14c (i) (10.3)
Metabolic: fasting serum glucose level mg per dl (SMD)	MCEVOY2007 SIKICH2008	RCT	Serious ¹	Serious ⁵	Serious ⁴	Serious ²	Reporting bias ³	K = 2; N = 108	-0.11 [-0.73, 0.52]	Very low ^{1,2,3,4,5}	Appendix 14c (i) (10.4)
Metabolic: fasting total	MCEVOY2007	RCT	Serious ¹	No serious	Serious ⁴	Serious ²	Reporting	K = 1; N = 74	-0.16	Very	Appendix 14c

cholesterol mg per dl (SMD)				inconsistency			bias ³		[-0.61, 0.30]	low ^{1,2,3,4}	(i) (10.5)
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high- density lipoprotein cholesterol mg per dl (SMD)	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 74	0.67 [0.20, 1.14]**	Very low ^{1,2,3,4}	Appendix 14c (i) (10.6)
Metabolic: fasting low- density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting triglycerides	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 74	-0.57 [-1.04, -0.11]*	Very low ^{1,2,3,4}	Appendix 14c (i) (10.7)
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP (SMD)	MCEVOY2007	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 74	-0.76 [-1.23 <i>,</i> -0.28]*	Very low ^{1,2,3,4}	Appendix 14c (i) (10.8)
Cardio: diastolic BP (SMD)	MCEVOY2007 SIKICH2008	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 2; N = 108	-0.44 [-0.84, -0.04]*	Very low ^{1,2,3,4}	Appendix 14c (i) (10.9)
Cardio: tachycardia	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin (SMD)	MCEVOY2007 SIKICH2008	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 2; N = 108	1.67 [1.22, 2.11]**	Very low ^{1,2,3,4}	Appendix 14c (i) (10.10)
Hormonal: prolactin (RR)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS (RR)	SIKICH2008	RCT	Serious ¹	No serious inconsistency	No serious indirect- ness	Serious ²	Reporting bias ³	K = 1; N = 33	0.04 [-0.65, 0.73]	Very low ^{1,2,3}	Appendix 14c (i) (10.11)
Neurological: SAS (RR)	ROBINSON2006 SIKICH2008	RCT	Serious ¹	No serious inconsistency	No serious	Serious ²	Reporting bias ³	K = 3; N = 168	0.34 [0.00, 0.67]	Very low ^{1,2,3}	Appendix 14c (i) (10.12)

	VANBRUGGEN 2003				indirect- ness						
Sensitivity analysis: neurological: SAS (SMD)	SIKICH2008 VANBRUGGEN 2003	RCT	Serious ¹	No serious inconsistency	No serious indirect- ness	Serious ²	Reporting bias ³	K = 2; N = 56	0.03 [-0.50, 0.56]	Very low ^{1,2,3}	Appendix 14c (i) (10.13)
Neurological: BARS (RR)	SIKICH2008	RCT	Serious ¹	No serious inconsistency	No serious indirect- ness	Serious ²	Reporting bias ³	K = 1; N = 33	0.36 [-0.34, 1.06]	Very low ^{1,2,3}	Appendix 14c (i) (10.14)
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	ROBINSON2006	RCT	Serious ¹	No serious inconsistency	No serious indirect- ness	Serious ²	Reporting bias ³	K = 1; N = 112	0.56 [0.20, 1.55]	Very low ^{1,2,3}	Appendix 14c (i) (10.15)
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	VANBRUGGEN 2003	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 1; N = 31	0.95 [0.34, 2.68]	Very low ^{1,2,3,4}	Appendix 14c (i) (10.16)
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	MCEVOY2007 ROBINSON2006 VANBRUGGEN 2003	RCT	Serious ¹	No serious inconsistency	Serious ⁴	Serious ²	Reporting bias ³	K = 3; N = 430	1.04 [0.89, 1.21]	Very low ^{1,2,} _{3,4}	Appendix 14c (i) (10.17)

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

*Favours risperidone

**Favours olanzapine

¹ Serious risk of bias (including serious or unclear sequence generation and allocation concealment, unclear rater blinding trial registration couldn't be found; analysis included modified ITT population; large discrepancies in length of untreated psychosis in each treatment group and antipsychotic use; unclear treatment of participants considered to be in remission and actively

symptomatic during treatment, LOCF reported but high dropout) ²OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met. ³ Serious risk of reporting bias ⁴ Serious risk of indirectness (upper age limit includes adults over 40 years and may not therefore be representative of a CYP population) ⁵ I² \ge 50%, p<.05

Quetiapine (200 mg per day) versus quetiapine (400 mg per day): post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Total symptoms (SMD)	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 91	0.35 [-0.06, 0.77]	Very low ^{1,2,3}	Appendix 14c (i) (11.1)
Positive symptoms	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 91	0.37 [-0.04, 0.79]	Very low ^{1,2,3}	Appendix 14c (i) (11.2)
Negative symptoms	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 91	0.32 [-0.10, 0.73]	Very low ^{1,2,3}	Appendix 14c (i) (11.3)
Global state (severity) (SMD)	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 91	0.44 [0.02, 0.85]*	Very low ^{1,2,3}	Appendix 14c (i) (11.4)
Depression (SMD)	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 91		Very low ^{1,2,3}	Appendix 14c (i) (11.5)
Mania	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 91	0.34 [-0.07, 0.76]	Very low ^{1,2,3}	Appendix 14c (i) (11.6)
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 91	0.19 [-0.22, 0.60]	Very low ^{1,2,3}	Appendix 14c (i) (11.7)
Social functioning	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 91	-0.01 [-0.42, 0.40]	Very low ^{1,2,3}	Appendix 14c (i) (11.8)
Response (RR)	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 141	1.39 [0.78, 2.49]	Very low ^{1,2,3}	Appendix 14c (i) (11.9)
Remission (RR)	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 141	0.43 [0.16, 1.17]	Very low ^{1,2,3}	Appendix 14c (i) (11.10)

*Favours 400 mg/day. ¹Serious risk of bias (including blinding of participants and providers in part 2 not maintained; available case analysis used). ²OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met. ³Serious risk of reporting bias.

Quetiapine (200 mg per day) versus quetiapine (400 mg per day): post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Metabolic: weight (SMD)	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 106	-0.04 [-0.54, 0.47]	Very low ^{1,2,3}	Appendix 14c (i) (12.1)
Metabolic: weight (RR) (N pts with >7% gain)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting serum glucose level mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting total cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting low-density lipoprotein	-	-	-	-	-	-	-	-	-	-	-

cholesterol mg per dl (SMD)											
Metabolic: fasting triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
<i>Cardio: systolic BP</i> (<i>SMD</i>)	-	-	-	-	-	-	-	-	-	-	-
<i>Cardio: diastolic BP</i> (<i>SMD</i>)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin (SMD)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin (RR)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	BERGER2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	Reporting bias ³	K = 1; N = 91	-0.37 [-0.78, 0.04]	Very low ^{1,2,3}	Appendix 14c (i) (12.2)
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological:	-	-	-	-	-	-	-	-	-	-	-

dystonia (RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
dyskinesia (RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
extrapyramidal											
disorder (RR)											
<i>Mortality (RR)</i>	-	-	-	-	-	-	-	-	-	-	-
Leaving the study	BERGER2008	RCT	Serious ¹	No serious	No serious	Serious ²	Reporting	K = 1;	0.91	Very	Appendix 14c (i)
early for any reason				inconsistency	indirectness		bias ³	N = 141	[0.35, 2.38]	low ^{1,2,3}	(12.3)
(RR)				-					_		

Note.^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

¹Serious risk of bias (including blinding of participants and providers in part 2 not maintained; available case analysis used). ²OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

³Serious risk of reporting bias.

APPENDIX 17C (II): ANTIPSYCHOTICS IN THE TREATMENT OF SUBSEQUENT ACUTE EPISODES OF PSYCHOSIS AND SCHIZOPHRENIA

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Total symptoms (SMD)	AstraZeneca D1441C00112 FINDLING2008A KRYZHANOVS- KAYA2009B SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias ²	K = 4; N = 557	-0.32 [-0.51, -0.14]*	Low ^{1,2}	Appendix 14c (ii) (1.1)
Positive symptoms (SMD)	AstraZeneca D1441C00112 FINDLING2008A HAAS2009B KRYZHANOVS- KAYA2009B PALLIERE- MARTINOT1995 SINGH2011	RCT	Serious ¹	Serious ⁴	No serious indirectness	No serious imprecision	Reporting bias ²	K = 6; N = 685	-0.31 [-0.59, -0.02] *	Very low ^{1,2,4}	Appendix 14c (ii) (1.3)
Negative symptoms (SMD)	AstraZeneca D1441C00112 FINDLING2008A HAAS2009B KRYZHANOVS- KAYA2009B PALLIERE- MARTINOT1995 SINGH2011	RCT	Serious ¹	Serious ⁴	No serious indirectness	No serious imprecision	Reporting bias ²	K = 6; N = 685	-0.33 [-0.49, -0.16]*	Very low ^{1,2,4}	Appendix 14c (ii) (1.5)
Global state (severity)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias ²	K = 3; N = 452	-0.38 [-0.57,	Low ^{1,2}	Appendix 14c (ii) (1.7)

'Lower dose' antipsychotic versus placebo: post-treatment efficacy outcomes

(SMD)	FINDLING2008A								-0.18]*		
	KRYZHANOVS-								-		
	KAYA2009B										
Depression	AstraZeneca	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 3; N =	-0.20 [-0.44,	Very	Appendix 14c
(SMD)	D1441C00112			inconsistency	indirectness		bias ²	173	0.04]	low ^{1,2,3}	(ii) (1.9)
	PALLIERE-										
	MARTINOT1995										
	SINGH2011										
Mania	_	-	-	-	-	-	-	-	-	-	-
Quality of life	FINDLING2008A	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1; N =	-0.29 [-0.71,	Very	Appendix 14c
(SMD)				inconsistency	indirectness		bias ²	197	0.13]	low ^{1,2,3}	(ii) (1.11)
Psychosocial	AstraZeneca	RCT	Serious ¹	No serious	No serious	Low	Reporting	K = 4; N =	-0.29 [-0.51,	Low ^{1,2}	Appendix 14c
functioning	D1441C00112			inconsistency	indirectness		bias ²	535	-0.06]*		(ii) (1.12)
(SMD)	FINDLING2008A										
	HAAS2009B										
	SINGH2011										
Social	-	-	-	-	-	-	-	-	-	-	-
functioning											
Response (RR)	AstraZeneca	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1; N =	1.98 [1.28,	Very	Appendix 14c
	D1441C00112			inconsistency	indirectness		bias ²	149	3.05]	low ^{1,2,3}	(ii) (1.13)
Remission						+			1		

*Favours 'lower dose'

¹Serious risk of bias (including unclear sequence generation and/or allocation concealment, unclear rater blinding procedures, , participants excluded if they had a previous non-response to study treatment, treatment exposure (time) differ between groups, study reports LOCF analysis, but high dropout).

²Serious risk of reporting bias

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

 ${}^{4}\mathrm{I}^{2} \ge 50\%$, p<.05

Outcome or subgroup	Study ID	Antipsychotic (dose)	Design	Risk of bias	Inconsistency	Indirectness	Imprec- ision	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Metabolic: weight (SMD)	FINDLING20 08A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 197	0.34 [0.06, 0.62] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.1)
	KRYZHAN- OVSKAYA 2009B	Olanzapine (11.1 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 107	1.33 [0.88, 1.77] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.1)
	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 146	0.75 [0.41, 1.08] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.1)
	SINGH2011	Paliperidone (1.5 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 105	0.19 [-0.20, 0.57]	Very low ^{1,2,3}	Appendix 14c (ii) (2.1)
Metabolic: BMI (SMD)	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 197	0.33 [0.05, 0.61] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.2)
	KRYZHAN- OVSKAYA 2009B	Olanzapine (11.1 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 107	1.31 [0.87, 1.75] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.2)
Metabolic: fasting serum glucose level	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 127	0.38 [0.03, 0.74] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.3)
mg per dl (SMD)	KRYZHAN- OVSKAYA 2009B	Olanzapine (11.1 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 80	0.43 [-0.04, 0.91]	Very low ^{1,2,3}	Appendix 14c (ii) (2.3)
	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 135	0.14 [-0.20, 0.48]	Very low ^{1,2,3}	Appendix 14c (ii) (2.3)
Metabolic: fasting total	FINDLING 2008A	Aripiprazole (10 mg per	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 191	0.23 [-0.06, 0.51]	Very low ^{1,2,3}	Appendix 14c (ii) (2.4)

'Lower dose' antipsychotic versus placebo: post-treatment side effect outcomes

cholesterol mg		day)										
per dl	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 125	0.58 [0.22, 0.94] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.4)
Metabolic: fasting high- density	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 92	0.39 [-0.02, 0.81]	Very low ^{1,2,3}	Appendix 14c (ii) (2.5)
lipoprotein cholesterol mg per dl (SMD)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 125	0.04 [-0.31, 0.39]	Very low ^{1,2,3}	Appendix 14c (ii) (2.5)
Metabolic: fasting low- density lipoprotein cholesterol mg per dl (SMD)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 125	0.58 [0.22, 0.93] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.6)
per dl (SMD) Metabolic: fasting triglycerides	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 92	0.04 [-0.37, 0.45]	Very low ^{1,2,3}	Appendix 14c (ii) (2.7)
	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 125	0.36 [0.00, 0.71]	Very low ^{1,2,3}	Appendix 14c (ii) (2.7)
	KRYZHAN- OVSKAYA 2009B	Olanzapine (11.1 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 80	0.54 [0.05, 1.02] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.7)
Cardio: QT interval (SMD)	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 194	0.09 [-0.19, 0.37]	Very low ^{1,2,3}	Appendix 14c (ii) (2.8)
A E K V	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 129	-0.28 [-0.63, 0.06]	Very low ^{1,2,3}	Appendix 14c (ii) (2.8)
	KRYZHANO VSKAYA 2009B	Olanzapine (11.1 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 92	0.09 [-0.35, 0.53]	Very low ^{1,2,3}	Appendix 14c (ii) (2.8)

Cardio: QT interval (RR) (Incidence of	AstraZenecaD 1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 148	3.08 [0.13, 74.43]	Very low ^{1,2,3}	Appendix 14c (ii) (2.9)
prolonged QT)	SINGH2011	Paliperidone (1.5 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 105	Not estimable (no events in either group)	Very low ^{1,2,3}	Appendix 14c (ii) (2.9)
<i>Cardio:</i> systolic BP (SMD)	AstraZenecaD 1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 146	0.40 [0.07, 0.73] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.10)
Cardio: diastolic BP (SMD)	AstraZenecaD 1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 146	0.40 [0.07, 0.73] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.11)
tachycardia 1 (RR)	AstraZenecaD 1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 148	9.24 [0.51, 168.69]	Very low ^{1,2,3}	Appendix 14c (ii) (2.12)
	SINGH2011	Paliperidone (1.5 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 105	Not estimable (no events in either group)	Very low ^{1,2,3}	Appendix 14c (ii) (2.12)
	HAAS2009B	Risperidone (1-3 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 109	0.98 [0.21, 4.65]	Very low ^{1,2,3}	Appendix 14c (ii) (2.12)
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	AstraZenecaD 1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 146	0.67 [0.33, 1.00] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.13)
	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 194	-0.15 [-0.43, 0.14]	Very low ^{1,2,3}	Appendix 14c (ii) (2.14)
	KRYZHAN- OVSKAYA 2009B	Olanzapine (11.1 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 94	0.71 [0.26, 1.15] **	Very low ^{1,2,3}	Appendix 14c (ii) (2.14)

	AstraZeneca D1441C00112	Quetiapine (400 mg per	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 125	0.33 [-0.02, 0.68]	Very low ^{1,2,3}	Appendix 14c (ii) (2.14)
	SINGH2011	day) Paliperidone (1.5 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 92	0.06 [-0.35, 0.47]	Very low ^{1,2,3}	Appendix 14c (ii) (2.14)
	HAAS2009B	Risperidone (1-3 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 109	1.05 [0.65, 1.45]**	Very low ^{1,2,3}	Appendix 14c (ii) (2.14)
Hormonal: insulin	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 122	0.28 [-0.08, 0.63]	Very low ^{1,2,3}	Appendix 14c (ii) (2.15)
Neurological: EPS (RR)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 148	3.08 [0.13, 74.43]	Very low ^{1,2,3}	Appendix 14c (ii) (2.16)
Neurological: AIMS	HAAS2009B	Risperidone (1-3 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 109	0.23 [-0.15, 0.61]	Very low ^{1,2,3}	Appendix 14c (ii) (2.17)
Neurological: SAS	HAAS2009B	Risperidone (1-3 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 109	0.00 [-0.38, 0.38]	Very low ^{1,2,3}	Appendix 14c (ii) (2.18)
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	2.14 [0.91, 5.03]	Very low ^{1,2,3}	Appendix 14c (ii) (2.19)
Neurological: tremor (RR)	AstraZenecaD 1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 148	1.54 [0.27, 8.96]	Very low ^{1,2,3}	Appendix 14c (ii) (2.20)
Neurological: akathisia (RR)	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	1.00 [0.33, 3.00]	Very low ^{1,2,3}	Appendix 14c (ii) (2.21)

	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 148	1.54 [0.27, 8.96]	Very low ^{1,2,3}	Appendix 14c (ii) (2.21)
Neurological: dystonia (RR)	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	9.00 [0.49, 165.00]	Very low ^{1,2,3}	Appendix 14c (ii) (2.22
Neurological: dyskinesia (RR)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 148	5.14 [0.25, 105.17]	Very low ^{1,2,3}	Appendix 14c (ii) (2.23)
Neurological: extrapyrami- dal disorder (RR)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 148	3.08 [0.13, 74.43]	Very low ^{1,2,3}	Appendix 14c (ii) (2.24)
Mortality (RR)	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	Not estimable (no events in either group)	Very low ^{1,2,3}	Appendix 14c (ii) (2.25)
	HAAS2009B	Risperidone (1-3 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 109	Not estimable (no events in either group)	Very low ^{1,2,3}	Appendix 14c (ii) (2.25)
Leaving the study early for any reason (RR)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 148	0.62 [0.37, 1.04]	Very low ^{1,2,3}	Appendix 14c (ii) (2.26)
	FINDLING 2008A	Aripiprazole (10 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	1.60 [0.76, 3.35]	Very low ^{1,2,3}	Appendix 14c (ii) (2.26)
	KRYZHAN- OVSKAYA 2009B	Olanzapine (11.1 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 94	0.56 [0.36, 0.87]*	Very low ^{1,2,3}	Appendix 14c (ii) (2.26)

MARTINOT	Amisulpride (50-100 mg per day)	RCT	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 17	1.11 [0.45, 2.78]	5	Appendix 14c (ii) (2.26)
HAAS2009B	Risperidone (1-3 mg per day)	RCT	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 109	0.55 [0.28, 1.07]	5	Appendix 14c (ii) (2.26)

Note.^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail. *Favours 'lower dose'.

*Favours lower dos

**Favours placebo.

¹ Serious risk of bias (including unclear sequence generation and/or allocation concealment, unclear rater blinding procedures, participants excluded if they had a previous non-response to study treatment, treatment exposure [time] differed between groups, LOCF analysis, but high dropout).

 $^2\!Serious$ risk of reporting bias.

³ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

'Higher dose' antipsychotic versus placebo: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Total symptoms (SMD)	AstraZeneca D1441C00112 FINDLING2008A SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprec- ision	No serious indirectness	K = 3; N = 443	-0.48 [-0.66, -0.29]*	Low ^{1,2}	Appendix 14c (ii) (3.1)
Positive symptoms (SMD)	AstraZeneca D1441C00112 FINDLING2008A HAAS2009B SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprec- ision	Reporting bias ²	K = 4; N = 547	-0.49 [-0.66, -0.32]*	Low ^{1,2}	Appendix 14c (ii) (3.2)
Negative symptoms (SMD)	AstraZeneca D1441C00112; FINDLING2008A HAAS2009B SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprec- ision	Reporting bias ²	K = 4; N = 546	-0.34 [-0.53, -0.15]*	Low ^{1,2}	Appendix 14c (ii) (3.3)
Global state	AstraZeneca	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 2;	-0.44 [-0.65,	Very	Appendix 14c

(severity) (SMD)	D1441C00112 FINDLING2008A			inconsistency	indirectness		bias ²	N = 344	-0.22] *	low ^{1,2,3}	(ii) (3.4)
Depression (SMD)	AstraZeneca D1441C00112 SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 2; N = 248	-0.28 [-0.53, -0.03]*	Very low ^{1,2,3}	Appendix 14c (ii) (3.5)
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	FINDLING2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 195	-0.42 [-0.83, -0.01] *	Very low ^{1,2,3}	Appendix 14c (ii) (3.6)
Psychosocial functioning (SMD)	AstraZeneca D1441C00112 FINDLING2008A HAAS2009B SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	No serious imprec- ision	Reporting bias ²	K = 4; N = 543	-0.48 [-0.65, -0.31]*	Low ^{1,2}	Appendix 14c (ii) (3.7)
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 148	1.85 [1.19, 2.88]	Very low ^{1,2,3}	Appendix 14c (ii) (3.8)
Remission	-	-	-	-	-	-	-	-	-	-	-

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

*Favours 'higher dose'.

¹Serious risk of bias (including unclear sequence generation and/or allocation concealment, unclear rate blinding procedures, participants excluded if they had a previous non-response to study treatment, treatment exposure [time] differed between groups, patients who did not complete 4 weeks of daily medication because of voluntary withdrawal or for administrative reasons were not included in the analyses for efficacy ratings and were replaced by new patients, study reports LOCF analysis, but high dropout).

² Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerat- ions	Number of studies/ participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Total symptoms (SMD)	SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 98	-0.32 [-0.72, 0.08]	Very low ^{1,2,3}	Appendix 14c (ii) (4.1)
Positive symptoms (SMD)	SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 98	-0.27 [-0.67, 0.13]	Very low ^{1,2,3}	Appendix 14c (ii) (4.2)
Negative symptoms (SMD)	SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 98	L /	Very low ^{1,2,3}	Appendix 14c (ii) (4.3)
Global state (severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 98	-0.24 [-0.63, 0.16]	Very low ^{1,2,3}	Appendix 14c (ii) (4.4)
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	SINGH2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 98	-0.28 [-0.68, 0.12]	Very low ^{1,2,3}	Appendix 14c (ii) (4.5)
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Additional (high) dose paliperidone versus placebo: post-treatment efficacy outcomes

Note.^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

*Favours 6 to 12 mg per day paliperidone.

¹Serious risk of bias (study reports LOCF analysis, but high dropout, each treatment group exposed to treatment for different lengths of time).

² Serious risk of reporting bias.

³ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Outcome or subgroup	Study ID	Antipsychotic (dose)	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Metabolic: weight (SMD)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 146	0.58 [0.25, 0.91] **	Very low ^{1,2,3}	Appendix 14c (ii) (5.1)
	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 195	0.41 [0.12, 0.69] **	Very low ^{1,2,3}	Appendix 14c (ii) (5.1)
	SINGH 2011	Paliperidone (3-6 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 100	0.57 [0.17, 0.97] **	Very low ^{1,2,3}	Appendix 14c (ii) (5.1)
Metabolic: BMI (SMD)	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 195	0.33 [0.05, 0.61] **	Very low ^{1,2,3}	Appendix 14c (ii) (5.2)
Metabolic: fasting serum glucose level	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 137	0.03 [-0.30, 0.37]	Very low ^{1,2,3}	Appendix 14c (ii) (5.3)
mg per dl (SMD)	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 120	0.17 [-0.19, 0.53]	Very low ^{1,2,3}	Appendix 14c (ii) (5.3)
Metabolic: fasting total cholesterol mg	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 119	0.12 [-0.24, 0.48]	Very low ^{1,2,3}	Appendix 14c (ii) (5.4)
per dl (SMD)	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 194	0.11 [-0.17, 0.39]	Very low ^{1,2,3}	Appendix 14c (ii) (5.4)
Metabolic: fasting high- density	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 123	-0.16 [-0.51, 0.20]	Very low ^{1,2,3}	Appendix 14c (ii) (5.5)

'Higher dose' antipsychotic versus placebo: post-treatment side effect outcomes

lipoprotein cholesterol mg per dl (SMD)	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 85	0.38 [-0.05, 0.81]	Very low ^{1,2,3}	Appendix 14c (ii) (5.5)
Metabolic: fasting low- density lipoprotein cholesterol mg per dl (SMD)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 123	0.41 [0.05, 0.77]	Very low ^{1,2,3}	Appendix 14c (ii) (5.6)
Metabolic: fasting triglycerides	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 123	0.61 [0.25, 0.98] **	Very low ^{1,2,3}	Appendix 14c (ii) (5.7)
	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 85	0.11 [-0.32, 0.53]	Very low ^{1,2,3}	Appendix 14c (ii) (5.7)
Cardio: QT interval (SMD)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 129	0.37 [0.03, 0.72] **	Very low ^{1,2,3}	Appendix 14c (ii) (5.8)
	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 198	0.21 [-0.08, 0.49]	Very low ^{1,2,3}	Appendix 14c (ii) (5.8)
Cardio: QT interval (RR) (incidence of	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 149	3.04 [0.13, 73.44]	Very low ^{1,2,3}	Appendix 14c (ii) (5.9)
prolonged QT)	SINGH2011	Paliperidone (3-6 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 99	Not estimable (no events in either group)	Very low ^{1,2,3}	Appendix 14c (ii) (5.9)
Cardio: systolic BP (SMD)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 147	0.13 [-0.19, 0.46]	Very low ^{1,2,3}	Appendix 14c (ii) (5.10)
Cardio: diastolic BP (SMD)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 147	0.25 [-0.07, 0.58]	Very low ^{1,2,3}	Appendix 14c (ii) (5.11)

Cardio: tachycardia (RR)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 149	13.17 [0.76, 229.73]	Very low ^{1,2,3}	Appendix 14c (ii) (5.12)
	HAAS2009B	Risperidone (4-6 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 105	0.71 [0.12, 4.05]	Very low ^{1,2,3}	Appendix 14c (ii) (5.12)
	SINGH2011	Paliperidone (3-6 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 99	7.43 [0.39, 140.15]	Very low ^{1,2,3}	Appendix 14c (ii) (5.12)
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 147	0.31 [-0.02, 0.63]	Very low ^{1,2,3}	Appendix 14c (ii) (5.13)
Hormonal: prolactin	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 123	0.37 [0.02, 0.73] **	Very low ^{1,2,3}	Appendix 14c (ii) (5.14)
	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 188	-0.26 [-0.55, 0.03]	Very low ^{1,2,3}	Appendix 14c (ii) (5.14)
	HAAS2009B	Risperidone (4-6 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 105	1.38 [0.95, 1.81] **	Very low ^{1,2,3}	Appendix 14c (ii) (5.14)
	SINGH2011	Paliperidone (3-6 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 83	0.09 [-0.34, 0.52]	Very low ^{1,2,3}	Appendix 14c (ii) (5.14)
Hormonal: insulin	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 119	0.12 [-0.24, 0.48]	Very low ^{1,2,3}	Appendix 14c (ii) (5.15)
Neurological: EPS (RR)	POOL1976	Haloperidol (11.9 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 59	17.28 [2.50, 119.55]**	Very low ^{1,2,3}	Appendix 14c (ii) (5.16)
Neurological: AIMS	HAAS2009B	Risperidone (4-6 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 105	0.35 [-0.03, 0.74] **	Very low ^{1,2,3}	Appendix 14c (ii) (5.17)

Neurological: SAS	HAAS2009B	Risperidone (4-6 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 105	0.45 [0.06, 0.84] **	Very low ^{1,2,3}	Appendix 14c (ii) (5.18)
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	4.43 [2.05, 9.58]**	Very low ^{1,2,3}	Appendix 14c (ii) (5.19)
Neurological: tremor (RR)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 149	1.52 [0.26, 8.84]	Very low ^{1,2,3}	Appendix 14c (ii) (5.20)
Neurological: akathisia (RR)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 149	1.52 [0.26, 8.84]	Very low ^{1,2,3}	Appendix 14c (ii) (5.21)
	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	2.00 [0.78, 5.12]	Very low ^{1,2,3}	Appendix 14c (ii) (5.21)
Neurological: dystonia (RR)	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	5.00 [0.24, 102.85]	Very low ^{1,2,3}	Appendix 14c (ii) (5.22)
Neurological: dyskinesia (RR)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness		Reporting bias ²	K = 1; N = 149	Not estimable (no events in either group)	Very low ^{1,2,3}	Appendix 14c (ii) (5.23)
Neurological extrapyrami- dal disorder (RR)	AstraZeneca D1441C00112	Quetiapine (400 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 149	3.04 [0.13, 73.44]	Very low ^{1,2,3}	Appendix 14c (ii) (5.24)
Mortality (RR)	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	Not estimable (no events in either group)	Very low ^{1,2,3}	Appendix 14c (ii) (5.25)

	HAAS2009B	Risperidone	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	Not	Very	Appendix 14c
		(4-6 mg per			inconsistency	indirectness		bias ²	N = 105	estimable	low ^{1,2,3}	(ii) (5.25)
		day)								(no events		
										in either		
										group)		
Leaving the	AstraZeneca	Quetiapine	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	0.47 [0.27,	Very	Appendix 14c
study early for	D1441C00112	(400 mg per			inconsistency	indirectness		bias ²	N = 149	0.84]*	low ^{1,2,3}	(ii) (5.26)
any reason		day)										
(RR)	FINDLING	Aripiprazole	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	1.76 [0.86,	Very	Appendix 14c
	2008A	(30 mg per			inconsistency	indirectness		bias ²	N = 202	3.63]	low ^{1,2,3}	(ii) (5.26)
		day)										

*Favours 'higher dose'.

**Favours placebo.

¹Serious risk of bias (including unclear sequence generation and/or allocation concealment, unclear rate blinding procedures, participants excluded if they had a previous non-response to study treatment, treatment exposure [time] differed between groups, patients who did not complete 4 weeks of daily medication because of voluntary withdrawal or for administrative reasons were not included in the analyses for efficacy ratings and were replaced by new patients, LOCF analysis, but high dropout).

² Serious risk of reporting bias.

³ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Additional (high) dose paliperidone versus placebo: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Metabolic: weight kg (SMD)	SINGH	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1; N = 98	0.72 [0.31,	Very	Appendix 14c
	2011			inconsistency	indirectness		bias ²		1.13]*	low ^{1,2,3}	(ii) (6.1)
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting serum glucose level mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting total cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high-density	-	-	-	-	-	-	-	-	-	-	-

lipoprotein cholesterol mg per dl (SMD)											
Metabolic: fasting low-density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT interval	SINGH 2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 98	1.00 [0.00, 0.00]	Very low ^{1,2,3}	Appendix 14c (ii) (6.2)
Cardio: QT interval (RR) (Incidence of prolonged QT)	-	-	-	-	-	-	-	-	-	-	-
<i>Cardio: systolic BP (SMD)</i>	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia (RR)	SINGH 2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 98	9.75 [0.54, 176.36]	Very low ^{1,2,3}	Appendix 14c (ii) (6.3)
Cardio: sitting pulse	-							-	-	-	-
Cardio: standing pulse	-							-	-	-	-
Hormonal: prolactin	SINGH 2011	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 83	-0.10 [-0.53, 0.33]	Very low ^{1,2,3}	Appendix 14c (ii) (6.4)
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	_	-	-	-	-
Neurological: UKU	-	-	-	-	_	-	_	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	_	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	_	-	_	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	-	-	-	-	-	-	-	-	-	-	-
Note. ^a The GRADE approach was used	d to grade	the qualit	y of eviden	ce for each outcom	ne, see Section 3	.5.5 in the fu	all guideline fo	or further detail.			

*Favours placebo. 1 Serious risk of bias (study reports LOCE analysis

¹Serious risk of bias (study reports LOCF analysis, but high dropout, each treatment group exposed to treatment for different lengths of time). ²Serious risk of reporting bias.

³ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Risperidone versus olanzapine: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecisi on	Other consideratio ns	Number of studies/ participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
<i>Total symptoms (SMD)</i>	MOZES2006 SIKICH2004	RCT	Serious ¹	No serious	No serious indirectness	Serious ³	Reporting bias ²	K = 2; N = 60	0.38	Very low ^{1,2,3}	Appendix 14c
Positive symptoms (SMD)	MOZES2006 SIKICH2004	RCT	Serious ¹	inconsistency Serious ⁴	No serious indirectness	Serious ³	Reporting bias ²	K = 2; N = 60	[-0.14, 0.89] 0.38 [-0.13, 0.89]	Very low ^{1,2,3}	(ii) (7.1) Appendix 14c (ii) (7.2)
Negative symptoms (SMD)	MOZES2006 SIKICH2004	RCT	Serious ¹	Serious ⁴	No serious indirectness	Serious ³	Reporting bias ²	K = 2; N = 60	0.22 [-0.51, 0.96]	Very low ^{1,2,3,4}	Appendix 14c (ii) (7.3)
Global state (severity) (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 35	0.15 [-0.52, 0.82]	Very low ^{1,2,3}	Appendix 14c (ii) (7.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
<i>Quality of life (SMD)</i>	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	MOZES2006	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 15	0.25 [-0.54, 1.04]	Very low ^{1,2,3}	Appendix 14c (ii) (7.5)
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

¹ Serious risk of bias (unclear sequence generation and allocation concealment, open-label trial, trial registration cannot be found, LOCF analysis, but high dropout).

² Serious risk of reporting bias.

³ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

 4 I² \geq 50%, p<.05.

Risperidone versus olanzapine: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies/ participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Metabolic: weight (RR)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: weight kg (SMD)	MOZES2006 SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 2; N = 60	-0.36 [-0.87, 0.16]	Very low ^{1,2,3}	Appendix 14c (ii) (8.1)
Metabolic: BMI (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 35	-0.09 [-0.75, 0.58]	Very low ^{1,2,3}	Appendix 14c (ii) (8.2)
Metabolic: fasting serum glucose level mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting total cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high- density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting low-density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT interval (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 35	0.00 [-0.67, 0.67]	Very low ^{1,2,3}	Appendix 14c (ii) (8.3)
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	_	-	-	-	-

Neurological: EPS (SAS) (RR) MOZES	2006 RC	ст с		5	indirectness						
			Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 25	0.95	low ^{1,2,3} Very low ^{1,2,3}	(ii) (8.4) Appendix 14c (ii) (8.5)
Neurological: BARS MOZES	2006 RC	CT S	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 25	3.25 [0.39,	Very low ^{1,2,3}	Appendix 14c (ii) (8.6)
Neurological: UKU -	-	-	-	_	-	-	-	-	-	-	-
Neurological: parkinsonism - (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR) MOZES	2006 RC	CT S	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 15	1.38 [0.71, 2.71]	Very low ^{1,2,3}	Appendix 14c (ii) (8.7)
Neurological: akathisia (RR) -	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR) -	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR) -	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal - disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR) -	-	-	-	-	-	-	-	-	-	-	-
<i>Leaving the study early for</i> MOZES <i>any reason (RR)</i> SIKICH		CT S		No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 2; N = 61	3.90 [1.25, 12.17]*	Very low ^{1,2,3}	Appendix 14c (ii) (8.8)

¹Serious risk of bias (unclear sequence generation and allocation concealment, open-label trial, trial registration cannot be found, LOCF analysis, but high dropout). ²Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies/ participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Total symptoms (SMD)	SIKICH2004 YAO2003/ KENNEDY2012	RCT	Serious ^{1,4}	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 2; N = 76	-0.33 [-0.79, 0.12]	Very low ^{1,2,3,4}	Appendix 14c (ii) (9.1)
Positive symptoms (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 34	-0.25 [-0.93, 0.43]	Very low ^{1,2,3}	Appendix 14c (ii) (9.2)
Negative symptoms (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 34	-0.11 [-0.79, 0.57]	Very low ^{1,2,3}	Appendix 14c (ii) (9.3)
Global state (severity) (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 34	-0.54 [-1.23, 0.15]	Very low ^{1,2,3}	Appendix 14c (ii) (9.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Risperidone versus haloperidol: post-treatment efficacy outcomes

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

¹Serious risk of bias (including unclear allocation concealment, unclear rater blinding procedures, trial registration could not be found, LOCF analysis, but high dropout). ²Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

⁴Sequence generation, analysis and selective outcome reporting not reported by KENNEDY2012.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies/ participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Metabolic: weight kg (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 34	[-1.09, 0.28]	Very low ^{1,2,3}	Appendix 14c (ii) (10.1)
Metabolic: BMI (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 34	-0.55 [-1.24, 0.14]	Very low ^{1,2,3}	Appendix 14c (ii) (10.2)
Metabolic: fasting serum glucose level mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting total cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high- density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting low- density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT interval	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 34	0.00 [-0.68, 0.68]	Very low ^{1,2,3}	Appendix 14c (ii) (10.3)
<i>Cardio: systolic BP</i> (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia	-	-	-	-	-	-	-	-	-	-	-

(RR)											
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS	YAO2003/	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1; N = 42	0.12	Low 1,3,4	Appendix 14c
(RR)	KENNEDY2012		,4	inconsistency	indirectness		bias ²		[0.04, 0.37]*		(ii) (10.4)
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological:	-	-	-	-	-	-	-	-	-	-	-
parkinsonism (RR)											
Neurological: tremor	-	-	-	-	-	-	-	-	-	-	-
(RR)											
Neurological: akathisia	-	-	-	-	-	-	-	-	-	-	-
(RR)											
Neurological: dystonia	-	-	-	-	-	-	-	-	-	-	-
(RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
dyskinesia (RR)											
Neurological:	-	-	-	-	-	-	-	-	-	-	-
extrapyramidal											
disorder (RR) Mortality (RR)											
	-	-	- C1	-	-	-	-	- K - 1 NI - 24	-	-	-
0 0 0	SIKICH2004	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting bias ²	K = 1; N = 34		Very	Appendix 14c
for any reason (RR) Note. ^a The GRADE appr				inconsistency	indirectness				[0.53, 2.15]	low ^{1,2,3}	(ii) (10.5)

*Favours risperidone.

¹Serious risk of bias (including unclear allocation concealment, unclear rater blinding procedures, trial registration could not be found).

²Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

⁴Sequence generation, analysis and selective outcome reporting not reported by KENNEDY2012.

Risperidone versus	chlorpromazine	post-treatment efficacy outcomes
- T	I	r

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec- ision	Other considera- tions	Number of studies/ participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Total symptoms (SMD)	XIONG2004/ KENNEDY2012	RCT	Serious ^{1,4}	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 60	-0.29 [-0.80, 0.22]	Low ^{1, 2, 3,4}	Appendix 14c (ii) (11.1)
Positive symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Negative symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-
Note. ^a The GRADE approact ¹ Serious risk of bias (includi ² Serious risk of reporting bia ³ OIS (for dichotomous outco ⁴ Sequence generation, analy	ng unclear allocation as. omes, OIS = 300 even	n conceal nts; for co	ment, unclea	ar rater blinding). tcomes, OIS = 400) participants) no		ull guideline f	or further detail.			

Risperidone versus chlorpromazine: post-treatment side effect outcomes

Outcome or subgroup	Study ID	0	Risk of bias	Inconsistency	Indirectness		considera-	studies/	estimate	Quality of evidence (GRADE) ^a	Forest plot
Metabolic: weight kg (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting serum	-	-	-	-	-	-	-	-	-	-	-
glucose level mg per dl											

(SMD)		1	Γ								
<i>Metabolic: fasting total</i>	-	-	-	-	-	-	-	-	-	-	-
cholesterol mg per dl (SMD)											
Metabolic: lipid level change	-	-	-	-	-	-	-	-	-	-	-
in total cholesterol mg per dl											
Metabolic: fasting high-	-	-	-	-	-	-	-	-	-	-	-
density lipoprotein											
cholesterol mg per dl (SMD)											
Metabolic: fasting low-	-	-	-	-	-	-	-	-	-	-	-
density lipoprotein											
cholesterol mg per dl (SMD)											
Metabolic: fasting	-	-	-	-	-	-	-	-	-	-	-
triglycerides											
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	XIONG2004/ KENNEDY 2012	RCT	Serious ^{1,4}	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 60	0.50 [0.05, 5.22]	Low ^{1, 2, 3,4}	Appendix 14c (ii) (12.1)
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia	-	-	-	-	-	-	-	-	-	-	-
(RR)											

Neurological:	-	-	-	-	-	-	-	-	-	-	-
extrapyramidal disorder											
(RR)											
<i>Mortality (RR)</i>	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for	-	-	-	-	-	-	-	-	-	-	-
any reason (RR)											
Note. ^a The GRADE approach	was used to grade	the quali	ity of evidend	e for each outcom	ne, see Section 3.	5.5 in the f	ull guideline fo	or further detail.			
¹ Serious risk of bias (including	g unclear allocation	n conceal	ment, unclea	r rater blinding).							
² Serious risk of reporting bias											
³ OIS (for dichotomous outcom	nes, OIS = 300 ever	nts; for co	ontinuous ou	tcomes, $OIS = 400$	participants) no	t met.					
⁴ Sequence generation, analysi	is and selective ou	tcome rej	porting not re	eported by KENN	EDY2012.						

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecis- ion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Total symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Positive symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Negative symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	JENSEN	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1; N = 20		Very	Appendix 14c
	2008			inconsistency	indirectness		bias ²		[0.19, 1.86]	low ^{1,2,3}	(ii) (13.1)
Remission	-	-	-	-	-	-	-	-	-	-	-

Olanzapine versus quetiapine: post-treatment efficacy outcomes

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

¹ Serious risk of bias including unclear allocation concealment, open-label trial study reports LOCF analysis, but high dropout).

² Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Olanzapine versus quetiapine: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Metabolic: weight kg (RR)	JENSEN 2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 20	1.20 [0.54, 2.67]	Very low ^{1,2,3}	Appendix 14c (ii) (14.1)
Match all a DML (CMD)		DCT	$C \cdot 1$	<i>J</i>		$C \cdot 2$		K 1 NL 20			
Metabolic: BMI (SMD)	JENSEN 2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious	Reporting bias ²	K = 1; N = 20	[-0.38, 1.40]	Very low ^{1,2,3}	Appendix 14c (ii) (14.2)
Metabolic: fasting serum glucose level mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting total cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting low-density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-							-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	JENSEN 2008	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 20	-0.43 [-1.32, 0.46]	Very low ^{1,2,3}	Appendix 14c (ii) (14.3)

Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	JENSEN	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1; N = 20		Very	Appendix 14c
	2008			inconsistency	indirectness		bias ²		[0.21, 18.69]	low ^{1,2,3}	(ii) (14.4)
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any	JENSEN	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1; N = 20	1.00	Very	Appendix 14c
reason (RR)	2008			inconsistency	indirectness		bias ²		[0.34, 2.93]	low ^{1,2,3}	(ii) (14.5)

¹Serious risk of bias (including unclear allocation concealment, open-label trial, study reports LOCF analysis, but high dropout).

²Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Olanzapine versus haloperidol: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecis- ion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Total symptoms (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 31	1 /	Very low ^{1,2,3}	Appendix 14c (ii) (15.1)
Positive symptoms (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 31	-0.58 [-1.30, 0.14]	Very low ^{1,2,3}	Appendix 14c (ii) (15.2)
Negative symptoms (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 31	0.00 [-0.70, 0.70]	Very low ^{1,2,3}	Appendix 14c (ii) (15.3)
Global state (severity) (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 31	-0.70 [-1.43, 0.03]	Very low ^{1,2,3}	Appendix 14c (ii) (15.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning	-	-	-	-	-	-	-	-	-	-	-

(SMD)											
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

¹ Serious risk of bias (including unclear allocation concealment, unclear rater blinding procedures, trial registration could not be found, study reports LOCF analysis, but high dropout). ² Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Olanzapine versus haloperidol: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecis- ion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Metabolic: weight kg (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 31	-0.08 [-0.79, 0.62]	Very low ^{1,2,3}	Appendix 14c (ii) (16.1)
Metabolic: BMI (SMD)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 31	-0.21 [-0.92, 0.50]	Very low ^{1,2,3}	Appendix 14c (ii) (16.2)
Metabolic: fasting serum glucose level mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting total cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high- density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting low- density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT interval	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 31	0.00 -0.70, 0.70]	Very low ^{1,2,3}	Appendix 14c (ii) (16.3)

Caudian anatalia DD (CMD)											
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 31		Very low ^{1,2,3}	Appendix 14c (ii) (16.4)
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	SIKICH2004	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 31	0.27 [0.07, 1.09]	Very low ^{1,2,3}	Appendix 14c (ii) (16.5)

*Favours olanzapine.

¹ Serious risk of bias (including unclear allocation concealment, unclear rater blinding procedures, trial registration could not be found, study reports LOCF analysis but high dropout). ² Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecis- ion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Total symptoms (SMD)	AstraZenecaD1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 109	0.07 [-0.31, 0.44]	Very low ^{1,2}	Appendix 14c (ii) (17.1)
Positive symptoms (SMD)	AstraZenecaD1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 109	0.16 [-0.22, 0.53]	Very low ^{1,2}	Appendix 14c (ii) (17.2)
Negative symptoms (SMD)	AstraZenecaD1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 109	-0.03 [-0.40, 0.35]	Very low ^{1,2}	Appendix 14c (ii) (17.3)
Global state (severity) (SMD)	AstraZenecaD1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 110	0.14 [-0.23, 0.51]	Very low ^{1,2}	Appendix 14c (ii) (17.4)
Depression (SMD)	AstraZenecaD1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 109	0.09 [-0.29, 0.46]	Very low ^{1,2}	Appendix 14c (ii) (17.5)
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	AstraZenecaD1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 128	0.15 [-0.19, 0.50]	Very low ^{1,2}	Appendix 14c (ii) (17.6)
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	AstraZenecaD1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 110	1.06 [0.78, 1.46]	Very low ^{1,2}	Appendix 14c (ii) (17.7)
Remission	-	-	-	-	-	-	-	-	-	-	-

Quetiapine 400 mg per day versus quetiapine 800 mg per day: post-treatment efficacy outcomes

 2 OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Metabolic: weight kg (SMD)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 105	-0.05 [-0.37, 0.28]	Very low ^{1,2,3}	Appendix 14c (ii) (18.1)
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting serum glucose level mg per dl (SMD)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 138	0.12 [-0.21, 0.46]	Very low ^{1,2,3}	Appendix 14c (ii) (18.3)
Metabolic: fasting total cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: lipid level change in total cholesterol mg per dl	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 121	0.01 [-0.34, 0.37]	Very low ^{1,2,3}	Appendix 14c (ii) (18.4)
Metabolic: fasting high- density lipoprotein cholesterol mg per dl (SMD)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 125	0.04 [-0.31, 0.39]	Very low ^{1,2,3}	Appendix 14c (ii) (18.5)
Metabolic: fasting low-density lipoprotein cholesterol mg per dl (SMD)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 122	0.17 [-0.18, 0.53]	Very low ^{1,2,3}	Appendix 14c (ii) (18.6)
Metabolic: fasting triglycerides	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 122	-0.10 [-0.46, 0.25]	Very low ^{1,2,3}	Appendix 14c (ii) (18.7)
Cardio: QT interval (SMD)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 128	0.29 [-0.06, 0.64]	Very low ^{1,2,3}	Appendix 14c (ii) (18.8)
Cardio: QT interval (RR) (Prolonged QT interval)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 147	1.01 [0.06, 15.90]	Very low ^{1,2,3}	Appendix 14c (ii) (18.9)
Cardio: systolic BP (SMD)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 147	0.26 [-0.07, 0.58]	Very low ^{1,2,3}	Appendix 14c (ii) (18.10)
Cardio: diastolic BP (SMD)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 147	0.10 [-0.22, 0.43]	Very low ^{1,2,3}	Appendix 14c (ii) (18.11)
Cardio: tachycardia (RR)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 147	0.68 [0.20, 2.30]	Very low ^{1,2,3}	Appendix 14c (ii) (18.12)

Quetiapine 400 mg per day versus quetiapine 800 mg: post-treatment side effect outcomes

Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 147	0.27 [-0.06, 0.59]	Very low ^{1,2,3}	Appendix 14c (ii) (18.13)
Hormonal: prolactin	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 123	-0.12 [-0.48, 0.23]	Very low ^{1,2,3}	Appendix 14c (ii) (18.14)
Hormonal: insulin	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 121	0.17 [-0.19, 0.52]	Very low ^{1,2,3}	Appendix 14c (ii) (18.16)
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 147	1.01 [0.21, 4.86]	Very low ^{1,2,3}	Appendix 14c (ii) (18.19)
Neurological: dystonia (RR)	-	-	-	-	_	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	_	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 148	1.03 [0.07, 16.12]	Very low ^{1,2,3}	Appendix 14c (ii) (18.20)
<i>Mortality (RR)</i>	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	AstraZeneca D1441C00112	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ²	None	K = 1; N = 147	1.33 [0.70, 2.53]	Very low ^{1,2,3}	Appendix 14c (ii) (18.28)

¹ Serious risk of bias (including unclear sequence generation, unclear rater blinding; study reports LOCF analysis, but high dropout). ² OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

³ Serious risk of reporting bias.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Total symptoms (SMD)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 198	0.13 [-0.15, 0.41]	Very low ^{1,2,3}	Appendix 14c (ii) (17.1)
Positive symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Negative symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity) (SMD)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 196	0.10 [-0.18, 0.38]	Very low ^{1,2,3}	Appendix 14c (ii) (17.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 196	0.63 [0.42, 0.84]*	Very low ^{1,2,3}	Appendix 14c (ii) (17.8)
Psychosocial functioning (SMD)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 198	0.01 [-0.27, 0.29]	Very low ^{1,2,3}	Appendix 14c (ii) (17.6)
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Aripiprazole 10 mg per day versus aripiprazole 30 mg per day: post-treatment efficacy outcomes

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

*Favours aripiprazole 30 mg per day.

¹ Serious risk of bias (including unclear allocation concealment, unclear rater blinding in the double-blind design; study reports LOCF analysis, but high dropout). ² Serious risk of reporting bias.

³ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecis ion	Other considerat ions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Metabolic: weight kg	FINDLING	RCT	Serious ¹	No serious	No serious	Serious ³	1 0	K = 1; N = 196	-0.09	Very	Appendix 14c
(SMD)	2008A			inconsistency	indirectness		bias ²		[-0.37, 0.19]	low ^{1,2,3}	(ii) (18.1)
Metabolic: BMI (SMD)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 196	0.00 [-0.28, 0.28]	Very low ^{1,2,3}	Appendix 14c (ii) (18.2)
Metabolic: fasting serum glucose level mg per dl (SMD)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 117	0.26 [-0.10, 0.63]	Very low ^{1,2,3}	Appendix 14c (ii) (18.3)
Metabolic: fasting total cholesterol mg per dl (SMD)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 193	-0.09 [-0.38, 0.19]	Very low ^{1,2,3}	Appendix 14c (ii) (18.4)
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high- density lipoprotein cholesterol mg per dl (SMD)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 107	0.09 [-0.29, 0.48]	Very low ^{1,2,3}	Appendix 14c (ii) (18.5)
Metabolic: fasting low- density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting triglycerides	FINDLING 2008A		Serious ¹	No serious inconsistency	No serious indirectness		bias ²	K = 1; N = 87	-0.08 [-0.50, 0.35]	Very low ^{1,2,3}	Appendix 14c (ii) (18.7)
Cardio: QT interval (SMD)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 196	0.28 [-0.00, 0.56]	Very low ^{1,2,3}	Appendix 14c (ii) (18.8)
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
<i>Cardio: diastolic BP</i> (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-

Aripiprazole 10 mg per day versus aripiprazole 30 mg per day: post-treatment side effect outcomes

Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness		Reporting bias ²	K = 1; N = 190	0.13 [-0.16, 0.41]	Very low ^{1,2,3}	Appendix 140 (ii) (18.14)
Hormonal: insulin	-	_	_	-	-	_	-	-	-	-	-
Neurological: EPS (RR)	_	-	-	-	_	-	-	_	-	-	_
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	0.48 [0.28, 0.84]*	Very low ^{1,2,3}	Appendix 140 (ii) (18.23)
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	0.50 [0.20, 1.28]	Very low ^{1,2,3}	Appendix 14c (ii) (18.19)
Neurological: dystonia (RR)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	2.00 [0.37, 10.67]	Very low ^{1,2,3}	Appendix 14c (ii) (18.22)
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 200	Not estimable (no events in either group)	Very low ^{1,2,3}	Appendix 140 (ii) (18.27)
Leaving the study early for any reason (RR)	FINDLING 2008A	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 202	0.91 [0.49, 1.68]	Very low ^{1,2,3}	Appendix 140 (ii) (18.28)

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail. *Favours aripiprazole 10 mg per day. ¹Serious risk of bias (including unclear allocation concealment, unclear rater blinding in the double-blind design; study reports LOCF analysis, but high dropout). ²Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
<i>Total symptoms (SMD)</i>	-	-	-	-	-	-	-	-	-	-	-
Positive symptoms (SMD)	HAAS2009B	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 104	0.03 [-0.35, 0.42]	Very low ^{1,2,3}	Appendix 14c (ii) (17.2)
Negative symptoms (SMD)	HAAS2009B	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 104	-0.09 [-0.47, 0.30]	Very low ^{1,2,3}	Appendix 14c (ii) (17.3)
Global state (severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
<i>Quality of life (SMD)</i>	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	HAAS2009B	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 99	-0.12 [-0.51, 0.28]	Very low ^{1,2,3}	Appendix 14c (ii) (17.6)
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day: post-treatment efficacy outcomes

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

¹Serious risk of bias (including unclear allocation concealment, unclear rater blinding in the double-blind design, study reports LOCF but high dropout).

²Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Outcome or subgroup	Study ID			Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Metabolic: weight kg (SMD)	HAAS	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	-0.44	Very	Appendix 14c
	2009B			inconsistency	indirectness		bias ²	N = 157	-0.69, -0.19]*	low ^{1,2,3}	(ii) (18.1)
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting serum glucose level mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting total cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting low-density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia (RR)	HAAS 2009B	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 106	1.39 [0.24, 7.99]	Very low ^{1,2,3}	Appendix 14c (ii) (18.12)
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin (SMD)	HAAS 2009B	RCT	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	Reporting bias ²	K = 1; N = 106	-0.41 [-0.79, -0.02]*	Very low ^{1,2,3}	Appendix 14c (ii) (18.14)
Hormonal: prolactin (RR) (number of patients with elevated prolactin)				<u>_</u>				K = 1; N = 157	0.74 [0.58, 0.96]*	Very low ^{1,2,3}	Appendix 14c (ii) (18.15)

Risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day: post-treatment side effect outcomes

Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	HAAS 2009B	RCT	Serious ¹	No serious risk of	No serious risk of	Serious ³	Reporting bias ²	K = 1; N = 106	0.83 [0.50, 1.39]	Very low ^{1,2,3}	Appendix 14c (ii) (18.21)
Nauralagical, AIMAC	HAAS	RCT	Serious ¹	inconsistency No serious	indirectness	Serious ³	Denerting	K = 1;	0.23	Varia	A
Neurological: AIMS	ПАА5 2009В	KCI	Serious	risk of	No serious risk of	Serious	Reporting bias ²	K = 1; N = 109	[-0.15, 0.61]	Very low ^{1,2,3}	Appendix 14c (ii) (18.17)
Numero and CAC		DCT		inconsistency	indirectness	<u>с</u> ,		IZ 1	0.00	X 7	A 1: 14
Neurological: SAS	HAAS 2009B	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 106	-0.39 [-0.78, -0.01]*	Very low ^{1,2,3}	Appendix 14c (ii) (18.18)
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	HAAS 2009B	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 157	0.33 [0.15, 0.71]*	Very low ^{1,2,3}	Appendix 14c (ii) (18.22)
Neurological: dyskinesia (RR)	-							-	-	-	-
Neurological: extrapyramidal disorder (RR)	HAAS 2009B	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 106	0.58 [0.20, 1.66]	Very low ^{1,2,3}	Appendix 14c (ii) (18.20)
Mortality (RR)	HAAS 2009B	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 106	Not estimable (no events in either group)	Very low ^{1,2,3}	Appendix 14c (ii) (18.27)
Leaving the study early for any reason (RR)	HAAS 2009B	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 106	1.32 [0.55, 3.22]	Very low ^{1,2,3}	Appendix 14c (ii) (18.28)

*Favours 1-3 mg per day.

¹ Serious risk of bias (including unclear allocation concealment, unclear rater blinding in the double-blind design, study reports LOCF but high dropout).

² Serious risk of reporting bias.

³ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecis ion	Other considerat ions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Total symptoms (SMD)	HAAS 2009	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 256	0.34 [0.09, 0.59]*	Very low ^{1,2,3}	Appendix 14c (ii) (17.1)
Positive symptoms (SMD)	HAAS 2009	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 256	0.42 [0.17, 0.67]*	Very low ^{1,2,3}	Appendix 14c (ii) (17.2)
Negative symptoms (SMD)	HAAS 2009	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 256	0.42 [0.17, 0.67]*	Very low ^{1,2,3}	Appendix 14c (ii) (17.3)
Global state (severity) (SMD)	HAAS 2009	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 256	0.41 [0.16, 0.66]*	Very low ^{1,2,3}	Appendix 14c (ii) (17.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
<i>Quality of life (SMD)</i>	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Risperidone 0.15 to 0.6 mg per day versus risperidone 1.5 to 6.0 mg per day: post-treatment efficacy outcomes

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.

*Favours 1.5-6.0 mg per day.

¹ Serious risk of bias (including unclear allocation concealment, unclear whether rater blinding in the double-blind design, study reports LOCF but high dropout).

² Serious risk of reporting bias.

³ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Risperidone 0.15 to 0.6 mg per day versus risperidone 1.5 to 6.0 mg: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsi stency	Indirec tness	Imprecis ion	Other considerat ions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Metabolic: weight kg (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting serum glucose level mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting total cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: lipid level change in total cholesterol mg per dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting low-density lipoprotein cholesterol mg per dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
<i>Cardio: systolic BP (SMD)</i>	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	HAAS 2009	RCT	Serious ¹	Low	Low	Serious ³	Reporting bias ²	K = 1; N = 257	0.74 [0.58, 0.96]*	Very low ^{1,2,3}	Appendix 14c (ii) (18.15)
Hormonal: insulin	-							-	-	-	-
Neurological: EPS (RR)	HAAS 2009	RCT	Serious ¹	Low	Low	Serious ³	Reporting bias ²	K = 1; N = 157	0.30 [0.17, 0.53]*	Very low ^{1,2,3}	Appendix 14c (ii) (18.21)
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: symptoms of parkinsonism (RR)	HAAS 2009	RCT	Serious ¹	Low	Low	Serious ³	Reporting bias ²	K = 1; N = 157	0.09 [0.00, 1.54]	Very low ^{1,2,3}	Appendix 14c (ii) (18.24)

Neurological: tremor (RR)	HAAS	RCT	Serious ¹	Low	Low	Serious ³	Reporting	K = 1; N = 157	0.29 [0.10, 0.87]*	Very	Appendix 14c
-	2009						bias ²			low ^{1,2,3}	(ii) (18.26)
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	HAAS 2009B	RCT	Serious ¹	Low	Low	Serious ³	Reporting bias ²	K = 1; N = 157	0.33 [0.15, 0.71]*	Very low ^{1,2,3}	Appendix 14c (ii) (18.22)
Neurological: dyskinesia (RR)	HAAS 2009	RCT	Serious ¹	Low	Low	Serious ³	Reporting bias ²	K = 1; N = 157	0.27 [0.06, 1.28]	Very low ^{1,2,3}	Appendix 14c (ii) (18.25)
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	HAAS 2009	RCT	Serious ¹	Low	Low	Serious ³	Reporting bias ²	K = 1; N = 157	1.35 [0.95, 1.93]	Very low ^{1,2,3}	Appendix 14c (ii) (18.28)
<i>Note.</i> ^a The GRADE approach was used to grade *Fayours 0.15-0.6 mg per day.	e the qualit	y of evide	nce for eacl	h outcome	e, see Sect	ion 3.5.5 in	the full guid	eline for further d	letail.		

¹ Serious risk of bias (including unclear allocation concealment, unclear whether rater blinding in the double-blind design, study reports LOCF but high dropout). ² Serious risk of reporting bias.

³ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Paliperidone 1.5 mg per day versus paliperidone 3 to 6 mg per day versus paliperidone 6 to 12 mg: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Dose comparison	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies/ participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE) ^a	Forest plot
Total symptoms (SMD)	2011	1.5 mg per day versus 3-6 mg per day	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 102	0.48 [0.09, 0.88]	Very low ^{1,2,3}	Appendix 14c (ii) (17.1)
	SINGH	3-6 mg per day versus 6- 12 mg per day	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 95	-0.23 [-0.63, 0.17]*	Very low ^{1,2,3}	Appendix 14c (ii) (20.1)
		1.5 mg per day versus 6- 12 mg per day	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 101	0.25 [-0.15, 0.64]	Very low ^{1,2,3}	Appendix 14c (ii) (19.1)
Positive symptoms (SMD)	SINGH 2011	1.5 mg per day versus 3-6	RCT	Serious ¹	No serious risk of	No serious risk of	Serious ³	Reporting bias ²	K = 1; N = 102	0.48 [0.08, 0.87]	Very low ^{1,2,3}	Appendix 14c (ii) (17.2)

		mg per day			inconsistency	indirectness						
	SINGH	3-6 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	-0.19 [-0.59,	Very low	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 95	0.22]	1,2,3	(ii) (20.2)
		12 mg per day			inconsistency	indirectness				-		
	SINGH	1.5 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	0.31	Very	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 101	[-0.08, 0.71]	low ^{1,2,3}	(ii) (19.2)
		12 mg per day			inconsistency	indirectness						
Negative	SINGH	1.5 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	0.31	Very	Appendix 14c
symptoms (SMD)	2011	day versus 3-6			risk of	risk of		bias ²	N = 102	[-0.08, 0.71]	low ^{1,2,3}	(ii) (17.3)
		mg per day			inconsistency	indirectness						
	SINGH	3-6 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	-0.27	Very	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 95	[-0.67, 0.13]*	low ^{1,2,3}	(ii) (20.3)
		12 mg per day			inconsistency	indirectness						
	SINGH	1.5 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	0.00	Very	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 101	[-0.39, 0.39]	low ^{1,2,3}	(ii) (19.3)
		12 mg per day			inconsistency	indirectness						
Global state (severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Depression	SINGH	1.5 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	0.18	Very	Appendix 14c
(SMD)	2011	day versus 3-6			risk of	risk of		bias ²	N = 102	[-0.21, 0.57]	low ^{1,2,3}	(ii) (17.5)
		mg per day			inconsistency	indirectness						
	SINGH	3-6 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	-0.03	Very	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 95	[-0.43, 0.37]	low ^{1,2,3}	(ii) (20.4)
		12 mg per day			inconsistency	indirectness						
	SINGH	1.5 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	0.15	Very	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 101	[-0.25, 0.54]	low ^{1,2,3}	(ii) (19.4)
		12 mg per day			inconsistency	indirectness						
Mania	-	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-	
Psychosocial	SINGH	1.5 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	0.76	Very	Appendix 14c
functioning	2011	day versus 3-6			risk of	risk of		bias ²	N = 102	[0.36, 1.16]	low ^{1,2,3}	(ii) (17.6)
(SMD)		mg per day			inconsistency	indirectness						
	SINGH	3-6 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	-0.38	Very	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 95	[-0.79, 0.02]*	low ^{1,2,3}	(ii) (20.5)

		12 mg per day			inconsistency	indirectness						
	SINGH	1.5 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	0.38	Very	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 101	[-0.01, 0.78]	low ^{1,2,3}	(ii) (19.5)
		12 mg per day			inconsistency	indirectness						
Social functioning	-	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-	-

*Favours 3-6 mg per day.

¹Serious risk of bias (study reports LOCF but high dropout, each treatment group exposed to treatment for different lengths of time).

²Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Paliperidone 1.5 mg per day versus paliperidone 3 to 6 mg per day versus paliperidone 6 to 12 mg: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Dose comparison	Design	Risk of bias	Inconsistency	Indirectness	Imprecis ion	Other consideratio ns	Number of studies/ participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
<i>Metabolic: weight</i>	SINGH	1.5 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	1 0	K = 1;	-0.43	Very	Appendix 14c
kg (SMD)	2011	day versus 3-6 mg per day			risk of inconsistency	risk of indirectness		bias ²	N = 102	[-0.83, -0.04]*	low ^{1,2,3}	(ii) (18.1)
	SINGH	3-6 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	-0.14	Very	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 95	[-0.54, 0.26]	low ^{1,2,3}	(ii) (22.1)
		12 mg per day			inconsistency	indirectness						
	SINGH	1.5 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	-0.59	Very	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 101	[-0.99, -0.19]*	low ^{1,2,3}	(ii) (21.1)
		12 mg per day			inconsistency	indirectness						
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: fasting	-	-	-	-	-	-	-	-	-	-	-	-
serum glucose												
level mg per dl												
(SMD)												
Metabolic: fasting	-	-	-	-	-	-	-	-	-	-	-	-

	1					1	1	1		1	1	1
total cholesterol												
mg per dl (SMD)												
Metabolic: lipid	-	-	-	-	-	-	-	-	-	-	-	-
level change in												
total cholesterol												
mg per dl												
Metabolic: fasting	-	-	-	-	-	-	-	-	-	-	-	-
high-density												
lipoprotein												
cholesterol mg per												
dl (SMD)												
Metabolic: fasting	-	-	-	-	-	-	-	-	-	-	-	-
low-density												
lipoprotein												
cholesterol mg per												
dl (SMD)												
Metabolic: fasting	-	-	-	-	-	-	-	-	-	-	-	-
triglycerides												
Cardio: QT	SINGH	1.5 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	Not	Very	Appendix 14c
interval	2011	day versus 3-6			risk of	risk of		bias ²	N = 102	estimable	low ^{1,2,3}	(ii) (18.9)
		mg per day			inconsistency	indirectness				(no events in		()())
		01								either		
										group)		
	SINGH	3-6 mg per	RCT	Serious ¹	No serious	No serious	Serious ³	Reporting	K = 1;	Not	Very	Appendix 14c
	2011	day versus 6-	ner	Serious	risk of	risk of	oerrous	bias ²	N = 95	estimable	$1000^{1,2,3}$	(ii) (22.2)
	2011	12 mg per day			inconsistency	indirectness		0103	10 55	(no events in	10 10	(11) (22.2)
		12 mg per day			inconsistency	munectiless				either		
	CINCU	15	RCT	Serious ¹	No serious	No serious	Serious ³	Donoutina	K = 1;	group) Not	Vor	Appendix 14-
	SINGH	01	KUI	Serious			Serious	Reporting	· ·		Very low ^{1,2,3}	Appendix 14c
	2011	day versus 6-			risk of	risk of		bias ²	N = 101	estimable	10W ^{1,2,3}	(ii) (21.2)
		12 mg per day			inconsistency	indirectness				(no events in		
										either		
									ļ	group)		
<i>Cardio: systolic</i>	-	-	-	-	-	-	-	-	-	-	-	-
BP (SMD)												
Cardio: diastolic	_									_		

BP (SMD)												
Cardio: tachycardia (RR)	SINGH 2011	1.5 mg per day versus 3-6 mg per day	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 102	0.13 [0.01, 2.40]	Very low ^{1,2,3}	Appendix 14c (ii) (18.12)
	SINGH 2011	3-6 mg per day versus 6- 12 mg per day	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 95	0.73 [0.17, 3.11]	Very low ^{1,2,3}	Appendix 14c (ii) (22.3)
	SINGH 2011	1.5 mg per day versus 6- 12 mg per day	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 101	0.10 [0.01, 1.76]	Very low ^{1,2,3}	Appendix 14c (ii) (21.3)
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	SINGH 2011	1.5 mg per day versus 3-6 mg per day	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 93	-0.62 [-1.03, -0.20]*	Very low ^{1,2,3}	Appendix 14c (ii) (18.14)
	SINGH 2011	3.6 mg per day versus 6- 12 mg per day	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 84	-0.03 [-0.46, 0.39]	Very low ^{1,2,3}	Appendix 14c (ii) (22.4)
	SINGH 2011	1.5 mg per day versus 6- 12 mg per day	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 93	-0.53 [-0.94, -0.11]*	Very low ^{1,2,3}	Appendix 14c (ii) (21.4)
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism	-	-	-	-	-	-	-	-	-	-	-	-

(RR)												
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-	-
<i>Mortality (RR)</i>	-	-	-	-	-	-	-	_	-	-	-	-
Leaving the study early for any reason (RR)	-	-	-	-	-	-	-	-	-	-	-	-

*Favours 1.5 mg per day

¹Serious risk of bias (study reports LOCF but high dropout, each treatment group exposed to treatment for different lengths of time).

²Serious risk of reporting bias.

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

APPENDIX 17C (III): ANTIPSYCHOTICS IN CHILDREN AND YOUNG PEOPLE WITH PSYCHOSIS AND SCHIZOPHRENIA WHOSE ILLNESS HAS NOT RESPONDED ADEQUATELY TO PHARMACOLOGICAL TREATMENT

Clozapine versus another antipsychotic: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Total symptoms (SMD)	KUMRA1996 KUMRA2008A SHAW2006	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 3; N = 85	0.50 [0.06, 0.94]*	Very low ^{1,2,3}	Appendix 14c (iii) (1.1)
Positive symptoms (SMD)	KUMRA1996 KUMRA2008A SHAW2006	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 3; N = 85	0.71 [0.27, 1.16] *	Very low ^{1,2,3}	Appendix 14c (iii) (1.3)
Negative symptoms (SMD)	KUMRA1996 KUMRA2008A SHAW2006	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 3; N = 85	0.53 [0.10, 0.97] *	Very low ^{1,2,3}	Appendix 14c (iii) (1.5)
Global state (severity) (SMD)	KUMRA2008A SHAW2006	-	-	-	-	-	-	K = 2; N = 64	0.51 [0.01, 1.01] *	Very low ^{1,2,3}	Appendix 14c (iii) (1.7)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning	KUMRA1996 KUMRA2008A	RCT	Serious ¹	Serious ⁴	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 2; N = 60	0.80 [-0.43, 2.03]	Very low ^{1,2,3,4}	Appendix 14c (iii) (1.8)
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note. ^aThe GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail. *Favours clozapine.

¹Downgraded due to risk of bias (including unclear allocation concealment, blinding of raters unclear; ITT method of analysis unclear or available case analysis used, high dropout, eligibility criteria states that patients must be not be treatment refractory to the study medication, trial registration could not be found). ²Serious risk of reporting bias .

³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.⁴I² \ge 50%, p<.05.

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Number of studies/ participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)ª	Forest plot
Metabolic: weight kg	SHAW2006	RCT	Serious ¹	No serious risk	No serious risk	Serious ³	Reporting	K = 1; N =	0.04 [-0.82,	Very	Appendix 14c
(SMD)				of inconsistency	of indirectness		bias ²	25	0.75]	low ^{1,2,3}	(iii) (2.1)
Metabolic: BMI (SMD)	KUMRA2008A	RCT	Serious ¹	No serious risk	No serious risk	Serious ³	Reporting	K = 2; N =	-0.03 [-0.47,	Very	Appendix 14c
	SHAW2006			of inconsistency	of indirectness		bias ²	63	-0.52]*	low ^{1,2,3}	(iii) (2.2)
Metabolic: fasting	KUMRA2008A	RCT	Serious ¹	No serious risk	No serious risk	Serious ³	Reporting	K = 1;	-0.79 [-1.45, -	Very low ^{1,2,}	Appendix 14c
serum glucose level mg per dl (SMD)				of inconsistency	of indirectness		bias ²	N = 38	0.12]*	3	(iii) (2.3)
Metabolic: fasting total	KUMRA2008A	RCT	Serious ¹	No serious risk	No serious risk	Serious ³	Reporting	K = 1;	0.31	Very	Appendix 14c
cholesterol mg per dl				of inconsistency	of indirectness		bias ²	N = 38	[-0.34, 0.95]	low ^{1,2,3}	(iii) (2.4)
(SMD)											
Metabolic: lipid level	-	-	-	-	-	-	-	-	-	-	-
change in total											
cholesterol mg per dl											
Metabolic: fasting high-	-	-	-	-	-	-	-	-	-	-	-
density lipoprotein											
cholesterol mg per dl											
(SMD)											
Metabolic: fasting low-	-	-	-	-	-	-	-	-	-	-	-
density lipoprotein											
cholesterol mg per dl											
(SMD)		D.OT	<u> </u>				D	76 4			
Metabolic: fasting	KUMRA2008A	RCT	Serious ¹	No serious risk	No serious risk	Serious ³	Reporting	K = 1;	-0.28	Very	Appendix 14c
triglycerides				of inconsistency	of indirectness		bias ²	N = 38	[-0.92, 0.37]	low ^{1,2,3}	(iii) (2.5)
Cardio: QT interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
<i>Cardio: diastolic BP</i> (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia	KUMRA1996	RCT	Serious ¹	No serious risk	No serious risk	Serious ³	Reporting	K = 1;	0.18	Very	Appendix 14c

Clozapine versus another antipsychotic: post-treatment side effect outcomes

(RR)				of inconsistency	of indirectness		bias ²	N = 21	[0.01, 3.41]	low ^{1,2,3}	(iii) (2.6)
	SHAW2006	RCT	Serious ¹	No serious risk	No serious risk	Serious ³	Reporting	K = 1;	4.80 [1.30,	Very	Appendix 14c
				of inconsistency	of indirectness		bias ²	N = 22	17.66]**	low ^{1,2,3}	(iii) (2.6)
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	KUMRA1996	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 21	0.02 [-0.83, 0.88]	Very low ^{1,2,3}	Appendix 14c (iii) (2.7)
Neurological: SAS	KUMRA1996	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 1; N = 21	0.66	Very low ^{1,2,3}	Appendix 14c (iii) (2.8)
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
<i>Mortality (RR)</i>	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	KUMRA1996 KUMRA2008A SHAW2006	RCT	Serious ¹	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ²	K = 3; N = 85	1.15 [0.43, 3.03]	Very low ^{1,2,3}	Appendix 14c (iii) (2.9)

*Favours olanzapine.

**Favours clozapine.

¹Downgraded due to risk of bias (including unclear allocation concealment, blinding of raters unclear; ITT method of analysis unclear or available case analysis used, high dropout, eligibility

criteria states that patients must be not be treatment refractory to study medication, trial registration could not be found). ²Serious risk of reporting bias. ³OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

APPENDIX 14C (IV): OBSERVATIONAL STUDIES – SIDE EFFECTS

Comparison Design Risk of Quality of Forest plot Outcome or Study ID Other Studies/ Effect Inconsistency Indirectness Imprecibias consideraevidence sion subgroup number estimate (GRADE)^a tions of (SMD or partici-RR) pants Metabolic: CASTRO-Quetiapine OS Serious³ No serious Serious⁴ Reporting -0.02 Appendix No serious K = 1; Verv weight [-0.64, low^{3,4,5} 14c (iv) FORNIELES versus risk of risk of bias⁵ N = 46change kg indirectness (1.1) 2008^{1} risperidone inconsistency 0.601 (SMD) CASTRO-OS No serious K = 1; Very Ouetiapine Serious³ No serious Serious⁴ Reporting -0.96 Appendix low^{3,4,5} 14c (iv) FORNIELES risk of risk of bias⁵ N = 29versus [-1.73, - $0.18]^*$ 2008¹ olanzapine inconsistency indirectness (1.2)OS CASTRO-Olanzapine Serious³ No serious No serious Serious⁴ Reporting K = 2;1.75 Verv Appendix FORNIELES (SOT) versus risk of risk of bias⁵ N = 81[0.30, low^{3,4,5} 14c (iv) indirectness 3.21]** (1.3)2008¹ risperidone inconsistency CROCO2007² No serious 1.02 Olanzapine OS Serious⁴ Reporting K = ; Appendix CROCO2007² Serious³ No serious Verv risk of (ODT) risk of [0.36, low^{3,4,5} 14c (iv) bias⁵ N = 42versus indirectness 1.69]** (1.4)inconsistency risperidone OS Reporting CROCO2007² Olanzapine Serious³ No serious Serious⁴ K = ; -1.62 Appendix No serious Verv (SOT) versus risk of risk of N = 26[-2.54, low^{3,4,5} bias⁵ 14c (iv) olanzapine 0.69]*** indirectness inconsistency (1.5)(ODT) Metabolic: CROCO2007² Olanzapine OS Serious³ No serious No serious Reporting 2.17 Appendix Serious⁴ K = 1; Verv BMI change [1.27, low^{3,4,5} (SOT) versus risk of risk of bias⁵ N = 3614c (iv) (SMD) risperidone 3.08]** (2.1)inconsistency indirectness CROCO2007² Olanzapine OS K = ; Appendix Serious³ No serious No serious Serious⁴ Reporting 0.93 Verv (ODT) risk of [0.27, low^{3,4,5} 14c (iv) risk of bias⁵ N = 421.59]** versus indirectness (2.2)inconsistency risperidone

Extractable metabolic side effect outcomes

(SMD)(CMD)		CROCQ2007 ²	Olanzapine (SOT) versus olanzapine (ODT)	OS	Serious ³	No serious risk of inconsistency	No serious risk of indirectness	Serious ⁴	Reporting bias ⁵	K = 1; N = 26	-1.06 [-1.91, - 0.21]***	Very low ^{3,4,5}	Appendix 14c (iv) (2.3)
serum giucose level mg per dl (SMD) Metabolic: - GMD Meta		-	-	-	-	-	-	-	-	-	-	-	-
glucose level mg per dl (SMD) Metabolic: (SMD) Metabolic: invi level (SMD) Metabolic: invi level (SMD) Metabolic: invi level invi level (SMD) Metabolic: invi level invi													
Image of l (SMD)Image of l (SMD)													
Metabolic: fasting total cholesterol mg per dl (SMD) </td <td>mg per dl</td> <td></td>	mg per dl												
fasting total cholesterol mg per dl image and cholesterol image and		_	_	-	_	-	_	_	-	_	_	_	_
cholesterol mg per all (SMD)cholesterol mg per allcholesterol mg per allmg per allcho													
(SMD)Image: Constraint of the second sec	cholesterol												
Metabolic: lipid level change in total cholesterol mg per dl- - metabolic: passing high- density lipoprotein cholesterol mg per dl- 	mg per dl												
lipid level change in total cholesterol mg per dllipid level cholesterol mg per dllipid													
change in total cholesterol mg per dl Metabolic: fasting low- density lipoprotein cholesterol mg per dl (SMD)		-	-	-	-	-	-	-	-	-	-	-	-
total cholesterol mg per dl -													
cholesterol mg per dlImage: second s	change in												
mg per dlImage													
Metabolic: fasting high- density lipoprotein cholesterol mg per dl (SMD) <td></td>													
fasting high- density lipoprotein cholesterol mg per dl (SMD)subset of subset of mg per dl cholesterolsubset of subset of subset of subset of mg per dl (SMD)subset of subset of su	Metabolic:	_	-	-	_	-	_	_	-	_	_	_	_
density lipoprotein cholesterol mg per dl (SMD)enden													
cholesterol mg per dl (SMD)end <td>density</td> <td></td>	density												
mg per dl (SMD)end <t< td=""><td>lipoprotein</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	lipoprotein												
(SMD)Image: SMD in the second sec													
fasting low- density lipoprotein cholesterol mg per dl (SMD)	(SMD)												
density Ipoprotein lipoprotein Image: Cholesterol mg per dl Image: Cholesterol (SMD) Image: Cholesterol		-	-	-	-	-	-	-	-	-	-	-	-
lipoprotein cholesterol mg per dl (SMD)	fasting low-												
cholesterol mg per dl (SMD)	density												
mg per dl (SMD)	lipoprotein												
(SMD)													
	(SMD)												
	(SNID) Metabolic:	 _	_	-	_	_		_			-	-	

fasting triglycerides												
Note. ^a The GF	RADE approach w	as used to grade	e the qual	ity of evide	ence for each outc	ome, see Section	3.5.5 in th	e full guideline	e for further	detail.		
*Favours que	etiapine											
**Favours ris	speridone											
***Favours of	lanzapine (ODT)										
¹ 26 weeks' tr	reatment											
² 12 weeks' tr	reatment											
³ Serious risk	³ Serious risk of bias (including: observational study)											
⁴ OIS (for dic	⁴ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.											
⁵ Serious risk	⁵ Serious risk of reporting bias											

Extractable neurological side effect outcomes

Outcome or subgroup	STUDY ID	Comparison	Design	Risk of bias	Inconsistency	Indirectness	Impreci- sion	Other considera- tions	Studies/ number of partici- pants	Effect estim- ate (SMD or RR)	Hetero- geneity	Quality of evidence (GRADE) ^a	Forest plot
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU (SMD)	CASTRO- FORNIELES 2008 ¹	Quetiapine versus risperidone	OS	Serious ²	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ⁴	K = 1; N = 46	-0.28 [-0.90, 0.34]	N/A	Very low ^{2,3,4}	Appendix 14c (iv) (3.1)
	CASTRO- FORNIELES 2008 ¹	Quetiapine versus olanzapine	OS	Serious ²	No serious risk of inconsistency	No serious risk of indirectness	Serious ³	Reporting bias ⁴	K = 1; N = 29	0.11 [- 0.62, 0.84]	N/A	Very low ^{2,3,4}	Appendix 14c (iv) (3.2)
	CASTRO- FORNIELES 2008 ¹	Olanzapin e (SOT)	OS	Serious ²	No serious risk of	No serious risk of	Serious ³	Reporting bias ⁴	K = 1; N = 45	-0.39 [-1.03,	N/A	Very low ^{2,3,4}	Appendix 14c (iv)

		versus risperidone			inconsistency	indirectness				0.25]			(3.3)
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyrami- dal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
<i>Note.</i> ^a The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail. ¹ 26 weeks' treatment.													

²Serious risk of bias (including: observational).
³ OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

⁴Serious risk of reporting bias.