APPENDIX 17C: CLINICAL EVIDENCE PROFILES: PHARMACOLOGICAL INTERVENTIONS

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. [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.
*Favours olanzapine.
[1] Serious 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.
[3] Serious risk of reporting bias.
[4] $I^2 \geq 50\%$, $p < .05$.
[5] Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young people).

Olanzapine versus quetiapine: post-treatment side effect 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
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)

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	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic 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) (2.8)
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	0.92 [0.06, 13.95]	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 (RR)	ARANGO2009	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 1; N = 60	6.48 [0.35, 119.32]	Very low[1,2,3,4]	Appendix 14c (i) (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.[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.
*Favours olanzapine.
**Favours quetiapine.
[1]Serious 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).
[2] OIS (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 range 44.4 years may not be representative of children and young people).

PHARMACOLOGICAL INTERVENTIONS IN CHILDREN AND YOUNG PEOPLE 25 YEARS AND YOUNGER

Risperidone versus quetiapine: post-treatment efficacy 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
Total symptoms (SMD)	MCEVOY2007 SWADI2010	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2; N = 103	-0.28 [-0.67, 0.11]	Very low[1,2,3,4]	Appendix 14c (i) (3.1)
Total symptoms (RR: response)	SWADI2010	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 1; N = 22	1.25 [0.45, 3.45]	Very low[1,2,3]	Appendix 14c (i) (3.2)
Positive symptoms	MCEVOY2007 SWADI2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 2; N = 103	-0.43 [-0.82, -0.03]	Very low[1,2,3,4]	Appendix 14c (i) (3.3)
Negative symptoms	MCEVOY2007 SWADI2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 2; N = 103	-0.22 [-0.61, 0.17]	Very low[1,2,3,4]	Appendix 14c (i) (3.4)
Global state (severity) (SMD)	MCEVOY2007 SWADI2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 2; N = 103	-0.14 [-0.53, 0.25]	Very low[1,2,3,4]	Appendix 14c (i) (3.5)
Global state (severity) (RR: response)	SWADI2010	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 1; N = 22	0.83 [0.36, 1.94]	Very low[1,2,3]	Appendix 14c (i) (3.6)
Depression (SMD)	MCEVOY2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 1; N = 81	0.38 [-0.07, 0.82]	Very low[1,2,3,4]	Appendix 14c (i) (3.7)
Depression (RR: response)	SWADI2010	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 1; N = 22	0.71 [0.33, 1.57]	Very low[1,2,3]	Appendix 14c (i) (3.8)
Mania (RR: response)	SWADI2010	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 1; N = 22	0.70 [0.43, 1.14]	Very low[1,2,3]	Appendix 14c (i) (3.9)
Quality of life	MCEVOY2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 1; N = 81	-0.30 [-0.60, -0.00]*	Very low[1,2,3,4]	Appendix 14c (i) (3.10)
Psychosocial functioning	-	-	-	-	-	-	-	-	-	-	-
Social functioning	-	-	-	-	-	-	-	-	-	-	-

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

Note. [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.
*Favours risperidone.
[1]Downgraded 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.
[3]Serious risk of reporting bias.
[4]Serious 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)
Cardio: diastolic BP (SMD)	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 early for any reason (RR)	MCEVOY2007 SWADI2010	RCT	Serious[1]	Serious[4]	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2; N = 289	0.51 [0.06, 4.08]	Very low[1,2,3,4]	Appendix 14c (i) (4.15)

Note.[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.
* Favours risperidone.
**Favours quetiapine.
[1]Serious 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.
[3]Serious risk of reporting bias.
[4] $I^2 = \geq 50\%$, $p<.05$.
[5]Serious 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 subgroup	**Study ID**	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of studies / participants**	**Effect estimate (SMD or RR)**	**Quality of evidence (GRADE)[a]**	**Forest plot**
Total symptoms (SMD)	LIEBERMAN 2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 1; N = 251	-0.21 [-0.46, 0.04]	Very low[1,2,3,4]	Appendix 14c (i) (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 2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 1; N = 252	-0.25 [-0.50, -	Very low[1,2,3,4]	Appendix 14c (i) (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. [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.
*Favours olanzapine.
[1]Serious risk of bias (including: unclear sequence generation & allocation concealment; unclear rater blinding, trial registration couldn't be found, LOCF reported but dropout high).
[2]OIS (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 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	Imprecision	Other consider-ations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight (SMD)	LIEBERMAN 2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 1; N = 263	0.70 [0.45, 0.95]**	Very low[1,2,3,4]	Appendix 14c (i) (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)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin (RR)	LIEBERMAN 2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 1; N = 263	-0.34 [-0.59, -0.10]*	Very low[1,2,3,4]	Appendix 14c (i) (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)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	LIEBERMAN 2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K = 1; N = 263	0.87 [0.77, 0.97]*	Very low[1,2,3,4]	Appendix 14c (i) (6.3)

Note. [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.
*Favours olanzapine.
**Favours haloperidol.
[1]Serious risk of bias (including: unclear sequence generation and allocation concealment; unclear rater blinding, trial registration could not be found, LOCF reported but dropout high).
[2]OIS (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 (inclusion upper age range was 40. May not be representative of children and young people**).**

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

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

Note. [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]Serious 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).
[2]Serious risk of indirectness (48% population had bipolar disorder).
[3]Serious risk of reporting bias.

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

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 (SMD)	SCHOOLER 2005	RCT	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	Reporting bias[4]	K = 1; N = 415	0.11 [-0.08, 0.30]	Very Low[1,3,4]	Appendix 14c (i) (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	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-

Hormonal: prolactin (SMD)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin (RR)	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)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (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)

Note.[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.
*Favours haloperidol.
[1]Serious 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).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Serious risk of indirectness (48% population had bipolar disorder).
[4]Serious risk of reporting bias.

Risperidone versus olanzapine: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other considerations	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	-	-	-	-	-	-	-	-	-	-	-

Response	ROBINSON2006	RCT	Serious[1]	No serious inconsistency	No serious indirect-ness	Serious[2]	None	K = 1; N = 120	1. 25 [0.84, 1.86]	Very low[1,2]	Appendix 14c (i) (9.7)
Remission	VANBRUGGEN2003	RCT	Serious[1]	No serious inconsistency	No serious indirect-ness	Serious[2]	Reporting bias[3]	K = 1; N = 44	0.55 [0.17, 1.78]	Very low[1,2,3]	Appendix 14c (i) (9.8)

Note. [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] 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)
[2]OIS (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] $I^2 \geq 50\%$, $p<.05$

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	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight (SMD)	MCEVOY2007 SIKICH2008 VANBRUGGEN 2003	RCT	Serious[1]	Serious[5]	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]	K = 1; N = 74	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, -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. [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.
*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)
[2]OIS (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] $I^2 \geq 50\%$, $p<.05$

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	-0.08 [-0.49, 0.33]	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)

Note. [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.

*Favours 400 mg/day.
[1]Serious risk of bias (including blinding of participants and providers in part 2 not maintained; available case analysis used).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious 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	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
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)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	BERGER2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 1; N = 141	0.91 [0.35, 2.38]	Very low[1,2,3]	Appendix 14c (i) (12.3)

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

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

'Lower dose' antipsychotic versus placebo: 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)	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)

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

Note.[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.
*Favours 'lower dose'
[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) differ between groups, 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
[4] $I^2 \geq 50\%$, $p<.05$

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

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)	FINDLING2008A	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 mg per dl (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 = 127	0.38 [0.03, 0.74] **	Very low[1,2,3]	Appendix 14c (ii) (2.3)
	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)

cholesterol mg per dl		day)										
	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 lipoprotein cholesterol mg per dl (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 = 92	0.39 [-0.02, 0.81]	Very low[1,2,3]	Appendix 14c (ii) (2.5)
	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)
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)
	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)
	KRYZHANOVSKAYA 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 prolonged QT)	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)
	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)
Cardio: 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)
Cardio: tachycardia (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)
Hormonal: prolactin	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 day)	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	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)

	PALLIERE-MARTINOT 1995	Amisulpride (50-100 mg per day)	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 17	1.11 [0.45, 2.78]	Very low[1,2,3]	Appendix 14c (ii) (2.26)
	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	0.55 [0.28, 1.07]	Very low[1,2,3]	Appendix 14c (ii) (2.26)

Note.[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.
*Favours 'lower dose'.
**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	Imprecision	Other considerations	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 imprecision	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 imprecision	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 imprecision	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. [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.
*Favours 'higher dose'.
[1] Serious 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.
[3] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

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

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	-0.41 [-0.80, -0.01]*	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	-	-	-	-	-	-	-	-	-	-	-

Note.[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.
*Favours 6 to 12 mg per day paliperidone.
[1] Serious 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.

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

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 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 = 137	0.03 [-0.30, 0.37]	Very low[1,2,3]	Appendix 14c (ii) (5.3)
	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 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 = 119	0.12 [-0.24, 0.48]	Very low[1,2,3]	Appendix 14c (ii) (5.4)
	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)

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 prolonged QT)	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)
	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	Serious[3]	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 (4-6 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) (5.25)
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 = 149	0.47 [0.27, 0.84]*	Very low[1,2,3]	Appendix 14c (ii) (5.26)
	FINDLING 2008A	Aripiprazole (30 mg per day)	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 202	1.76 [0.86, 3.63]	Very low[1,2,3]	Appendix 14c (ii) (5.26)

Note.[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.
*Favours 'higher dose'.
**Favours placebo.
[1] Serious 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	Imprecision	Other considerations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	SINGH 2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 98	0.72 [0.31, 1.13]*	Very low[1,2,3]	Appendix 14c (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)	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
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 to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.											

*Favours placebo.
[1] Serious 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.

Risperidone versus olanzapine: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	MOZES2006 SIKICH2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 2; N = 60	0.38 [-0.14, 0.89]	Very low[1,2,3]	Appendix 14c (ii) (7.1)
Positive symptoms (SMD)	MOZES2006 SIKICH2004	RCT	Serious[1]	Serious[4]	No serious indirectness	Serious[3]	Reporting bias[2]	K = 2; N = 60	0.38 [-0.13, 0.89]	Very low[1,2,3]	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	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
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. [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] 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] $I^2 \geq 50\%$, $p<.05$.

Risperidone versus olanzapine: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	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: SAS	SIKICH2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 35	0.09 [-0.58, 0.75]	Very low[1,2,3]	Appendix 14c (ii) (8.4)
Neurological: EPS (SAS) (RR)	MOZES2006	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 25	0.95 [0.50, 1.80]	Very low[1,2,3]	Appendix 14c (ii) (8.5)
Neurological: BARS	MOZES2006	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 25	3.25 [0.39, 27.15]	Very low[1,2,3]	Appendix 14c (ii) (8.6)
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	MOZES2006	RCT	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)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	MOZES2006 SIKICH2004	RCT	Serious[1]	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)

Note. [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.
*Favours olanzapine.
[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.

Risperidone versus haloperidol: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	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	-	-	-	-	-	-	-	-	-	-	-

Note. [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]Serious risk of bias (including unclear allocation concealment, unclear rater blinding procedures, trial registration could not 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] Sequence generation, analysis and selective outcome reporting not reported by KENNEDY2012.

Risperidone versus haloperidol: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	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	-0.40 [-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)
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia	-	-	-	-	-	-	-	-	-	-	-

(RR)											
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	YAO2003/ KENNEDY2012	RCT	Serious[1,4]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 42	0.12 [0.04, 0.37]*	Low [1,3,4]	Appendix 14c (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)	-	-	-	-	-	-	-	-	-	-	-
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 = 34	1.07 [0.53, 2.15]	Very low[1,2,3]	Appendix 14c (ii) (10.5)

Note. [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.
*Favours risperidone.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding procedures, trial registration could not be found).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Sequence generation, analysis and selective outcome reporting not reported by KENNEDY2012.

Risperidone versus chlorpromazine: post-treatment efficacy 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
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 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, unclear rater blinding).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Sequence generation, analysis and selective outcome reporting not reported by KENNEDY2012.

Risperidone versus chlorpromazine: 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)	-	-	-	-	-	-	-	-	-	-	-
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)	-	-	-	-	-	-	-	-	-	-	-
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)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Note. [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]Serious risk of bias (including unclear allocation concealment, unclear rater blinding).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Sequence generation, analysis and selective outcome reporting not reported by KENNEDY2012.

Olanzapine versus quetiapine: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	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 2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 20	0.60 [0.19, 1.86]	Very low[1,2,3]	Appendix 14c (ii) (13.1)
Remission	-	-	-	-	-	-	-	-	-	-	-

Note. [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] Serious risk of bias including unclear allocation concealment, open-label trial 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.

Olanzapine versus quetiapine: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	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)
Metabolic: BMI (SMD)	JENSEN 2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 20	0.51 [-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 2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 20	2.00 [0.21, 18.69]	Very low[1,2,3]	Appendix 14c (ii) (14.4)
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	JENSEN 2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 20	1.00 [0.34, 2.93]	Very low[1,2,3]	Appendix 14c (ii) (14.5)

Note. [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]Serious risk of bias (including unclear allocation concealment, open-label trial, 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.

Olanzapine versus haloperidol: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	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	-0.68 [-1.41, 0.05]	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	-	-	-	-	-	-	-	-	-	-	-

Note. [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] 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.
[3]OIS (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	Imprecision	Other considerations	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)

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	-0.73 [-1.46, -0.00]*	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)

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

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

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	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	-	-	-	-	-	-	-	-	-	-	-

Note. [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] 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.

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

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	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)

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)
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
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)

Note. [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] 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.

Aripiprazole 10 mg per day versus aripiprazole 30 mg per day: 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)	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	-	-	-	-	-	-	-	-	-	-	-

Note. [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.
*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.

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

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	FINDLING 2008A	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 196	-0.09 [-0.37, 0.19]	Very low[1,2,3]	Appendix 14c (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	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting 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)	-	-	-	-	-	-	-	-	-	-	-
Cardio: diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: sitting pulse	-	-	-	-	-	-	-	-	-	-	-

Cardio: standing pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	FINDLING 2008A	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 190	0.13 [-0.16, 0.41]	Very low[1,2,3]	Appendix 14c (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 14c (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 14c (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 14c (ii) (18.28)

Note. [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.
*Favours aripiprazole 10 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.

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

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
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	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
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	-	-	-	-	-	-	-	-	-	-	-

Note. [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]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.

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

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	HAAS 2009B	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 157	-0.44 -0.69, -0.19]*	Very low[1,2,3]	Appendix 14c (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)								K = 1; N = 157	0.74 [0.58, 0.96]*	Very low[1,2,3]	Appendix 14c (ii) (18.15)

Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (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	0.83 [0.50, 1.39]	Very low[1,2,3]	Appendix 14c (ii) (18.21)
Neurological: AIMS	HAAS 2009B	RCT	Serious[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 109	0.23 [-0.15, 0.61]	Very low[1,2,3]	Appendix 14c (ii) (18.17)
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)

Note. [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.
*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.

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

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	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	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note. [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.
*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	Inconsistency	Indirectness	Imprecision	Other considerations	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	-	-	-	-	-	-	-	-	-	-	-
Cardio: systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
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 2009	RCT	Serious[1]	Low	Low	Serious[3]	Reporting bias[2]	K = 1; N = 157	0.29 [0.10, 0.87]*	Very low[1,2,3]	Appendix 14c (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)

Note. [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.
*Favours 0.15-0.6 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.

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	Imprecision	Other considerations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	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	0.48 [0.09, 0.88]	Very low[1,2,3]	Appendix 14c (ii) (17.1)
	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	-0.23 [-0.63, 0.17]*	Very low[1,2,3]	Appendix 14c (ii) (20.1)
	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	0.25 [-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 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	-0.19 [-0.59, 0.22]	Very low [1,2,3]	Appendix 14c (ii) (20.2)
	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	0.31 [-0.08, 0.71]	Very low[1,2,3]	Appendix 14c (ii) (19.2)
Negative symptoms (SMD)	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	0.31 [-0.08, 0.71]	Very low[1,2,3]	Appendix 14c (ii) (17.3)
	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	-0.27 [-0.67, 0.13]*	Very low[1,2,3]	Appendix 14c (ii) (20.3)
	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	0.00 [-0.39, 0.39]	Very low[1,2,3]	Appendix 14c (ii) (19.3)
Global state (severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	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	0.18 [-0.21, 0.57]	Very low[1,2,3]	Appendix 14c (ii) (17.5)
	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	-0.03 [-0.43, 0.37]	Very low[1,2,3]	Appendix 14c (ii) (20.4)
	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 = 101	0.15 [-0.25, 0.54]	Very low[1,2,3]	Appendix 14c (ii) (19.4)
Mania	-	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-	
Psychosocial functioning (SMD)	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	0.76 [0.36, 1.16]	Very low[1,2,3]	Appendix 14c (ii) (17.6)
	SINGH 2011	3-6 mg per day versus 6-	RCT	Serious[1]	No serious risk of	No serious risk of	Serious[3]	Reporting bias[2]	K = 1; N = 95	-0.38 [-0.79, 0.02]*	Very low[1,2,3]	Appendix 14c (ii) (20.5)

		12 mg per day			inconsistency	indirectness						
	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	0.38 [-0.01, 0.78]	Very low[1,2,3]	Appendix 14c (ii) (19.5)
Social functioning	-	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-	-

Note. [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.
*Favours 3-6 mg per day.
[1]Serious risk of bias (study reports LOCF 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.

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	Imprecision	Other considerations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	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	-0.43 [-0.83, -0.04]*	Very low[1,2,3]	Appendix 14c (ii) (18.1)
	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	-0.14 [-0.54, 0.26]	Very low[1,2,3]	Appendix 14c (ii) (22.1)
	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	-0.59 [-0.99, -0.19]*	Very low[1,2,3]	Appendix 14c (ii) (21.1)
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	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	Not estimable (no events in either group)	Very low[1,2,3]	Appendix 14c (ii) (18.9)
	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	Not estimable (no events in either group)	Very low[1,2,3]	Appendix 14c (ii) (22.2)
	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	Not estimable (no events in either group)	Very low[1,2,3]	Appendix 14c (ii) (21.2)
Cardio: systolic 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)	-	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	-	-	-	-	-	-	-	-	-	-	-	-

Note. [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.
*Favours 1.5 mg per day
[1]Serious risk of bias (study reports LOCF 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.

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	Imprecision	Other considerations	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. [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.
*Favours clozapine.
[1]Downgraded 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).
[2]Serious risk of reporting bias .
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.[4]$I^2 \geq 50\%$, $p<.05$.

Clozapine versus another antipsychotic: post-treatment side effect outcomes

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

(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 of inconsistency	No serious risk of indirectness	Serious[3]	Reporting bias[2]	K = 1; N = 22	4.80 [1.30, 17.66]**	Very low[1,2,3]	Appendix 14c (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 [-0.23, 1.54]	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)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
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)

Note. [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.
*Favours olanzapine.
**Favours clozapine.
[1]Downgraded 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).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

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

Extractable metabolic side effect outcomes

Outcome or subgroup	Study ID	Comparison	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Studies/ number of participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight change kg (SMD)	CASTRO-FORNIELES 2008[1]	Quetiapine versus risperidone	OS	Serious[3]	No serious risk of inconsistency	No serious risk of indirectness	Serious[4]	Reporting bias[5]	K = 1; N = 46	-0.02 [-0.64, 0.60]	Very low[3,4,5]	Appendix 14c (iv) (1.1)
	CASTRO-FORNIELES 2008[1]	Quetiapine versus olanzapine	OS	Serious[3]	No serious risk of inconsistency	No serious risk of indirectness	Serious[4]	Reporting bias[5]	K = 1; N = 29	-0.96 [-1.73, -0.18]*	Very low[3,4,5]	Appendix 14c (iv) (1.2)
	CASTRO-FORNIELES 2008[1] CROCQ2007[2]	Olanzapine (SOT) versus risperidone	OS	Serious[3]	No serious risk of inconsistency	No serious risk of indirectness	Serious[4]	Reporting bias[5]	K = 2; N = 81	1.75 [0.30, 3.21]**	Very low[3,4,5]	Appendix 14c (iv) (1.3)
	CROCQ2007[2]	Olanzapine (ODT) versus risperidone	OS	Serious[3]	No serious risk of inconsistency	No serious risk of indirectness	Serious[4]	Reporting bias[5]	K = ; N = 42	1.02 [0.36, 1.69]**	Very low[3,4,5]	Appendix 14c (iv) (1.4)
	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 = ; N = 26	-1.62 [-2.54, -0.69]***	Very low[3,4,5]	Appendix 14c (iv) (1.5)
Metabolic: BMI change (SMD)	CROCQ2007[2]	Olanzapine (SOT) versus risperidone	OS	Serious[3]	No serious risk of inconsistency	No serious risk of indirectness	Serious[4]	Reporting bias[5]	K = 1; N = 36	2.17 [1.27, 3.08]**	Very low[3,4,5]	Appendix 14c (iv) (2.1)
	CROCQ2007[2]	Olanzapine (ODT) versus risperidone	OS	Serious[3]	No serious risk of inconsistency	No serious risk of indirectness	Serious[4]	Reporting bias[5]	K = ; N = 42	0.93 [0.27, 1.59]**	Very low[3,4,5]	Appendix 14c (iv) (2.2)

	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)
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												

Note. [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.
*Favours quetiapine
**Favours risperidone
***Favours olanzapine (ODT)
[1] 26 weeks' treatment
[2] 12 weeks' treatment
[3] Serious risk of bias (including: observational study)
[4] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[5] Serious risk of reporting bias

Extractable neurological side effect outcomes

Outcome or subgroup	STUDY ID	Comparison	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Studies/ number of participants	Effect estimate (SMD or RR)	Heterogeneity	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]	Olanzapine (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)	-	-	-	-	-	-	-	-	-	-	-	-	-

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