APPENDIX 17: CLINICAL AND ECONOMIC EVIDENCE PROFILES

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1. CLINICAL EVIDENCE PROFILES

APPENDIX 17a: RECOGNITION AND AT RISK MENTAL STATES OF PSYCHOSIS IN CHILDREN AND YOUNG PEOPLE EVIDENCE PROFILES:

Olanzapine versus placebo at 52 weeks post-treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	MCGLASHAN 2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=59	-0.12 [-0.63, 0.39]	Very low[1,2,3]	Appendix 14a (1.1)
Symptoms: Positive (SMD)	MCGLASHAN 2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=59	-0.40 [-0.91, 0.12]	Very low[1,2,3]	Appendix 14a (1.2)
Symptoms: Negative (SMD)	MCGLASHAN 2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=59	0.05 [-0.46, 0.56]	Very low[1,2,3]	Appendix 14a (1.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	MCGLASHAN 2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=59	-0.17 [-0.68, 0.34]	Very low[1,2,3]	Appendix 14a (1.4)
Depression (SMD)	MCGLASHAN 2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=59	0.32 [-0.19, 0.83]	Very low[1,2,3]	Appendix 14a (1.5)
Mania (SMD)	MCGLASHAN 2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=59	-0.15 [-0.66, 0.36]	Very low[1,2,3]	Appendix 14a (1.6)
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	MCGLASHAN 2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=59	-0.16 [-0.67, 0.35]	Very low[1,2,3]	Appendix 14a (1.7)

Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Sensitivity analysis: Transition to Psychosis (assuming drop outs transitioned; RR)	MCGLASHAN 2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=60	0.43 [0.17, 1.08]	Very low[1,2,3]	Appendix 14a (1.8)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment and missing data).
[2]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Olanzapine versus placebo at 52 weeks post-treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight gain (kg)	MCGLASHAN2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	1.18 [0.62, 1.73]*	Very low[1,2,3]	Appendix 14a (3.1)
Metabolic: BMI	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT Interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: Systolic BP	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Sitting Pulse (beats/min; SMD)	MCGLASHAN2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=60	0.61 [0.08, 1.13]*	Very low[1,2,3]	Appendix 14a (3.2)
Cardio: Standing Pulse (beats/min; SMD)	MCGLASHAN2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	0.37 [-0.15, 0.88]	Very low[1,2,3]	Appendix 14a (3.3)
Hormonal: Prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-

Neurological: Extrapyramidal Symptoms (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	MCGLASHAN2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=60	1.59 [0.88, 2.88]	Very low[1,2,3]	Appendix 14.a(2.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours placebo
[1]Serious risk of bias (including unclear sequence generation and allocation concealment and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Olanzapine versus placebo at 104 weeks follow-up (change scores from post-treatment until follow-up when no treatment was received)

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Transition to Psychosis (RR)	-	-	-	-	-	-	-	-	-	-	-

Olanzapine versus placebo at 104 weeks follow-up (change scores from post-treatment until follow-up when no treatment was received)

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies/ participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight gain (kg)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: BMI	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT Interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: Systolic BP	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Sitting Pulse (beats/min; SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse (beats/min; SMD)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-

Neurological: Extrapyramidal Symptoms (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	MCGLASHAN2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K= 1, N=60	0.98 [0.71, 1.35]	Very low[1,2,3]	Appendix 14a (4.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Risperidone plus CBT versus supportive at post-treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=101	-0.13 [-0.53, 0.26]	Very low[1,2,3]	Appendix 14a (5.1)
Symptoms: Positive (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=2, N=101	-0.16 [-0.55, 0.23]	Very low[1,2,3]	Appendix 14a (5.2)
Symptoms: Negative (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=2, N=101	-0.03 [-0.59, 0.52]	Very low[1,2,3]	Appendix 14a (5.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity; SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	-0.32 [-0.83, 0.20]	Very low[1,2,3]	Appendix 14a (5.4)
Mania (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	-0.20 [-0.71, 0.32]	Very low[1,2,3]	Appendix 14a (5.5)
Anxiety (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	-0.15 [-0.66, 0.36]	Very low[1,2,3]	Appendix 14a (5.6)
Psychosocial Functioning (SMD)	PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=43	-0.12 [-0.73, 0.49]	Very low[1,2,3]	Appendix 14a (5.7)
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=2, N=102	-0.08 [-0.47, 0.31]	Very low[1,2,3]	Appendix 14a (5.8)
Sensitivity analysis: Transition to Psychosis (assuming drop outs transitioned; RR)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=2, N=130	0.48 [0.17, 1.32]	Very low[1,2,3]	Appendix 14a (5.9)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.

[1]Seriousrisk of bias (including unclear sequence generation, allocation concealment, participants and providers unblind to psychological intervention, trial registration not found, uneven sample sizes and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Risperidone plus CBT versus supportive at post-treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight gain (kg)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: BMI	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT Interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: Systolic BP	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Sitting Pulse (beats/min; SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse (beats/min; SMD)	-	-	-	-	-	-	-	-	-	-	-

Hormonal: Prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Symptoms (RR)	PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=21	0.55 [0.13, 2.38]	Very low[1,2,3]	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=2, N=130	1.16 [0.60, 2.25]	Very low[1,2,3]	Appendix 14a (6.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Seriousrisk of bias (including unclear sequence generation, allocation concealment, participants and providers unblind to psychological intervention, trial registration not found, uneven sample sizes and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Risperidone plus CBT versus supportive at 52 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	0.21 [-0.30, 0.73]	Very low[1,2,3]	Appendix 14a (7.1)
Symptoms: Positive (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	0.21 [-0.30, 0.72]	Very low[1,2,3]	Appendix 14a (7.2)
Symptoms: Negative (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	-0.06 [-0.57, 0.45]	Very low[1,2,3]	Appendix 14a (7.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity; SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	0.14 [-0.37, 0.65]	Very low[1,2,3]	Appendix 14a (7.4)
Mania (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=58	0.00 [-0.52, 0.52]	Very low[1,2,3]	Appendix 14a (7.5)
Anxiety (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	0.06 [-0.45, 0.57]	Very low[1,2,3]	Appendix 14a (7.6)
Psychosocial Functioning (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	0.00 [-0.51, 0.51]	Very low[1,2,3]	Appendix 14a (7.7)
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	0.04 [-0.47, 0.55]	Very low[1,2,3]	Appendix 14a (7.8)
Sensitivity analysis: Transition to Psychosis (assuming drop outs transitioned; RR)	MCGORRY2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	0.54 [0.23, 1.30]	Very low[1,2,3]	Appendix 14a (7.9)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Seriousrisk of bias (including unclear sequence generation, allocation concealment, participants, providers and raters unblind to psychological intervention, trial registration could not be found and missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Risperidone plus CBT versus supportive at 52 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other conside rations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight gain (kg)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: BMI	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT Interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: Systolic BP	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Sitting Pulse (beats/min; SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse (beats/min; SMD)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Symptoms (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-

Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Risperidone plus CBT versus supportive at 156-208 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=41	-0.33 [-0.96, 0.29]	Very low[1,2,3]	Appendix 14a (8.1)
Symptoms: Positive (SMD)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=41	-0.04 [-0.66, 0.58]	Very low[1,2,3]	Appendix 14a (8.2)
Symptoms: Negative (SMD)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=41	-0.24 [-0.87, 0.38]	Very low[1,2,3]	Appendix 14a (8.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity; SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=41	0.23 [-0.39, 0.86]	Very low[1,2,3]	Appendix 14a (8.4)
Mania (SMD)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=41	-0.36 [-0.98, 0.27]	Very low[1,2,3]	Appendix 14a (8.5)
Anxiety (SMD)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=41	0.14 [-0.49, 0.76]	Very low[1,2,3]	Appendix 14a (8.6)
Psychosocial Functioning (SMD)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=41	-0.15 [-0.77, 0.47]	Very low[1,2,3]	Appendix 14a (8.7)
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=41	-0.08 [-0.71, 0.54]	very low[1,2,3]	Appendix 14a (8.8)
Sensitivity analysis: Transition to Psychosis (assuming drop outs transitioned; RR)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	0.75 [0.39, 1.46]	very low[1,2,3]	Appendix 14a (8.9)
Number of participants requiring hospitalisation (RR)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=41	0.51 [0.19, 1.33]	very low[1,2,3]	Appendix 14a (8.10)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Seriousrisk of bias (including unclear sequence generation, allocation concealment, participants, providers and raters unblind to psychological intervention, trial registration could not be found and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Risperidone plus CBT versus supportive at 156-208 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies/ participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight gain (kg)	-							-	-	-	-
Metabolic: BMI	-							-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl	-							-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl	-							-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-							-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl	-							-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl	-							-	-	-	-
Metabolic: Fasting Triglycerides	-							-	-	-	-
Cardio: QT Interval	-							-	-	-	-
Cardio: Systolic BP	-							-	-	-	-
Cardio: Diastolic BP	-							-	-	-	-
Cardio: Tachycardia (RR)	-							-	-	-	-
Cardio: Sitting Pulse (beats/min; SMD)	-							-	-	-	-
Cardio: Standing Pulse (beats/min; SMD)	-							-	-	-	-

Hormonal: Prolactin	-							-	-	-	-
Hormonal: Insulin	-							-	-	-	-
Neurological: Extrapyramidal Symptoms (RR)	-							-	-	-	-
Neurological: AIMS	-							-	-	-	-
Neurological: SAS	-							-	-	-	-
Neurological: BARS	-							-	-	-	-
Neurological: Parkinsonism (RR)	-							-	-	-	-
Neurological: Tremor (RR)	-							-	-	-	-
Neurological: Akathesia (RR)	-							-	-	-	-
Neurological: Dystonia (RR)	-							-	-	-	-
Neurological: Dyskenesia (RR)	-							-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-							-	-	-	-
Mortality (RR)	-							-	-	-	-
Leaving the Study Early for Any Reason (RR)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=59	0.57 [0.26, 1.28]	Very low[1,2,3]	Appendix 14a (9.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Seriousrisk of bias (including unclear sequence generation, allocation concealment, participants, providers and raters unblind to psychological intervention, trial registration could not be found and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Risperidone plus CBT versus placebo plus CBT at 52 weeks post-treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	PHILLIPS 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=51	-0.24 [-0.79, 0.31]	very low[1,2,3]	Appendix 14a (10.1)
Symptoms: Positive (SMD)	PHILLIPS 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=51	-0.07 [-0.62, 0.48]	very low[1,2,3]	Appendix 14a (10.2)
Symptoms: Negative (SMD)	PHILLIPS 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=51	0.12 [-0.43, 0.67]	very low[1,2,3]	Appendix 14a (10.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity; SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	PHILLIPS 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=52	0.24 [-0.31, 0.78]	very low[1,2,3]	Appendix 14a (10.4)
Social Functioning (SMD)	-							-	-	-	-
Quality of life (SMD)	PHILLIPS 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=51	-0.23 [-0.78, 0.33]	very low[1,2,3]	Appendix 14a (10.5)
Sensitivity analysis: Transition to psychosis (assuming drop outs transitioned; RR)	PHILLIPS 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=87	1.02 [0.39, 2.67]	very low[1,2,3]	Appendix 14a (10.6)

Note
Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Seriousrisk of bias (including unclear sequence generation, allocation concealment, participants, providers and raters unblind to psychological intervention, trial registration could not be found and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Risperidone plus CBT versus placebo plus CBT at 52 weeks post-treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight gain (kg)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: BMI	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT Interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: Systolic BP	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Sitting Pulse (beats/min; SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse (beats/min; SMD)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Prolactin	-	-	-	-	-	-	-	-	-	-	-

Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Symptoms (RR)	PHILLIPS 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=23	0.87 [0.18, 4.24]	Very low[1,2,3]	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	PHILLIPS 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=87	1.09 [0.62, 1.92]	Very low[1,2,3]	Appendix 14a (11.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Seriousrisk of bias (including unclear sequence generation, allocation concealment, participants and providers unblind to psychological intervention, trial registration not found, uneven sample sizes and available case analysis).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Omega-3 fatty acids versus placebo at 12 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity; SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Transition to Psychosis (RR)	AMMINGER 2010/MARS HALL2011	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1, N=76	0.13 [0.02, 0.95]*[1]	Low[2,3]	Appendix 14a (12.1)
Leaving the Study Early for Any Reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours omega-3 fatty acids
[1]Seriousrisk of bias (including dropout not reported therefore, an available case analysis has been used)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Omega-3 fatty acids versus placebo at 52 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	AMMINGER 2010	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	K=1, N=81	-1.26 [-1.74, 0.78]	Low[1, 2]	Appendix 14a (13.1)
Symptoms: Positive (SMD)	AMMINGER 2010	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	K=1, N=81	-2.08 [-2.63, -1.54]*	Low[1, 2]	Appendix 14a (13.2)
Symptoms: Negative (SMD)	AMMINGER 2010	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	K=1, N=81	-2.22 [-2.77, -1.66]*	Low[1, 2]	Appendix 14a (13.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	AMMINGER 2010	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	K=1, N=81	-0.56 [-1.01, -0.12]*	Low[1, 2]	Appendix 14a (13.4)
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	AMMINGER 2010	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	K=1, N=81	-1.28 [-1.76, -0.80]*	Low[1, 2]	Appendix 14a (13.5)
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Sensitivity analysis: Transition to Psychosis	AMMINGER 2010	RCT	No serious	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	K=1, N=81	0.18 [0.04, 0.75]*	Low[1, 2]	Appendix 14a (13.6)

(assuming drop outs transitioned; RR)			ROB								
Leaving the Study Early for Any Reason (RR)	AMMINGER 2010	RCT	No serious ROB	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	K=1, N=81	1.46 (0.26 to 8.30)	Low[1, 2]	Appendix 14a (14.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours omega-3 fatty acids
[1] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[2]Serious risk of reporting bias

CBT versus supportive counselling at post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	ADDINGTON2011, MORRISON2004, MORRISON2011, PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=4, N=350	-0.00 [-0.21, 0.21]	Low[1, 2]	Appendix 14a (15.1)
Symptoms: Positive (SMD)	ADDINGTON2011, MORRISON2004, PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=3, N=154	-0.15 [-0.48, 0.17]	Low[1, 2]	Appendix 14a (15.2)
Symptoms: Negative (SMD)	ADDINGTON2011, MORRISON2004, PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=3, N=154	0.10 [-0.22, 0.42]	Low[1, 2]	Appendix 14a (15.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-							-	-	-	-
Depression (SMD)	ADDINGTON2011, MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=2, N=236	0.04 [-0.21, 0.30]	Low[1, 2]	Appendix 14a (15.4)
Mania (SMD)	-							-	-	-	-
Anxiety (social; SMD)	MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N= 172	0.01 [-0.28, 0.31]	Low[1,2]	Appendix 14a (15.5)
Psychosocial Functioning (SMD)	ADDINGTON2011, MORRISON2011, PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=3, N= 291	0.02 [-0.22, 0.26]	Low[1,2]	Appendix 14a (15.6)
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	MORRISON2011, PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=2, N= 185	0.02 [-0.27, 0.31]	Low[1, 2]	Appendix 14a (15.7)
Sensitivity analysis: Transition to Psychosis	ADDINGTON2011*, MORRISON2004, MORRISON2011, PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	K=4, N= 469	0.62 [0.31, 1.22]	Moderate[1]	Appendix 14a (15.8)

(assuming drop outs transitioned; RR)											
Leaving the Study Early for Any Reason (RR)	ADDINGTON2011, MORRISON2004, MORRISON2011, PHILLIPS2009	RCT	Serious [1]	Serious[3]	No serious indirectness	Serious[2]	None	K=4, N= 469	0.71 [0.38, 1.34]	Low[1,3]	Appendix 14a (16.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* 15 weeks during treatment
[1]Serious risk of bias (including unclear sequence generation, participants, providers and outcome assessors unblind, trial registration could not be found, missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3] $I^2 \geq 50\%$, $p<.05$

CBT versus supportive counselling at 52 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	ADDINGTON2011 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=2, N=239	-0.30 [-0.56, -0.05]*	Low[1, 2]	Appendix 14a (17.1)
Symptoms: Positive (SMD)	ADDINGTON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=51	-0.27 [-0.82, 0.29]	Low[1, 2]	Appendix 14a (17.2)
Symptoms: Negative (SMD)	ADDINGTON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=51	0.06 [-0.49, 0.61]	Low[1, 2]	Appendix 14a (17.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	ADDINGTON2011 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=2, N=234	-0.01 [-0.26, 0.25]	Low[1, 2]	Appendix 14a (17.4)
Mania (SMD)	-							-	-	-	-
Anxiety (social; SMD)	MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N= 188	0.15 [-0.15, 0.44]	Low[1, 2]	Appendix 14a (17.5)
Psychosocial Functioning (SMD)	ADDINGTON2011 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=2, N=240	-0.10 [-0.36, 0.15]	Low[1, 2]	Appendix 14a (17.6)
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N= 134	-0.10 [-0.44, 0.24]	Low[1, 2]	Appendix 14a (17.7)
Transition to Psychosis (RR)	ADDINGTON2011 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=2, N= 339	0.55 [0.23, 1.29]	Low[1, 2]	Appendix 14a (17.8)
Leaving the Study Early for Any Reason (RR)	ADDINGTON2011 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=2, N=339	0.98 [0.74, 1.31]	Low[1, 2]	Appendix 14a (18.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.

*Favours CBT
[1]Serious risk of bias (including unclear sequence generation, participants, providers and outcome assessors unblind, trial registration could not be found, missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

CBT versus supportive counselling ≥ 78 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	ADDINGTON2011 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=2, N= 116	-0.17 [-0.53, 0.20]	Low[1,2]	Appendix 14a (19.1)
Symptoms: Positive (SMD)	ADDINGTON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=54	0.02 [-0.53, 0.57]	Low[1,2]	Appendix 14a (19.2)
Symptoms: Negative (SMD)	ADDINGTON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=54	-0.10 [-0.65, 0.45]	Low[1,2]	Appendix 14a (19.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	ADDINGTON2011 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=2, N= 112	-0.05 [-0.46, 0.37]	Low[1,2]	Appendix 14a (19.4)
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (social; SMD)	MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N= 58	-0.46 [-0.99, 0.06]	Low[1,2]	Appendix 14a (19.5)
Psychosocial Functioning (SMD)	ADDINGTON2011 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=2, N= 116	-0.03 [-0.45, 0.40]	Low[1,2]	Appendix 14a (19.6)
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N= 48	0.40 [-0.17, 0.98]	Low[1,2]	Appendix 14a (19.7)
Sensitivity analysis: Transition to Psychosis (assuming drop outs transitioned; RR)	ADDINGTON2011 MORRISON2004 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=3, N= 397	0.88 [0.70, 1.09]	Low[1,2]	Appendix 14a (19.8)
Leaving the Study Early for Any	ADDINGTON2011 MORRISON2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=3, N=397	1.01 [0.79, 1.28]	Low[1,2]	Appendix 14a (20.1)

Reason (RR)	MORRISON2011										

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including unclear sequence generation, participants, providers and outcome assessors unblind, trial registration could not be found, missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Integrated psychotherapy versus supportive counselling at 52 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-							-	-	-	-
Symptoms: Positive (SMD)	-							-	-	-	-
Symptoms: Negative (SMD)	-							-	-	-	-
Symptoms: General (SMD)	-							-	-	-	-
Global State (Severity) (SMD)	-							-	-	-	-
Depression (SMD)	-							-	-	-	-
Mania (SMD)	-							-	-	-	-
Anxiety (SMD)	-							-	-	-	-
Psychosocial Functioning (SMD)	-							-	-	-	-
Social Functioning (SMD)	-							-	-	-	-
Quality of Life (SMD)	-							-	-	-	-
Transition to Psychosis (RR)	BECHDOLF2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=113	0.20 [0.05, 0.86]*	Very low[1,2,3]	Appendix 14a (21.1)
Sensitivity analysis: Transition to Psychosis (assuming drop outs transitioned; RR)	BECHDOLF2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=128	0.67 [0.34, 1.31]	Very low[1,2,3]	Appendix 14a (21.2)

Leaving the Study Early for Any Reason (RR)	BECHDOLF2012	RCT	Serious [1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=128	1.55 [0.68, 3.53]	Very low[1,2,3]	Appendix 14a (22.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours IPS
[1] Serious risk of bias (participants, providers and outcome assessors unblind, missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of indirectness (participants classified as in the early initial prodromal state as opposed to a high risk mental state and transition is defined as the development of either attenuated/transient symptoms or a DSM-IV psychotic disorder)

Integrated psychotherapy versus supportive counselling at 104 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Transition to Psychosis (RR)	BECHDOLF2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=113	0.34 [0.12, 0.97]*	Very low[1,2,3]	Appendix 14a (23.1)
Sensitivity analysis: Transition to Psychosis (assuming drop outs transitioned; RR)	BECHDOLF2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=128	0.71 [0.38, 1.31]	Very low[1,2,3]	Appendix 14a (23.2)

Leaving the Study Early for Any Reason (RR)	BECHDOLF2012	RCT	Serious [1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=128	0.95 [0.61, 1.49]	Very low[1,2,3]	Appendix 14a (24.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours IPS
[1] Serious risk of bias (participants, providers and outcome assessors unblind, missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of indirectness (participants classified as in the early initial prodromal state as opposed to a high risk mental state and transition is defined as the development of either attenuated/transient symptoms or a DSM-IV psychotic disorder)

APPENDIX 17b: PSYCHOLOGICAL AND PSYCHOSOCIAL INTERVENTIONS: EVIDENCE PROFILES

CBT versus TAU at 26 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	JACKSON2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=46	-0.29 [-0.87, 0.30]	Low[1,2]	Appendix 14b (1.1)
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Relapse	-	-	-	-	-	-	-	-	-	-	-
Remission (RR)	-	-	-	-	-	-	-	-	-	-	-

Mortality (including suicide) (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	JACKSON2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=66	1.94 [0.85, 4.43]	Low[1,2]	Appendix 14b (1.2)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear allocation concealment, only raters were blind, trial registration not found and missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

CBT versus TAU at 26 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	JACKSON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=46	-0.05 [-0.65, 0.54]	Low[1,2]	Appendix 14b (2.1)
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Relapse	-	-	-	-	-	-	-	-	-	-	-
Remission (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (including suicide) (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	JACKSON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=46	1.77 [0.89, 3.52]	Low[1,2]	Appendix 14b (2.2)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear allocation concealment, only raters were blind, trial registration not found and missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

CBT versus EPPIC TAU at 14 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	JACKSON 2008	-	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=62	-0.05 [-0.55, 0.45]	Very low[1,2,3]	Appendix 14b (3.1)
Symptoms: Negative (SMD)	JACKSON 2008	-	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=62	-0.46 [-0.96, 0.05]	Very low[1,2,3]	Appendix 14b (3.2)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	JACKSON 2008	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=62	-0.40 [-0.90, 0.11]	Very low[1,2,3]	Appendix 14b (3.3)
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Relapse	-	-	-	-	-	-	-	-	-	-	-
Remission (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (including suicide) (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	JACKSON 2008	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=62	0.57 [0.19, 1.76]	Very low[1,2,3]	Appendix 14b (3.4)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear allocation concealment, only raters were blind, trial registration not found)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of indirectness as 21% of participants had bipolar and 8.1% of participants were receiving ECT

CBT versus EPPIC TAU at 52 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	JACKSON 2008	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=62	-0.08 [-0.58, 0.42]	Very low[1,2,3]	Appendix 14b (4.1)
Symptoms: Negative (SMD)	JACKSON 2008	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=62	-0.37 [-0.87, 0.13]	Very low[1,2,3]	Appendix 14b (4.2)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	JACKSON 2008	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=62	-0.08 [-0.58, 0.41]	Very low[1,2,3]	Appendix 14b (4.3)
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Relapse (number of participants requiring hospitalisation)(RR)	JACKSON 2008	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=57	5.00 [0.25, 100.08]	Very low[1,2,3]	Appendix 14b (4.4)
Remission (RR)	-	-	-	-	-	-	-	-	-	-	-
Suicide (number of participants; assuming drop outs did not commit suicide) (RR)	JACKSON 2008	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=62	1.35 [0.65, 2.80]	Very low[1,2,3]	Appendix 14b (4.5)
Leaving the Study Early for Any Reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear allocation concealment, only raters were blind, trial registration not found)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of indirectness as 21% of participants had bipolar and 8.1% of participants were receiving ECT

CBT versus EPPIC TAU in acutely suicidal patients at 10 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	POWER 2003	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=42	-0.04 [-0.54, 0.47]	Very low[1,2,3]	Appendix 14b (5.1)
Relapse	-	-	-	-	-	-	-	-	-	-	-
Remission (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (including suicide) (RR)	POWER 2003	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=56	0.81 [0.05, 12.26]	Very low[1,2,3]	Appendix 14b (6.2)
Leaving the Study Early for Any Reason (RR)	POWER 2003	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=56	-2.02 [0.72, 5.66]	Very low[1,2,3]	Appendix 14b (5.2)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear sequence generation and allocation concealment, only raters were blind, trial registration not found and missing data analysis not reported).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of indirectness as participants were acutely suicidal

CBT versus EPPIC TAU in acutely suicidal patients at 36 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	POWER 2003	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=33	0.03 [-0.66, 0.71]	Very low[1,2,3]	Appendix 14b (6.1)
Relapse	-	-	-	-	-	-	-	-	-	-	-
Remission (RR)	-	-	-	-	-	-	-	-	-	-	-
Suicide (number of participants; assuming drop outs did not commit suicide) (RR)	POWER 2003	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=56	0.81 [0.05, 12.26]	Very low[1,2,3]	Appendix 14b (6.2)
Leaving the Study Early for Any Reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear sequence generation and allocation concealment, only raters were blind, trial registration not found and missing data analysis not reported).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of indirectness as participants were acutely suicidal

CBT + clozapine versus clozapine in participants who have not adequately responded to treatment at 12 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=25	0.19 [-0.60, 0.98]	Low[1, 2]	Appendix 14b (7.1)
Symptoms: Negative (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=25	-0.30 [-1.09, 0.50]	Low[1, 2]	Appendix 14b (7.2)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=25	0.00 [-0.79, 0.79]	Low[1, 2]	Appendix 14b (7.3)
Depression (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=25	0.56 [-0.25, 1.37]	Low[1, 2]	Appendix 14b (7.4)
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	0.18 [-0.61, 0.97]	Low[1, 2]	Appendix 14b (7.5)
Quality of life (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	-0.04 [-0.83, 0.75]	Low[1, 2]	Appendix 14b (7.6)
Relapse	-	-	-	-	-	-	-	-	-	-	-
Remission (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (including suicide) (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early	-	-	-	-	-	-	-	-	-	-	-

for Any Reason (RR)											

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear sequence generation & allocation concealment, single blind trial but unclear if it is providers, participants or raters who were blind, trial registration not found and missing data not reported, 64.3% of clozapine only group were male compared to 90.9% of clozapine+CBT group and the average daily dose of clozapine was 44.8 mg/day higher in the clozapine only group than the clozapine+CBT group).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Full evidence profile of outcomes for CBT + clozapine versus clozapine in participants who have not adequately responded to treatment at 24 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	-0.24 [-1.03, 0.55]	Low[1, 2]	Appendix 14b (8.1)
Symptoms: Negative (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	-0.28 [-1.07, 0.51]	Low[1, 2]	Appendix 14b (8.2)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	0.12 [-0.67, 0.91]	Low[1, 2]	Appendix 14b (8.3)
Depression (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	0.62 [-0.19, 1.43]	Low[1, 2]	Appendix 14b (8.4)
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	-0.15 [-0.94, 0.64]	Low[1, 2]	Appendix 14b (8.5)
Quality of life (SMD)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	-0.56 [-1.36, 0.25]	Low[1, 2]	Appendix 14b (8.6)
Relapse	-	-	-	-	-	-	-	-	-	-	-
Sensitivity analysis: Remission (number of participants: assuming drop outs did not achieve remission) (RR)	EDWARDS 2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	1.09 [0.51, 2.31]	Low[1, 2]	Appendix 14b (8.7)

Mortality (including suicide) (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear sequence generation & allocation concealment, single blind trial but unclear if it is providers, participants or raters who were blind, trial registration not found and missing data not reported, 64.3% of clozapine only group were male compared to 90.9% of clozapine+CBT group and the average daily dose of clozapine was 44.8 mg/day higher in the clozapine only group than the clozapine+CBT group).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

CBT (individual) versus CBT (family) at 52 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Sensitivity analysis: Relapse (number of participants: assuming drop outs relapsed) (RR)	LINZEN 1996	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=76	0.95 [0.34, 2.68]	low[1,2]	Appendix 14b (9.1)
Remission (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (including suicide) (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear sequence generation and allocation concealment, only raters were blind, trial registration not found, and missing data analysis was not reported)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

CBT (individual & family) versus EPPIC TAU at 30.33 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	GLEESON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K= 1, N=63	-0.08 [-0.57, 0.42]	Low[1,2]	Appendix 14b (10.1)
Symptoms: Positive (SMD)	GLEESON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K= 1, N=63	-0.28 [-0.78, 0.22]	Low[1,2]	Appendix 14b (10.2)
Symptoms: Negative (SMD)	GLEESON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K= 1, N=63	-0.03 [-0.52, 0.47]	Low[1,2]	Appendix 14b (10.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	GLEESON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K= 1, N=63	-0.24 [-0.73, 0.26]	Low[1,2]	Appendix 14b (10.4)
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	GLEESON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K= 1, N=63	0.06 [-0.43, 0.56]	Low[1,2]	Appendix 14b (10.6)
Quality of Life (SMD)	GLEESON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K= 1, N=63	0.00 [-0.49, 0.49]	Low[1,2]	Appendix 14b (10.5)
Relapse (time in days)	GLEESON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K= 1, N=76	-3.26 [-3.96, -2.56]*	Low[1,2]	Appendix 14b (10.7)
Sensitivity analysis: Relapse (number of participants: assuming drop outs relapsed) (RR)	GLEESON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K= 1, N=82	0.45 [0.17, 1.19]	Low[1,2]	Appendix 14b (10.8)
Remission (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (including suicide) (RR)	-	-	-	-	-	-	-	-	-	-	-

Leaving the Study Early for Any Reason (RR)	GLEESON 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K= 1, N=82	1.40 [0.48, 4.05]	Low[1,2]	Appendix 14b (10.9)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours family therapy
[1] Serious risk of bias (only raters were blind and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Any psychological intervention in addition to EPPIC TAU versus EPPIC TAU at post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	EDWARDS2012 GLEESON2009 JACKSON2008	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=3, N=150	-0.11 [-0.43, 0.21]	Very low[1,2,3]	Appendix 14b (11.1)
Symptoms: Negative (SMD)	EDWARDS2012 GLEESON2009 JACKSON2008	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=3, N=150	-0.25 [-0.57, 0.08]	Very low[1,2,3]	Appendix 14b (11.2)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	EDWARDS2012 GLEESON2009	RCT	Serious[1]	Serious[4]	No serious indirectness	Serious[2]	None	K=2, N=63	0.10 [-0.68, 0.87]	Very low[1,2,4]	Appendix 14b (11.3)
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	GLEESON2009 JACKSON2008	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=2, N=125	-0.17 [-0.61, 0.28]	Very low[1,2,3]	Appendix 14b (11.5)
Quality of Life (SMD)	GLEESON2009 POWER2003	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=2, N=123	-0.02 [-0.37, 0.34]	Very low[1,2,3]	Appendix 14b (11.4)
Relapse	-	-	-	-	-	-	-	-	-	-	-
Remission (RR)	-	-	-	-	-	-	-	-	-	-	-
Suicide (number of participants; assuming drop outs did not commit suicide) (RR)	JACKSON2008 POWER2003	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=2, N=104	2.06 [0.28, 15.34]	Very low[1,2,3]	Appendix 14b (11.6)

Leaving the Study Early for Any Reason (RR)	GLEESON2009 JACKSON2008	RCT	Serious[1]	Serious[4]	Serious[3]	Serious[2]	None	K=2, N=144	0.91 [0.38, 2.19]	Very low[1,2,3,4]	Appendix 14b (11.7)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours family therapy
[1] Serious risk of bias (including unclear sequence generation & allocation concealment, unblinded, trial registration not found, missing data, 64.3% of clozapine only group were male compared to 90.9% of clozapine+CBT group and the average daily dose of clozapine was 44.8 mg/day. More serious in the clozapine only group than the clozapine+CBT group).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness (including acutely suicidal participants, participants with bipolar and participants receiving ECT).
[4] $I^2 \geq 50\%$, $p<.05$

APPENDIX 17ci: INITIAL TREATMENT WITH ANTIPSYCHOTIC MEDICATION: EVIDENCE PROFILES

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with olanzapine versus quetiapine as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (1.7)
Psychosocial Functioning	-	-	-	-	-	-	-	-	-	-	-
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB=risk of bias, RR = Relative risk; SMD = Standardised mean difference.
* Favours olanzapine
[1] Serious risk of bias (including sequence generation & allocation concealment; one open label trial (no blinding) or unclear blinding; errors in reporting of number of included participants; errors in reporting of outcome data across publications; one analysis of a modified intent-to-treat population; incomplete list of outcomes reported on trial registry)
[2] Optimal information size (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).

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with olanzapine versus quetiapine as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight (RR)	ARANGO2009 McEVOY2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=2; N=65	2.05 [1.41, 2.97]**	Very low[1,2,3,4]	Appendix 14ci (2.1)
Metabolic: Weight kg (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 14ci (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 14ci (2.3)
Metabolic: Fasting Serum Glucose Level mg/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 14ci (2.4)
Metabolic: Fasting Total Cholesterol mg/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 14ci (2.5)
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	No serious inconsistency	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/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 14ci (2.6)
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (2.11)
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: 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 14ci (2.12)
Neurological: Akathesia (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 14ci (2.13)
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (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=203	0.97 [0.83, 1.13]	Very low[1,2,3,4]	Appendix 14ci (2.14)

Note
ROB=risk of bias, RR = Relative risk; SMD = Standardised mean difference
* Favours olanzapine
**Favours quetiapine
[1]Serious risk of bias (including: sequence generation & allocation concealment; one open label trial (no blinding) or unclear blinding; errors in reporting of number of included participants; errors in reporting of outcome data across publications; one analysis of a modified intent-to-treat population; incomplete list of outcomes reported on trial registry)
[2] Optimal information size (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).

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with Risperidone versus quetiapine as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	McEVOY2007	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1; N=81	-0.28 [-0.72, 0.16]	Very low[1,2,3,4]	Appendix 14ci (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 14ci (3.2)
Positive Symptoms	McEVOY2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=81	-0.24 [-0.68, 0.20]	Very low[1,2,3,4]	Appendix 14ci (3.3)
Negative Symptoms	McEVOY2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=81	-0.39 [-0.83, 0.05]	Very low[1,2,3,4]	Appendix 14ci (3.4)
Global State (Severity) (SMD)	McEVOY2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=81	-0.14 [-0.58, 0.30]	Very low[1,2,3,4]	Appendix 14ci (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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (3.10)
Psychosocial Functioning	-	-	-	-	-	-	-	-	-	-	-
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response	-	-	-	-	-	-	-	-	-	-	-

Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours Risperidone
[1]Downgraded due to risk of bias (including: unclear sequence & allocation concealment; one open label trial (no blinding) or unclear blinding; one analysis of a modified intent-to-treat population; incomplete list of outcomes reported on trial registry; publication only reports dichotomous outcomes)
[2] Optimal information size (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

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with Risperidone versus quetiapine as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight (RR)	McEVOY2007	RCT	Serious[1]	No serious inconsistency	Serious[5]	Serious[2]	Reporting bias[3]	K=1; N=81	0.18 [-0.26, 0.62]	Very low [1,2,3,5]	Appendix 14ci (4.1)
Metabolic: Weight kg (SMD)	McEVOY2007 SWADI2010	RCT	Serious[1]	Serious[4]	Serious[5]	Serious[2]	Reporting bias[3]	K=2; N=103	1.30 [0.79, 2.13]	Very low [1,2,3,4,5]	Appendix 14ci (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 14ci (4.3)
Metabolic: Fasting Serum Glucose Level mg/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 14ci (4.4)
Metabolic: Fasting Total Cholesterol mg/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 14ci (4.5)
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/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 14ci (4.6)
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (4.11)
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (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 14ci (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 14ci (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 14ci (4.14)
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-

Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (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 14ci (4.15)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours risperidone
**Favours quetiapine
[1]Serious risk of bias (including: unclear sequence & allocation concealment; one open label trial (no blinding) or unclear blinding; one analysis of a modified intent-to-treat population; incomplete list of outcomes reported on trial registry; publication only reports dichotomous outcomes)
[2]Optimal information size (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).

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with olanzapine versus haloperidol as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	LIEBERMAN 2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=251	-0.31 [-0.56, -0.06]*	Very low[1,2,3,4]	Appendix 14ci (5.1)
Positive Symptoms	LIEBERMAN 2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=252	-0.09 [-0.34, 0.16]	Very low[1,2,3,4]	Appendix 14ci (5.2)
Negative Symptoms	LIEBERMAN 2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=252	-0.28 [-0.53, -0.03] *	Very low[1,2,3,4]	Appendix 14ci (5.3)
Global State (Severity) (SMD)	LIEBERMAN 2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=254	-0.25 [-0.50, -0.01] *	Very low[1,2,3,4]	Appendix 14ci (5.4)
Depression (SMD)	LIEBERMAN 2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=251	-0.32 [-0.57, -0.07]	Very low[1,2,3,4]	Appendix 14ci (5.5)
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of Life	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning	-	-	-	-	-	-	-	-	-	-	-
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours olanzapine
[1]Serious risk of bias (including: unclear sequence generation & allocation concealment; one open label trial, unclear blinding, not all outcomes reported; trial registration couldn't be found)
[2]Optimal information size (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)

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with olanzapine versus haloperidol as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight (SMD)	LIEBERMAN2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=263	0.70 [0.44, 0.95]**	Very low[1,2,3,4]	Appendix 14ci (6.1)
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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)	LIEBERMAN2003	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 14ci (6.2)
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-

Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	LIEBERMAN2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=253	1.95 [1.12, 3.39]**	Very low[1,2,3,4]	Appendix 14ci (6.3)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours olanzapine
**Favours haloperidol
[1]Serious risk of bias (including: unclear sequence generation & allocation concealment; one open label trial, unclear blinding, not all outcomes reported; trial registration couldn't be found)
[2]Optimal information size (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)

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with haloperidol versus Risperidone as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	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 14ci (7.1)
Positive Symptoms	SCHOOLER 2005	**RCT**	Serious[1]	No serious inconsistency	**Serious[2]**	No serious imprecision	Reporting bias[3]	K=1; N=528	0.05 [-0.12, 0.22]	Very Low[1,2,3]	Appendix 14ci (7.2)
Negative Symptoms	SCHOOLER 2005	**RCT**	Serious[1]	No serious inconsistency	**Serious[2]**	No serious imprecision	Reporting bias[3]	K=1; N=528	-0.12 [-0.29, 0.05]	Very Low[1,2,3]	Appendix 14ci (7.3)
Global State (Severity) (SMD)	SCHOOLER 2005	**RCT**	Serious[1]	No serious inconsistency	**Serious[2]**	No serious imprecision	Reporting bias[3]	K=1; N=528	0.06 [-0.11, 0.23]	Very Low[1,2,3]	Appendix 14ci (7.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of Life	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning	-	-	-	-	-	-	-	-	-	-	-
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (unclear blinding, unable to find trial registration; unclear at what time point data was taken; missing outcomes data)
[2] Serious risk of indirectness (48% population had bipolar disorder)
[3]Serious risk of reporting bias

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with haloperidol versus Risperidone as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight (SMD)	SCHOOLER2005	RCT	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	Reporting bias[4]	K=1; N=415	0.01 [-0.19, 0.20]	Very Low[1,3,4]	Appendix 14ci (8.1)
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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)	SCHOO	RCT	Serious[1]	No serious	Serious[3]	No serious	Reporting	K=1; N=507	Very Low[1,3,4]	Moderat	Appendix

	LER2005			inconsistency		imprecision	bias[4]			e[1]	14ci (8.2)
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	SCHOO LER2005	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 14ci (8.3)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours haloperidol
[1]Serious risk of bias (unclear blinding, unable to find trial registration; unclear at what time point data was taken; missing outcomes data)
[2]Optimal information size (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

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with Risperidone versus olanzapine as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	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 14ci (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 14ci (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 14ci (9.3)
Global State (Severity) (SMD)	MCEVOY2007 SIKICH2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=2; N=108	-0.06 [-0.44, 0.32]	Very low[1,2,3]	Appendix 14ci (9.4)
Depression (SMD)	MCEVOY2007 VANBRUGGEN2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=2; N=116	-0.60 [-1.74, 0.53]	Very low[1,2,3]	Appendix 14ci (9.5)
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of Life	MCEVOY2007	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1; N=74	-0.13 [-0.45, 0.19]	Very low[1,2,3]	Appendix 14ci (9.6)
Psychosocial Functioning	-	-	-	-	-	-	-	-	-	-	-
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response	ROBINSON	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1; N=120	1. 25 [0.84, 1.86]	Very low[1,2]	Appendix 14ci (9.7)
Remission	VANBRUGGEN2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1; N=44	0.55 [0.17, 1.78]	Very low[1,2,3]	Appendix 14ci (9.8)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including serious or unclear blinding bias (including one open label trial); unable to extract all outcomes; trial registration couldn't be found; analysis included modified intent-to-treat 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)
[2]Optimal information size (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] $I^2 \geq 50\%$, $p<.05$

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with Risperidone versus olanzapine as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight (SMD)	MCEVOY2007; VANBRUGGEN2003	RCT	Serious[1]	Serious[5]	Serious[4]	Serious[2]	Reporting bias[3]	K=2; N=105	-0.40 [-1.49, 0.69]	Very low[1,2,3,4,5]	Appendix 14ci (10.1)
Metabolic: Weight (RR) (N pts with >7% gain)	MCEVOY2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=47	0.68 [0.47, 0.98]*	Very low[1,2,3,4]	Appendix 14ci (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 14ci (10.3)
Metabolic: Fasting Serum Glucose Level mg/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 14ci (10.4)
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	MCEVOY2007	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=1; N=74	-0.16 [-0.61, 0.30]	Very low[1,2,3,4]	Appendix 14ci (10.5)
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/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 14ci (10.6)
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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 14ci (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 14ci (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 14ci (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 14ci (10.10)
Hormonal: Prolactin (RR)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS (RR)	SIKICH2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1; N=33	0.04 [-0.65, 0.73]	Very low[1,2,3]	Appendix 14ci (10.11)
Neurological: SAS (RR)	ROBINSON2006; SIKICH2008; VANBRUGGEN2003	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=3; N=168	0.34 [0.00, 0.67]	Very low[1,2,3]	Appendix 14ci (10.12)
Sensitivity analysis: Neurological: SAS (SMD)	*SIKICH2008; VANBRUGGEN2003*	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	*K=2; N=56*	*0.03 [-0.50, 0.56]*	Very low[1,2,3]	Appendix 14ci (10.13)
Neurological: BARS (RR)	SIKICH2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K=1; N=33	0.36 [-0.34, 1.06]	Very low[1,2,3]	Appendix 14ci (10.14)
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological:	ROBINSON200	RCT	Serious[1]	No serious	No	Serious[2]	Reporting	K=1; N=112	0.56 [0.20,	Very	Appendix

Parkinsonism (RR)	6			inconsistency	serious indirectness		bias[3]		1.55]	low[1,2,3]	14ci (10.15)
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	VANBRUGGEN2003	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 14ci (10.16)
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	MCEVOY2007; ROBINSON2006; SIKICH2008 VANBRUGGEN2003	RCT	Serious[1]	No serious inconsistency	Serious[4]	Serious[2]	Reporting bias[3]	K=4; N=422	1.04 [0.89, 1.21]	Very low[1,3,4]	Appendix 14ci (10.17)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*favours risperidone
**favours olanzapine[1] Serious risk of bias (including serious or unclear blinding bias (including one open label trial); unable to extract all outcomes; trial registration couldn't be found; analysis included modified intent-to-treat 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)
[2]Optimal information size (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] $I^2 \geq 50\%$, $p<.05$

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with quetiapine 200mg/day versus quetiapine 400mg/day as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (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 14ci (11.10)

Note
ROB= Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours 400mg/day
[1]Serious risk of bias (including blinding of participants and providers in part 2 not maintained; not all outcomes reported; not all data extractable)
[2]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with quetiapine 200mg/day versus quetiapine 400mg/day as initial treatment in children and young people with first episode psychosis

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight (SMD)	BERGER 2008	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 14ci (12.1)
Metabolic: Weight (RR) (N pts with >7% gain)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	BERGER 2008	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 14ci (12.2)
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	BERGER 2008	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 14ci (12.3)

Note
ROB= Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including blinding of participants and providers in part 2 not maintained; not all outcomes reported; not all data extractable)
[2]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

APPENDIX 17cii: ANTIPSYCHOTICS IN THE TREATMENT OF THE ACUTE EPISODE: EVIDENCE PROFILES

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with a 'lower dose' antipsychotic medication versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; KRYZHANOVSKAYA2009B;SINGH2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	K=4; N=516	-0.32 [-0.52, -0.13]*	Low[1,2]	Appendix 14cii (1.1)
Positive Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; KRYZHANOVSKAYA2009B; HAAS2009B; PALLIERE-MARTINOT1995; SINGH2011	RCT	Serious[1]	Serious[4]	No serious indirectness	No serious imprecision	Reporting bias[2]	K=6; N=634	-0.30 [-0.59, -0.01] *	Very low[1,2,4]	Appendix 14cii (1.3)
Negative Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; KRYZHANOVSKAYA2009B; HAAS2009B; PALLIERE-MARTINOT1995;	RCT	Serious[1]	Serious[4]	No serious indirectness	No serious imprecision	Reporting bias[2]	K=6; N=634	-0.33 [-0.50, -0.16] *	Very low[1,2,4]	Appendix 14cii (1.5)

	SINGH2011										
Global State (Severity) (SMD)	AstraZenecaD1441C0012; FINDLING2008A; KRYZHANOVSKAYA2009B	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	K=3; N=400	-0.38 [-0.58, -0.18] *	Low[1,2]	Appendix 14cii (1.7)
Depression (SMD)	AstraZenecaD1441C0012; PALLIERE-MARTINOT1995; SINGH2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K=2; N=202	-0.20 [-0.46, 0.07]	Very low[1,2,3]	Appendix 14cii (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 14cii (1.11)
Psychosocial Functioning (SMD)	AstraZenecaD1441C0012; FINDLING2008A; HAAS2009B; SINGH2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Low	Reporting bias[2]	K=4; N=535	-0.29 [-0.52, -0.06]	Low[1,2]	Appendix 14cii (1.12)
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	AstraZenecaD1441C0012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K=1; N=98	1.43 [0.95, 2.17]	Very low[1,2,3]	Appendix 14cii (1.13)
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB= Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours 'lower dose'
[1] Serious risk of bias (including unclear blinding procedures, reports LOCF analysis but the number of participants included results suggests available case analysis, participants excluded if they had a previous non-response to study treatment, some outcomes not reported; treatment exposure (time) differ between groups,
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[4] $I^2 \geq 50\%$, $p<.05$

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with a 'lower dose' antipsychotic medications versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Antipsychotic (dose)	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies/ participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight (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	0.34 [0.06, 0.62] **	Very low[1,2,3]	Appendix 14cii (2.1)
	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=107	1.33 [0.88, 1.77] **	Very low[1,2,3]	Appendix 14cii (2.1)
	AstraZenecaD1441C0012	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 14cii (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 14cii (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 14cii (2.2)
	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=107	1.31 [0.87, 1.75] **	Very low[1,2,3]	Appendix 14cii (2.2)
Metabolic: Fasting Serum Glucose Level mg/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 14cii (2.3)
	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=80	0.43 [-0.04, 0.91]	Very low[1,2,3]	Appendix 14cii (2.3)

	AstraZeneca D1441C0012	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 14cii (2.3)
Metabolic: Fasting Total Cholesterol mg/dl	FINDLING 2008A	Aripiprazole (10 mg per day)	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 14cii (2.4)
	AstraZeneca D1441C0012	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 14cii (2.4)
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/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 14cii (2.5)
	AstraZeneca D1441C0012	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 14cii (2.5)
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl (SMD)	AstraZeneca D1441C0012	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 14cii (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 14cii (2.7)
	AstraZeneca D1441C0012	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 14cii (2.7)
	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=80	0.54 [0.05, 1.02] **	Very low[1,2,3]	Appendix 14cii (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 14cii (2.8)

	AstraZenecaD1441C0012	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 14cii (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 14cii (2.8)
Cardio: QT Interval (RR) (Incidence of prolonged QT)	AstraZenecaD1441C0012	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 14cii (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 14cii (2.9)
Cardio: Systolic BP (SMD)	AstraZenecaD1441C0012	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 14cii (2.10)
Cardio: Diastolic BP (SMD)	AstraZenecaD1441C0012	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 14cii (2.11)
Cardio: Tachycardia (RR)	AstraZenecaD1441C0012	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 14cii (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 14cii (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 14cii (2.12)
Cardio: Sitting Pulse	-	-	-	-	-	-	-	-	-	-	-	-

Cardio: Standing Pulse	AstraZenecaD1441C0012	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 14cii (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 14cii (2.14)
	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=94	0.71 [0.26, 1.15] **	Very low[1,2,3]	Appendix 14cii (2.14)
	AstraZenecaD1441C0012	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 14cii (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 14cii (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 14cii (2.14)
Hormonal: Insulin	AstraZenecaD1441C0012	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 14cii (2.15)
Neurological: Extrapyramidal Side Effects (RR)	AstraZenecaD1441C0012	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 15cii (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 14cii (2.16)
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 14cii (2.17)
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 14cii (2.18)
Neurological: Tremor (RR)	AstraZeneca D1441C0012	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 14cii (2.19)
Neurological: Akathesia (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 14cii (2.20)
	AstraZeneca D1441C0012	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 14cii (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 14cii (2.21)
Neurological: Dyskenesia (RR)	AstraZeneca D1441C0012	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 14cii (2.22)
Neurological: Extrapyramidal Disorder (RR)	AstraZeneca D1441C0012	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 14cii (2.23)
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 14cii (2.24)
	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 14cii (2.24)

Leaving the Study Early for Any Reason (RR)	AstraZenecaD1441C0012	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 14cii (2.25)
	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 14cii (2.25)
	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=94	0.56 [0.36, 0.87]*	Very low[1,2,3]	Appendix 14cii (2.25)
	PALLIERE-MARTINO T1995	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 14cii (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	0.55 [0.28, 1.07]	Very low[1,2,3]	Appendix 14cii (2.25)

Note
ROB= Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours 'lower dose'
** Favours placebo
[1] Serious risk of bias (including unclear sequence generation, allocation concealment and blinding procedures, missing outcomes data, participants excluded if they had a previous non-response to study treatment; treatment exposure (time) differ between groups in one study)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with a higher dose antipsychotic medication versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; SINGH2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	No serious indirectness	K=3; N=402	-0.48 [-0.68, -0.28] *	Low[1,2]	Appendix 14cii (3.1)
Positive Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; HAAS2009B; SINGH2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	K=4; N=496	-0.48 [-0.66, -0.30] *	Low[1,2]	Appendix 14cii (3.2)
Negative Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; HAAS2009B; SINGH2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	K=4; N=495	-0.29 [-0.51, -0.07] *	Low[1,2]	Appendix 14cii (3.3)
Global State (Severity) (SMD)	AstraZenecaD1441C0012; FINDLING2008A	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K=2; N=292	-0.43 [-0.66, -0.20] *	Very low[1,2,3]	Appendix 14cii (3.4)
Depression (SMD)	AstraZenecaD1441C0012; SINGH2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K=2; N=197	-0.28 [-0.56, 0.00]	Very low[1,2,3]	Appendix 14cii (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 14cii (3.6)
Psychosocial Functioning	AstraZenecaD1441C0012;	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	K=4; N=522	-0.49 [-0.66, -0.31]*	Low[1,2]	Appendix 14cii (3.7)

(SMD)	FINDLING2008A										
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	AstraZenecaD1441C0012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K=1; N=98	1.35 [0.88, 2.05]	Very low[1,2,3]	Appendix 14cii (3.8)
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB= Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours 'higher dose'
[1] Serious risk of bias (including unclear blinding procedures, reports LOCF analysis but the number of participants included results suggests available case analysis, participants excluded if they had a previous non-response to study treatment, some outcomes not reported; treatment exposure (time) differ between groups, patients who failed to complete four 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)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with an additional higher dose of paliperidone versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	SINGH 2011	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 14cii (4.1)
Positive Symptoms (SMD)	SINGH 2011	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 14cii (4.2)
Negative Symptoms (SMD)	SINGH 2011	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 14cii (4.3)
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	SINGH 2011	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 14cii (4.4)
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	SINGH 2011	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 14cii (4.5)
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB=risk of bias
*favours 6 to 12 mg per day paliperidone
[1] Serious risk of bias (including some outcomes not reported; each treatment group exposed to treatment for different lengths of time)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with a higher dose antipsychotic medication versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Antipsychotic (dose)	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight (SMD)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.1)
	INDLING2008A	Aripiprazole (30mg 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 14cii (5.1)
	SINGH2011	Paliperidone (3-6mg 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 14cii (5.1)
Metabolic: BMI (SMD)	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.2)
Metabolic: Fasting Serum Glucose Level mg per dl (SMD)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.3)
	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.3)
Metabolic: Fasting Total Cholesterol mg per dl (SMD)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.4)
	INDLING2008A	Aripiprazole (30mg 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 14cii (5.4)

Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg per dl (SMD)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.5)
	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.5)
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg per dl (SMD)	AstraZenecaD1441C0012	Quetiapine (400mg per day)	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K=1; N=123	K=1; N=123	Very low[1,2,3]	Appendix 14cii (5.6)
Metabolic: Fasting Triglycerides	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.7)
	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.7)
Cardio: QT Interval (SMD)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.8)
	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.8)
Cardio: QT Interval (RR) (Incidence of prolonged QT)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.9)
	SINGH2011	Paliperidone (3-6mg 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 14cii (5.9)

Cardio: Systolic BP (SMD)	AstraZeneca D1441C0012	Quetiapine (400mg 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 14cii (5.10)
Cardio: Diastolic BP (SMD)	AstraZeneca D1441C0012	Quetiapine (400mg 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 14cii (5.10)
Cardio: Tachycardia (RR)	AstraZeneca D1441C0012	Quetiapine (400mg 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 14cii (5.12)
	HAAS2009B	Risperidone (4-6mg 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 14cii (5.12)
	SINGH2011	Paliperidone (3-6mg 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 14cii (5.12)
Cardio: Sitting Pulse	-	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse	AstraZeneca D1441C0012	Quetiapine (400mg 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 14cii (5.13)
Hormonal: Prolactin	AstraZeneca D1441C0012	Quetiapine (400mg 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 14cii (5.14)
	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.14)
	HAAS2009B	Risperidone (4-6mg 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 14cii (5.14)
	SINGH2011	Paliperidone (3-6mg 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 14cii (5.14)
Hormonal: Insulin	AstraZeneca D1441C0012	Quetiapine (400mg 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 14cii (5.15)

Neurological: Extrapyramidal Side Effects (RR)	POOL1976	Haloperidol (11.9mg 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 14cii (5.16)
Neurological: AIMS	HAAS2009B	Risperidone (4-6mg 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 14cii (5.17)
Neurological: SAS	HAAS2009B	Risperidone (4-6mg 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 14cii (5.18)
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.19)
Neurological: Tremor (RR)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.20)
Neurological: Akathesia (RR)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.21)
	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.21)
Neurological: Dystonia (RR)	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.22)
Neurological: Dyskenesia (RR)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.23)

Neurological Extrapyramidal Disorder (RR)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.24)
Mortality (RR)	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.25)
	HAAS2009B	Risperidone (4-6mg 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 14cii (5.25)
Leaving the Study Early for Any Reason (RR)	AstraZenecaD1441C0012	Quetiapine (400mg 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 14cii (5.26)
	FINDLING2008A	Aripiprazole (30mg 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 14cii (5.26)

Note
ROB=risk of bias
* Favours 'Higher dose'
**Favours placebo
[1] Serious risk of bias (including unclear blinding procedures, reports LOCF analysis but the number of participants included results suggests available case analysis, participants excluded if they had a previous non-response to study treatment, some outcomes not reported; treatment exposure (time) differ between groups, patients who failed to complete four 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)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with an additional higher dose of Paliperidone versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	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 14cii (6.1)
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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 14cii (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 14cii (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 14cii (6.4)
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Note
ROB=risk of bias
*favours placebo
[1] Serious risk of bias (including some outcomes not reported; each treatment group exposed to treatment for different lengths of time)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with Risperidone versus olanzapine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	MOZES2006; SIKICH2004	RCT	Serious[1]	Serious[4]	No serious indirectness	Serious[3]	Reporting bias[2]	K=2; N=60	0.25 [-0.53, 1.04]	Very low[1,2,3,4]	Appendix 14cii (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 14cii (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 14cii (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 14cii (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 14cii (7.5)
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including open label trial, minimal information regarding eligibility criteria; trial registration cannot be found; missing outcomes data)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[4] $I^2 \geq 50\%$, $p<.05$

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with Risperidone versus olanzapine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight (RR)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Weight kg (SMD)	MOZES 2006; SIKICH 2004	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 14cii (8.1)
Metabolic: BMI (SMD)	SIKICH 2004	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 14cii (8.2)
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT Interval (SMD)	SIKICH 2004	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 14cii (8.3)
Cardio: Systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Sitting Pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse	-	-	-	-	-	-	-	-	-	-	-

Hormonal: Prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	MOZES 2006; SIKICH 2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K=1; N=42	0.09 [-0.58, 0.75]	Very low[1,2,3]	Appendix 14cii (8.4)
Neurological: BARS	MOZES 2006	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 14cii (8.5)
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	MOZES 2006	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 14cii (8.6)
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	MOZES 2006; SIKICH 2004	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 14cii (8.7)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours olanzapine
[1] Serious risk of bias (including open label trial, minimal information regarding eligibility criteria; trial registration cannot be found; missing outcomes data)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with Risperidone versus haloperidol in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	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 14cii (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 14cii (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 14cii (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 14cii (9.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including inadequate allocation concealment, unclear blinding procedures, trial registration couldn't be found)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Sequence generation, allocation concealment, analysis and selective outcome reporting not reported by KENNEDY2012

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with Risperidone versus haloperidol in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies/ participants	Effect Estimate (SMD or RR)	Quality	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 14cii (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 14cii (10.2)
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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 14cii (10.3)
Cardio: Systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-

Cardio: Sitting Pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (RR)	YAO2003/ KENNEDY2012	RCT	Serious[1,4]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[2]	K=1; N=60	0.12 [0.04, 0.37]*	Low [1,3,4]	Appendix 14cii (10.4)
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (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 14cii (10.5)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* favours risperidone
[1] Serious risk of bias (inadequate allocation concealment, unclear sequence generation and blinding procedures, trial registration couldn't be found; missing outcomes data)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Sequence generation, allocation concealment, analysis and selective outcome reporting not reported by KENNEDY2012

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with Risperidone versus chlorpromazine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	XIONG2004 / KENNEDY 2012	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 14cii (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
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including open label trial, unable to extract all outcomes)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Sequence generation, allocation concealment, analysis and selective outcome reporting not reported by KENNEDY2012

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with Risperidone versus chlorpromazine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies/ participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight kg (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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: Extrapyramidal Side Effects (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 14cii (12.1)s
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including unclear sequence generation, allocation concealment and blinding procedures)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Sequence generation, allocation concealment, analysis and selective outcome reporting not reported by KENNEDY2012

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with olanzapine versus quetiapine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	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 14cii (13.1)
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including open label trial, unable to extract all outcomes)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with olanzapine versus quetiapine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies/ participants	Effect Estimate (SMD or RR)	Quality	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 14cii (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 14cii (14.2)
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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: Extrapyramidal	-	-	-	-	-	-	-	-	-	-	-

Side Effects (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 14cii (14.3)
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (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 14cii (14.4)
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (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 14cii (14.5)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including open label trial, unable to extract all outcomes)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with olanzapine versus haloperidol in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	SIKICH 2004	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 14cii (15.1)
Positive Symptoms (SMD)	SIKICH 2004	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 14cii (15.2)
Negative Symptoms (SMD)	SIKICH 2004	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 14cii (15.3)
Global State (Severity) (SMD)	SIKICH 2004	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 14cii (15.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including inadequate allocation concealment, unclear blinding procedures, trial registration couldn't be found)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with olanzapine versus haloperidol in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight kg (SMD)	SIKICH 2004	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 14cii (16.1)
Metabolic: BMI (SMD)	SIKICH 2004	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 14cii (16.2)
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Triglycerides	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT Interval	SIKICH 2004	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 14cii (16.3)
Cardio: Systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Sitting Pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Prolactin	-	-	-	-	-	-	-	-	-	-	-

Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	SIKICH 2004	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 14cii (16.4)
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	SIKICH 2004	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 14cii (16.5)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours olanzapine
[1] Serious risk of bias (including inadequate allocation concealment, unclear blinding procedures, trial registration couldn't be found)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with quetiapine 400mg per day versus quetiapine 800mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	AstraZenecaD1441C0012	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 14cii (16.1)
Positive Symptoms (SMD)	AstraZenecaD1441C0012	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 14cii (16.2)
Negative Symptoms (SMD)	AstraZenecaD1441C0012	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 14cii (16.3)
Global State (Severity) (SMD)	AstraZenecaD1441C0012	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 14cii (16.4)
Depression (SMD)	AstraZenecaD1441C0012	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 14cii (16.5)
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	AstraZenecaD1441C0012	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 14cii (16.6)
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	AstraZenecaD1441C0012	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 14cii (16.7)
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including unclear sequence generation, participants and providers blind, but unclear if raters blind; study reports LOCF analysis, but the number of participants included in reports results suggests available case was used)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with quetiapine 400mg per day versus quetiapine 800mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies/ participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight kg (SMD)	AstraZeneca D1441C0012	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]	Appendix 14cii (17.1)
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	AstraZeneca D1441C0012	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]	Appendix 14cii (17.3)
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	AstraZeneca D1441C0012	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]	Appendix 14cii (17.4)
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	AstraZeneca D1441C0012	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]	Appendix 14cii (17.5)
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl (SMD)	AstraZeneca D1441C0012	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]	Appendix 14cii (17.6)
Metabolic: Fasting Triglycerides	AstraZeneca D1441C0012	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]	Appendix 14cii (17.7)
Cardio: QT Interval (SMD)	AstraZeneca D1441C0012	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]	Appendix 14cii (17.8)
Cardio: QT Interval (RR) (Prolonged QT interval)	AstraZeneca D1441C0012	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]	Appendix 14cii (17.9)
Cardio: Systolic BP (SMD)	AstraZeneca D1441C0012	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]	Appendix 14cii (17.10)
Cardio: Diastolic BP (SMD)	AstraZeneca D1441C0012	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]	Appendix 14cii (17.11)
Cardio: Tachycardia (RR)	AstraZeneca	RCT	Serious[1]	No serious	No serious	Serious[2]	None	K=1; N=147	0.68 [0.20,	Very	Appendix

	D1441C0012			inconsistency	indirectness				2.30]	low[1,2]	14cii (17.12)
Cardio: Sitting Pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse	AstraZeneca D1441C0012	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]	Appendix 14cii (17.13)
Hormonal: Prolactin	AstraZeneca D1441C0012	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]	Appendix 14cii (17.14)
Hormonal: Insulin	AstraZeneca D1441C0012	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]	Appendix 14cii (17.16)
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	AstraZeneca D1441C0012	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]	Appendix 14cii (17.19)
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	AstraZeneca D1441C0012	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]	Appendix 14cii (17.20)
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the Study Early for Any Reason (RR)	AstraZeneca D1441C0012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1; N=147	1.33 [0.70, 2.53]	Low[1,2]	Appendix 14cii (17.28)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including unclear sequence generation, participants and providers blind, but unclear if raters blind; study reports LOCF analysis, but the number of participants included in reports results suggests available case was used)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with Aripiprazole 10mg per day versus Aripiprazole 30mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	FINDLIN G2008A	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 14cii (16.1)
Positive Symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Negative Symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	FINDLIN G2008A	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 14cii (16.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	FINDLIN G2008A	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 14cii (16.8)
Psychosocial Functioning (SMD)	FINDLIN G2008A	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 14cii (16.6)
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours Aripiprazole 30mg per day
[1] Serious risk of bias (including unclear sequence generation, unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design; study reports LOCF analysis, but the number of participants included in reports results suggests available case was used)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with Aripiprazole 10mg per day versus Aripiprazole 30mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight kg (SMD)	FINDLING2008A	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 14dcii (17.1)
Metabolic: BMI (SMD)	FINDLING2008A	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 14dcii (17.2)
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	FINDLING2008A	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 14dcii (17.3)
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	FINDLING2008A	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 14dcii (17.4)
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	FINDLING2008A	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 14dcii (17.5)
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Triglycerides	FINDLING2008A	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 14dcii (17.7)
Cardio: QT Interval (SMD)	FINDLING2008A	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 14dcii (17.8)
Cardio: Systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Sitting Pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse	-	-	-	-	-	-	-	-	-	-	-

Hormonal: Prolactin	FINDLIN G2008A	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 14dcii (17.14)
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	FINDLIN G2008A	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 14dcii (17.23)
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	FINDLIN G2008A	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 14dcii (17.19)
Neurological: Dystonia (RR)	FINDLIN G2008A	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 14dcii (17.22)
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	FINDLIN G2008A	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 14dcii (17.26)
Leaving the Study Early for Any Reason (RR)	FINDLIN G2008A	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 14dcii (17.28)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours Aripiprazole 10mg per day
[1] Serious risk of bias (including unclear sequence generation, unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design; study reports LOCF analysis, but the number of participants included in reports results suggests available case was used)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with Risperidone 1-3mg per day versus Risperidone 4-6mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Positive Symptoms (SMD)	HAAS 2009B	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 14dcii (16.2)
Negative Symptoms (SMD)	HAAS 2009B	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 14dcii (16.3)
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	HAAS 2009B	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 14dcii (16.6)
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including unclear sequence generation, unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with Risperidone 1-3mg per day versus Risperidone 4-6mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	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 14dcii (17.1)
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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 14dcii (17.12)
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 14dcii (17.14)
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 14dcii (7.15)
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (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 14dcii (17.21)
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 14dcii (17.17)
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (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 14dcii (17.22)
Neurological: Dyskenesia (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 14dcii (17.19)

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 14dcii (17.27)
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 14dcii (17.28)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours 1-3 mg per day
[1] Serious risk of bias (including unclear sequence generation, unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design, missing outcomes data)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with Risperidone 0.15-0.6mg per day versus Risperidone 1.5-6.0mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	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 14dcii (16.1)
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 14dcii (16.2)
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 14dcii (16.3)
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 14dcii (16.4)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
*Favours 1.5-6.0 mg per day
[1] Serious risk of bias (including unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design, unable to extract all outcomes)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with Risperidone 0.15-0.6mg per day versus Risperidone 1.5-6.0mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight kg (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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 14dcii (17.15)
Hormonal: Insulin	-							-	-	-	-
Neurological: Extrapyramidal Side Effects (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 14dcii (17.21)
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 14dcii (17.24)
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 14dcii (17.26)
Neurological: Akathesia (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 14dcii (17.22)
Neurological: Dyskenesia (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 14dcii (17.25)
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 14dcii (17.28)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours 0.15-0.6 mg per day
[1] Serious risk of bias (including unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design, unable to extract all outcomes)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with Paliperidone 1.5mg per day versus Paliperidone 3-6mg per day versus Paliperidone 6-12mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Dose comparison	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	SINGH 2011	1.5mg per day versus 3-6mg 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 14dcii (16.1)
	SINGH 2011	3-6mg per day versus 6-12mg 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 14dcii (19.1)
	SINGH 2011	1.5mg per day versus 6-12mg 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 14dcii (18.1)
Positive Symptoms (SMD)	SINGH 2011	1.5mg per day versus 3-6mg per day	RCT	Serious[1]	No serious risk of	No serious	Serious[3]	Reporting bias[2]	K=1; N=102	0.48 [0.08, 0.87]	Very low[1,2,3]	Appendix 14dcii (16.2)

					inconsistency	risk of indirectness						
	SINGH 2011	3-6mg per day versus 6-12mg 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 14dcii (19.2)
	SINGH 2011	1.5mg per day versus 6-12mg 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 14dcii (18.2)
Negative Symptoms (SMD)	SINGH 2011	1.5mg per day versus 3-6mg 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 14dcii (16.3)
	SINGH 2011	3-6mg per day versus 6-12mg per day	RCT	Serious[1]	No serious risk of inconsistency	No serious risk of indir	Serious[3]	Reporting bias[2]	K=1; N=95	-0.19 [-0.59, 0.22]	Very low[1,2,3]	Appendix 14dcii (19.3)

						ectness						
	SINGH 2011	1.5mg per day versus 6-12mg 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 14dcii (18.3)
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	SINGH 2011	1.5mg per day versus 3-6mg 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 14dcii (16.5)
	SINGH 2011	3-6mg per day versus 6-12mg 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 14dcii (19.4)
	SINGH 2011	1.5mg per day versus 6-12mg per day	RCT	Serious[1]	No serious risk of inconsistency	No serious risk of indirectne	Serious[3]	Reporting bias[2]	K=1; N=101	0.15 [-0.25, 0.54]	Very low[1,2,3]	Appendix 14dcii (18.4)

						ss						
Mania	-	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-	
Psychosocial Functioning (SMD)	SINGH 2011	1.5mg per day versus 3-6mg 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 14dcii (16.6)
	SINGH 2011	3-6mg per day versus 6-12mg per day	RCT	Serious[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious[3]	Reporting bias[2]	K=1; N=95	-0.38 [-0.79, 0.02]*	Very low[1,2,3]	Appendix 14dcii (19.5)
	SINGH 2011	1.5mg per day versus 6-12mg 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 14dcii (18.5)
Social Functioning	-	-	-	-	-	-	-	-	-	-	-	-
Response (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours 3-6mg per day
[1] Serious risk of bias (including some outcomes not reported; each treatment group exposed to treatment for different lengths of time)

[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for side effect outcomes reported at treatment endpoint associated with Paliperidone 1.5mg per day versus Paliperidone 3-6mg per day versus Paliperidone 6-12mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or Subgroup	Study ID	Dose comparison	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight kg (SMD)	SINGH 2011	1.5mg per day versus 3-6mg 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 14dcii (17.1)
	SINGH 2011	3-6mg per day versus 6-12mg 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 14dcii (21.1)
	SINGH 2011	1.5mg per day versus 6-12mg 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 14dcii (20.1)
Metabolic: BMI (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total	-	-	-	-	-	-	-	-	-	-	-	-

Cholesterol mg/dl												
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Triglycerides	-	-	-	-	-	-	-	-	-	-	-	-
Cardio: QT Interval	SINGH 2011	1.5mg per day versus 3-6mg 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 14dcii (17.9)
	SINGH 2011	3-6mg per day versus 6-12mg 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 14dcii (21.2)
	SINGH 2011	1.5mg per day versus 6-12mg 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 14dcii (20.2)
Cardio: Systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	SINGH 2011	1.5mg per day versus 3-	RCT	Serious[1]	No serious	No seriou	Serious[3]	Reporting bias[2]	K=1; N=102	0.13 [0.01, 2.40]	Very low[1,2,3]	Appendix 14dcii (17.12)

		6mg per day			risk of inconsistency	s risk of indirectness						
	SINGH 2011	3-6mg per day versus 6-12mg 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 14dcii (21.3)
	SINGH 2011	1.5mg per day versus 6-12mg 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 14dcii (20.3)
Cardio: Sitting Pulse	-	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse	-	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Prolactin	SINGH 2011	1.5mg per day versus 3-6mg 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 14dcii (17.14)
	SINGH 2011	3.6mg per day versus 6-12mg 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 14dcii (21.4)
	SINGH 2011	1.5mg per day versus 6-12mg per day	RCT	Serious[1]	No serious risk of inconsistency	No serious risk of indirec	Serious[3]	Reporting bias[2]	K=1; N=93	-0.53 [-0.94, -0.11]*	Very low[1,2,3]	Appendix 14dcii (20.4)

						tness						
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	-	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours 1.5 mg per day
[1] Serious risk of bias (including missing outcomes data; each treatment group exposed to treatment for different lengths of time)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

APPENDIX 17ciii: ANTIPSYCHOTICS FOR CHILDREN AND YOUNG PEOPLE WHOSE ILLNESS HAS NOT RESPONDED ADEQUATELY TO TREATMENT: EVIDENCE PROFILES

Summary evidence profile for efficacy outcomes reported associated with clozapine versus another antipsychotic in children and young people at treatment endpoint

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Total Symptoms (SMD)	KUMRA1996; UMRA2008A; 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 14ciii (1.1)
Positive Symptoms (SMD)	KUMRA1996; UMRA2008A; 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 14ciii (1.3)
Negative Symptoms (SMD)	KUMRA1996; UMRA2008A; 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 14ciii (1.5)
Global State (Severity) (SMD)	KUMRA2008A; HAW2006	-	-	-	-	-	-	K=2; N=64	0.51 [0.01, 1.01] *	Very low[1,2,3]	Appendix 14ciii (1.7)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning	KUMRA1996;	RCT	Serious[1]	Serious	No	Serious[3]	Reporting	K=3; N=60	0.80 [-0.43,	Very	Appendix

	KMRA2008A			[4]	serious risk of indirectness		bias[2]		2.03]	low[1,2,3,4]	14ciii (1.8)
Social Functioning	-	-	-	-	-	-	-	-	-	-	-
Response	-	-	-	-	-	-	-	-	-	-	-
Remission	-	-	-	-	-	-	-	-	-	-	-

ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours clozapine
[1]Downgraded due to risk of bias (including: method of allocation concealment unclear, blinding of raters unclear; ITT method of analysis unclear or available case analysis used, eligibility criteria states that patients must be not be treatment refractory to treatment of study meds, not all data reported sufficiently to allow for extraction and analysis and trial registration could not be found)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] $I^2 \geq 50\%$, $p<.05$

Summary evidence profile for side effect outcomes reported associated with clozapine versus another antipsychotic in children and young people at treatment endpoint

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight kg (SMD)	SHAW2006; KUMRA2008A	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 14ciii (2.1)
Metabolic: BMI (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]*	Low[1,2]	Appendix 14ciii (2.2)
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-							-	-	-	-
Metabolic: Fasting Total Cholesterol mg/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 14ciii (2.4)
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/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 14ciii (2.5)
Cardio: QT Interval	-	-	-	-	-	-	-	-	-	-	-
Cardio: Systolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Diastolic BP (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: Tachycardia (RR)	KUMRA1996	RCT	Serious[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious[3]	Reporting bias[2]	K=1; N=21	0.18 [0.01, 3.41]	Very low[1,2,3]	Appendix 14ciii (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 14ciii (2.6)
Cardio: Sitting Pulse	-	-	-	-	-	-	-	-	-	-	-
Cardio: Standing Pulse	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: Insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Side Effects (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 14ciii (2.7)
Neurological: SAS	KUMRA1996	RCT	Serious[1]	No serious	No seriou	Serious[3]	Reporting bias[2]	K=1; N=21	0.66 [-0.23, 1.54]	Very low[1,2,3]	Appendix 14ciii (2.8)

				risk of inconsistency	s risk of indirectness						
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (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=1; N=21	1.15 [0.43, 3.03]	Very low[1,2,3]	Appendix 14ciii (2.9)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours olanzapine
** Favours clozapine
[1]Downgraded due to risk of bias (including: method of allocation concealment unclear, blinding of raters unclear; ITT method of analysis unclear or available case analysis used, eligibility criteria states that patients must be not be treatment refractory to treatment of study meds, not all data reported sufficiently to allow for extraction and analysis and trial registration could not be found)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Summary evidence profile for extractable metabolic side effect outcomes in children and young people

Outcome or subgroup	STUDY ID	Comparison	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Studies/ number of participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Metabolic: Weight change kg (SMD)	CASTRO-FORNILES2008[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 14 civ (1.1)
	CASTRO-FORNILES2008[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 14 civ (1.2)
	CASTRO-FORNILES2008[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]	Appendix1 5 civ (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 14 civ (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 14 civ (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 14 civ (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 14 civ (2.2)
	CROCQ2007[2]	Olanzapine (SOT) versus	OS	Serious[3]	No serious risk of	No serious risk of	Serious[4]	Reporting bias[5]	K = 1; N = 26	-1.06 [-1.91, -0.21]***	Very low[3,4,5]	Appendix 14 civ (2.3)

		olanzapine (ODT)			inconsistency	indirectness						
Metabolic: Fasting Serum Glucose Level mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Total Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Lipid Level Change in Total Cholesterol mg/dl	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Serious-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl (SMD)	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic: Fasting Triglycerides	-	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference; OS= Observational study; ODT: Orally disintegrating tablet; SOT: Standard oral tablet
*Favours quetiapine
**Favours risperidone
*** Favours olanzapine (ODT)
[1] 26 weeks' treatment

[2] 12 weeks' treatment
[3] Serious risk of bias (including: observational study)
[4] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[5] Serious risk of reporting bias

Summary evidence profile for extractable neurological side effect outcomes in children and young people

Outcome or subgroup	STUDY ID	Comparison	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Studies/ number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Neurological: Extrapyramidal Side Effects (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: UKU (SMD)	CASTRO-FORNILES2008[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]	Appendix15 civ (3.1)
	CASTRO-FORNILES2008[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]	Appendix15 civ (3.2)
	CASTRO-FORNILES2	Olanzapine (SOT) versus	OS	Serious[2]	No serious risk of	No serious risk of	Serious[3]	Reporting bias[4]	K = 1; N = 45	-0.39 [-1.03, 0.25]	N/A	Very low[2,3,4]	Appendix15 civ (3.3)

	008[1]	risperidone			inconsistency	indirectness							
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Tremor (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Akathesia (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Dyskenesia (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-
Neurological: Extrapyramidal Disorder (RR)	-	-	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference; OS= Observational study
[1] 26 weeks' treatment
[2] Serious risk of bias (including: observational)
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Serious risk of reporting bias

APPENDIX 17d: COGNITION, EMPLOYMENT AND EDUCATION: EVIDENCE PROFILES

Cognitive Enhancement Therapy (CRT and group-based social cognition therapy) versus Psychoeducation at 104 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other conside rations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	EACK2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=58	-0.72 [-1.25, -0.19]*	Low[1, 2]	Appendix 14d (3.2)
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative(SMD)	EACK2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=58	-0.96 [-1.51, -0.41]*	Low[1, 2]	Appendix 14d (3.3)
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety/Depression (SMD)	EACK2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=58	-0.41 [-0.93, 0.11]	Low[1, 2]	Appendix 14d (3.1)
Psychosocial Functioning(SMD)	EACK2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=58	-0.86 [-1.41, -0.32]*	Low[1, 2]	Appendix 14d (3.4)
Social Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social Cognition (SMD)	EACK2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=58	-1.20 [-1.76, -0.64]*	Low[1, 2]	Appendix 14d (3.5)
Education	-	-	-	-	-	-	-	-	-	-	-
Sensitivity analysis: Employment (assuming drop outs did not gain employment; RR)	EACK2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=58	2.83 [1.05, 7.65]*	Low[1, 2]	Appendix 14d (3.6)

Leaving study early for any reason (RR)	EACK2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=58	1.22 [0.44, 3.40]	Low[1, 2]	Appendix 14d (3.15)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
*Favours CRT
[1]Serious risk of bias (including unblind and missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

CRT versus Psychoeducation at 26 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Number of studies / participants	Effect Estimate (SMD or RR)	Quality
Symptoms: Total (SMD)	UELAND 2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	None	-0.19 [-0.98, 0.60]	Low[1, 2]	Appendix 14d (1.1)
Symptoms: Positive (SMD)	UELAND 2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	-0.33 [-1.13, 0.47]	Low[1, 2]	Appendix 14d (1.2)
Symptoms: Negative (SMD)	UELAND 2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	-0.17 [-0.96, 0.62]	Low[1, 2]	Appendix 14d (1.3)
Symptoms: General (SMD)	-	-	-	-	-	-		-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-		-	-	-	-
Depression (SMD)	-	-	-	-	-	-		-	-	-	-
Mania (SMD)	-	-	-	-	-	-		-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-		-	-	-	-
Psychosocial Functioning(SMD)	UELAND 2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=26	-0.46 [-1.24, 0.32]	Low[1, 2]	Appendix 14d (1.4)
Social Functioning(SMD)	-	-	-	-	-	-		-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-		-	-	-	-
Cognition	-	-	-	-	-	-		-	-	-	-
Education	-	-	-	-	-	-		-	-	-	-
Employment	-	-	-	-	-	-		-	-	-	-
Leaving study early for any reason (RR)	-	-	-	-	-	-		-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1]Serious risk of bias (including unblind, trial registration not found and drop out not reported by group).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

CRT versus Psychoeducation at 52 weeks follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	UELAND 2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=24	-0.40 [-1.22, 0.42]	Low[1,2]	Appendix 14d (2.1)
Symptoms: Positive (SMD)	UELAND 2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=24	-0.35 [-1.17, 0.47]	Low[1,2]	Appendix 14d (2.2)
Symptoms: Negative (SMD)	UELAND 2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=24	-0.66 [-1.50, 0.17]	Low[1,2]	Appendix 14d (2.3)
Symptoms: General(SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning (SMD)	UELAND 2004	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=25	-0.15 [-0.94, 0.64]	Low[1,2]	Appendix 14d (2.4)
Social Functioning(SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cognition	-	-	-	-	-	-	-	-	-	-	-
Education	-	-	-	-	-	-	-	-	-	-	-
Employment	-	-	-	-	-	-	-	-	-	-	-
Leaving study early for any reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1]Serious risk of bias (including unblind, trial registration not found and drop out not reported by group).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

CRT versus TAU at 14 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cognition	-	-	-	-	-	-	-	-	-	-	-
Education	-	-	-	-	-	-	-	-	-	-	-
Employment (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving study early for any reason (RR)	WYKES 2007	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=40	1.03 [0.75, 1.40]	Low[1, 2]	Appendix 14d (4.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1]Serious risk of bias (including sequence generation unclear and unblind).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

CRT versus TAU at 26 weeks post follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cognition	-	-	-	-	-	-	-	-	-	-	-
Education	-	-	-	-	-	-	-	-	-	-	-
Employment (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving study early for any reason (RR)	WYKES 2007	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=40	0.97 [0.69, 1.35]	Low[1, 2]	Appendix 14d (5.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1]Serious risk of bias (including sequence generation unclear and unblind).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

CRT versus Computer Games at 26 weeks post follow-up

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	URBEN 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=28	0.26 [-0.49, 1.00]	Very low[1, 2, 3]	Appendix 14d (6.1)
Symptoms: Positive (SMD)	URBEN 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=28	0.35 [-0.39, 1.10]	Very low[1, 2, 3]	Appendix 14d (6.2)
Symptoms: Negative (SMD)	URBEN 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=28	0.29 [-0.46, 1.04]	Very low[1, 2, 3]	Appendix 14d (6.3)
Symptoms: General (SMD)	URBEN 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=28	0.23 [-0.52, 0.97]	Very low[1, 2, 3]	Appendix 14d (6.4)
Global State (Severity) (SMD)	URBEN 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=28	0.21 [-0.53, 0.96]	Very low[1, 2, 3]	Appendix 14d (6.5)
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning	-	-	-	-	-	-	-	-	-	-	
Social Functioning (SMD)	URBEN 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=28	0.31 [-0.44, 1.06]	Very low[1, 2, 3]	Appendix 14d (6.6)
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cognition	-	-	-	-	-	-	-	-	-	-	-
Education	-	-	-	-	-	-	-	-	-	-	-
Employment (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving study early for any reason (RR)	URBEN 2012	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[2]	None	K=1, N=32	1.17 [0.41, 3.35]	Very low[1, 2, 3]	Appendix 14d (6.7)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including sequence generation and allocation concealment unclear, only raters blind and trial registration not found).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Serious risk of indirectness (as sample contains participants at Serious risk of psychosis).

IPS versus EPPIC TAU at 26 weeks post treatment

Outcome or Subgroup	Study ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	Forest plot
Symptoms: Total (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Positive (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: Negative (SMD)	-	-	-	-	-	-	-	-	-	-	-
Symptoms: General (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global State (Severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial Functioning	-	-	-	-	-	-	-	-	-	-	-
Social Functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of Life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Cognition	-	-	-	-	-	-	-	-	-	-	-
Sensitivity analysis: Employed/ enrolled on a course (assuming drop outs did not gain employment; RR)	KILLACKEY2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=41	6.83 [1.76, 26.51]*	Low[1, 2]	Appendix 14d (8.1)
Number of weeks worked (SMD)	KILLACKEY2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=15	-0.49 [-1.99, 1.02]	Low[1, 2]	Appendix 14d (8.3)
Number of hours worked per week (SMD)	KILLACKEY2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=15	-0.71 [-2.22, 0.81]	Low[1, 2]	Appendix 14d (8.4)
Leaving the Study Early for Any Reason (RR)	KILLACKEY2008	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K=1, N=41	0.21 [0.03, 1.64]*	Low[1, 2]	Appendix 14d (8.5)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
*Favours IPS.
[1] Serious risk of bias (including unblind and more people in the TAU group were in marital or marital-like relationships. This would tend to bias the study against finding success for the vocational intervention, as people in marital relationships tend to function better socially and in employment).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

2. ECONOMIC EVIDENCE PROFILES

Study and country	Limitations	Applicability	Other comments	Incremental cost (£)[1]	Incremental effect (QALYs)	ICER (£/QALY)	Uncertainty
Valmaggia et al., 2009, UK	Potentially serious limitation 2	Partially applicable3	Study based on decision-analytic modelling Health sector and societal perspective Measure of outcome: probability of avoiding transition to psychosis Horizon 24 months Incremental analysis not undertaken in the study; ICER estimated based on study reported results	At 24 months: £1,264	0.15	At 24 months: £8,430 per person avoiding transition to psychosis	No reported for the findings from health sector perspective.

Study and country	Limitations	Applicability	Other comments	Incremental cost (£)[4]	Incremental effect (QALYs)	ICER (£/QALY)	Uncertainty
Phillips et al., 2009, Australia	Potentially serious limitations5	Partially applicable6	Cost minimisation study conducted alongside RCT. Transition probability to psychosis, HRSA, HRSD, BPRS, BPRS-P, SANS, MRS, QLS, GAF	0-6 months: £955 6-12 months: £600 12-36 months: - £9,621	Transition probability to psychosis, HRSA, HRSD, BPRS-P, SANS, MRS, QLS, GAF: No significant difference	Dominant	NA

1 Incremental costs uplifted to 20011 prices using HCHS inflation index.

2 The time duration of the model is short to capture lifelong characteristics of psychosis and the data used is not from randomised control trials.

3 Second year costs are not discounted.

4 Incremental costs uplifted to 20011 prices using HCHS inflation index.

5 Cost implication study, no treatment outcomes measured.

6 Cost implication study, no treatment outcomes measured, £3% discount rate used and Australian healthcare system not exactly similar to the UK.