APPENDIX 17A: CLINICAL AND ECONOMIC EVIDENCE PROFILES: AT RISK MENTAL STATES FOR PSYCHOSIS AND SCHIZOPHRENIA IN CHILDREN AND YOUNG PEOPLE

PHARMACOLOGICAL INTERVENTIONS IN CHILDREN AND YOUNG PEOPLE 25 YEARS AND YOUNGER 3

Olanzapine versus placebo: 52 weeks post-treatment efficacy outcomes 3

Olanzapine versus placebo: 52 weeks post-treatment side effect outcomes 4

Olanzapine versus placebo: 104 weeks' follow-up efficacy outcomes (change scores from post-treatment until follow-up when no treatment was received) 6

Olanzapine versus placebo: 104 weeks' follow-up side effect outcomes (change scores from post-treatment until follow-up when no treatment was received) 7

Risperidone + cognitive behavioural therapy (CBT) versus supportive counselling: post-treatment efficacy outcomes 9

Risperidone + CBT versus supportive counselling: post-treatment side effect outcomes 10

Risperidone + CBT versus supportive counselling: 52 weeks' follow-up efficacy outcomes 12

Risperidone + CBT versus supportive counselling: 52 weeks' follow-up side effect outcomes 13

Risperidone + CBT versus supportive counselling: 156 to 208 weeks' follow-up efficacy outcomes 15

Risperidone + CBT versus supportive counselling: 156 to 208 weeks' follow-up side effect outcomes 16

Risperidone + CBT versus placebo + CBT: 52 weeks post-treatment efficacy outcomes 18

Risperidone + CBT versus placebo + CBT: 52 weeks post-treatment side effect outcomes 19

DIETARY INTERVENTIONS IN CHILDREN AND YOUNG PEOPLE 25 YEARS AND YOUNGER 21

Omega-3 fatty acids versus placebo: 12 weeks post-treatment efficacy outcomes 21

Omega-3 fatty acids versus placebo: 52 weeks' follow-up efficacy and side effect outcomes 22

PSYCHOLOGICAL INTERVENTIONS IN CHILDREN AND YOUNG PEOPLE 18 YEARS AND YOUNGER COMBINED WITH THOSE AGED 25 YEARS AND YOUNGER 24

CBT versus supportive counselling: post-treatment (within/at 26 weeks)..... 24
CBT versus supportive counselling: 52 weeks' follow-up..... 26
CBT versus supportive counselling: follow-up of 78 weeks or more 28
PSYCHOLOGICAL INTERVENTIONS IN CHILDREN AND YOUNG PEOPLE 25 YEARS AND YOUNGER 30
Integrated psychotherapy versus supportive counselling: 52 weeks post-treatment 30
Integrated psychotherapy versus supportive counselling: 104 weeks' follow-up 31
ECONOMIC EVIDENCE PROFILES..... 33

Abbreviations

AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
BP	blood pressure
BPRS (-P)	Brief Psychiatric Rating Scale (-Psychotic Subscale)
CBT	cognitive behavioural therapy
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition
EPS	extrapyramidal symptoms
GAF	Global Assessment of Functioning
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
ICER	incremental cost-effectiveness ratio
OIS	optimal information size
QALY	quality-adjusted life year
QLS	Quality of Life Scale
QT	the interval between Q and T waves in the electrocardiogram
RCT	randomised controlled trial
RR	relative risk
SANS	Scale for the Assessment of Negative Symptoms
SAS	Simpson-Angus Extrapyramidal Side Effects Scale
SMD	standardised mean difference
YMRS	Young Mania Rating Scale

PHARMACOLOGICAL INTERVENTIONS IN CHILDREN AND YOUNG PEOPLE 25 YEARS AND YOUNGER

Olanzapine versus placebo: 52 weeks post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other consider-ations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (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)
Positive symptoms (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)
Negative symptoms (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)
General symptoms (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)	-	-	-	-	-	-	-	-	-	-	-

Completers analysis: transition to psychosis (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.[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment and missing data).
[2]Optimal information size (OIS) (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Olanzapine versus placebo: 52 weeks post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other consider-ations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight gain (kg)	MCGLASHAN 2003	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 (BPM; SMD)	MCGLASHAN 2003	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 (BPM; SMD)	MCGLASHAN 2003	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 (EPS) (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	MCGLASHAN 2003	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. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
*Favours placebo.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

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

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other consider-ations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE	Forest plot
Total symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Positive symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Negative symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
General symptoms (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: 104 weeks' follow-up side effect outcomes (change scores from post-treatment until follow-up when no treatment was received)

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	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 (BPM; SMD)	-	-	-	-	-	-	-	-	-	-	-

Cardio: standing pulse (BPM; SMD)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	MCGLASHAN 2003	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.[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Risperidone + cognitive behavioural therapy (CBT) versus supportive counselling: post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other consider-ations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 102	0.15 [-0.39, 0.70]	Very low[1,2,3]	Appendix 14a (5.1)
Positive symptoms (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 130	0.02 [-0.33, 0.37]	Very low[1,2,3]	Appendix 14a (5.2)
Negative symptoms (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 130	0.13 [-0.68, 0.94]	Very low[1,2,3]	Appendix 14a (5.3)
General symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity; SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 130	0.24 [-0.12, 0.59]	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 = 130	-0.13 [-0.49, 0.22]	Very low[1,2,3]	Appendix 14a (5.8)
Completer analysis: transition to psychosis (RR)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 130	0.35 [0.13, 0.95]	Very low[1,2,3]	Appendix 14a (5.9)

Note [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration not found, uneven sample sizes and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met. [3]Serious risk of reporting bias.

Risperidone + CBT versus supportive counselling: post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other consider-ations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	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 (BPM; SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse (BPM; SMD)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-

Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (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]	Appendix 14a (6.2)
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: Parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 130	0.76 [0.28, 2.03]	Very low[1,2,3]	Appendix 14a (6.1)

Note.[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration not found, uneven sample sizes and missing data)
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Risperidone + CBT versus supportive counselling: 52 weeks' follow-up efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other consider-ations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 101	0.07 [-0.32, 0.46]	Very low[1,2,3]	Appendix 14a (7.1)
Positive symptoms (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 101	0.05 [-0.35, 0.44]	Very low[1,2,3]	Appendix 14a (7.2)
Negative symptoms (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 101	0.08 [-0.31, 0.47]	Very low[1,2,3]	Appendix 14a (7.3)
General symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity; SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2,N = 68	0.15 [-0.33, 0.62]	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 = 59	0.00 [-0.51, 0.51]	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 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 102	0.07 [-0.46, 0.32]	Very low[1,2,3]	Appendix 14a (7.8)
Completer analysis: transition to psychosis (RR)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 130	0.63 [0.33, 1.21]	Very low[1,2,3]	Appendix 14a (7.9)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration could not be found and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Risperidone + CBT versus supportive counselling: 52 weeks' follow-up side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecis-ion	Other considerations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	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 (BPM; SMD)	-	-	-	-	-	-	-	-	-	-	-

Cardio: standing pulse (BPM; SMD)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)	-	-	-	-	-	-	-	-	-	-	-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	MCGORRY2002 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 2, N = 130	0.85 [0.43, 1.67]	Very low[1,2,3]	Appendix 14a (8.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration could not be found and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Risperidone + CBT versus supportive counselling: 156 to 208 weeks' follow-up efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other considera-tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	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 (9.1)
Positive symptoms (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 (9.2)
Negative symptoms (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 (9.3)
General symptoms (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 (9.4)
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 (9.5)
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 (9.6)
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 (9.7)
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 [-0.54, 0.71]	Very low[1,2,3]	Appendix 14a (9.8)
Completer analysis: transition to psychosis (RR)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 1, N = 41	0.59 [0.34, 1.04]	Very low[1,2,3]	Appendix 14a (9.9)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	MCGORRY 2002	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 1, N = 59	0.67 [0.46, 0.96]	-	Appendix 14a (9.10)
Number of participants	MCGORRY	RCT	Serious[1]	No serious	No serious	Serious[2]	Reporting	K = 1, N = 41	0.51	Very	Appendix

requiring hospitalisation (RR)	2002			inconsistency	indirectness		bias[3]		[0.19, 1.33]	low[1,2,3]	14a (9.11)

Note.[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration could not be found and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Risperidone + CBT versus supportive counselling: 156 to 208 weeks' follow-up side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other considera-tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight 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 (BPM; SMD)	-							-	-	-	-
Cardio: standing pulse (BPM; SMD)	-							-	-	-	-
Hormonal: prolactin	-							-	-	-	-
Hormonal: insulin	-							-	-	-	-
Neurological: EPS (RR)	-							-	-	-	-
Neurological: AIMS	-							-	-	-	-
Neurological: SAS	-							-	-	-	-
Neurological: BARS	-							-	-	-	-
Neurological: parkinsonism (RR)	-							-	-	-	-
Neurological: tremor (RR)	-							-	-	-	-
Neurological: akathisia (RR)	-							-	-	-	-
Neurological: dystonia (RR)	-							-	-	-	-
Neurological: dyskinesia (RR)	-							-	-	-	-
Neurological: extrapyramidal disorder (RR)	-							-	-	-	-
Mortality (RR)	-							-	-	-	-
Leaving the study early for any reason (RR)	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 (10.1)

Note.[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration could not be found and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Risperidone + CBT versus placebo + CBT: 52 weeks post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other considera-tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	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 (11.1)
Positive symptoms (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 (11.2)
Negative symptoms (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 (11.3)
General symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity; 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 (11.4)
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 (11.5)
Completer analysis: transition to psychosis (RR)	PHILLIPS 2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 1, N = 56	1.02 [0.39, 2.67]	Very low[1,2,3]	Appendix 14a (11.6)

Note.[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, trial registration could not be found and uneven sample sizes).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Risperidone + CBT versus placebo + CBT: 52 weeks post-treatment side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other considera-tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight 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 (BPM; SMD)	-	-	-	-	-	-	-	-	-	-	-
Cardio: standing pulse (BPM; SMD)	-	-	-	-	-	-	-	-	-	-	-
Hormonal: prolactin	-	-	-	-	-	-	-	-	-	-	-
Hormonal: insulin	-	-	-	-	-	-	-	-	-	-	-
Neurological: EPS (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]	Appendix 14a (12.1)

Neurological: AIMS	-	-	-	-	-	-	-	-	-	-	-
Neurological: SAS	-	-	-	-	-	-	-	-	-	-	-
Neurological: BARS	-	-	-	-	-	-	-	-	-	-	-
Neurological: parkinsonism (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: tremor (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: akathisia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dystonia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: dyskinesia (RR)	-	-	-	-	-	-	-	-	-	-	-
Neurological: extrapyramidal disorder (RR)											-
Mortality (RR)	-	-	-	-	-	-	-	-	-	-	-
Leaving the study early for any reason (RR)	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 (12.2)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, trial registration not found and uneven sample sizes).
[2] OIS (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: 12 weeks post-treatment efficacy outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other considera-tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Positive symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Negative symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
General symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity; SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	-	-	-	-	-	-	-	-	-	-	-
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Social functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-
Completer analysis: transition to psychosis (RR)	AMMINGER 2010	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 1, N = 76	0.13 [0.02, 0.95]*	Low[2,3]	Appendix 14a (13.1)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	AMMINGER 2010	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	Reporting bias[3]	K = 1, N = 81	0.39 [0.13, 1.14]*	-	Appendix 14a (13.2)
Leaving the study early for any reason (RR)	-	-	-	-	-	-	-	-	-	-	-

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
*Favours omega-3 fatty acids.
[1]Serious risk of bias (including dropout not reported and available case analysis).
[2] OIS (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: 52 weeks' follow-up efficacy and side effect outcomes

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other considera-tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	AMMINGER 2010	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[32]	K = 1, N = 81	-1.26 [-1.74, -0.78]*	Low[1,2]	Appendix 14a (14.1)
Positive symptoms (SMD)	AMMINGER 2010	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Reporting bias[2]	K = 1, N = 81	-2.08 [-2.63, -1.54]*	Low[2,31,2]	Appendix 14a (14.2)
Negative symptoms (SMD)	AMMINGER 2010	RCT	No serious risk of bias	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 (14.3)
General symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	AMMINGER 2010	RCT	No serious risk of bias	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 (14.4)
Mania (SMD)	-	-	-	-	-	-	-	-	-	-	-
Anxiety (SMD)	-	-	-	-	-	-	-	-	-	-	-
Psychosocial functioning (SMD)	AMMINGER 2010	RCT	No serious risk of bias	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 (14.5)
Social functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	-	-	-	-	-	-	-	-	-	-	-

Completer analysis: transition to psychosis (RR)	AMMINGER 2010	RCT	No serious risk of bias	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 (14.6)
Leaving the study early for any reason (RR)	AMMINGER 2010	RCT	No serious risk of bias	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 (15.1)

Note.[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
*Favours omega-3 fatty acids.
[1] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[2]Serious risk of reporting bias.

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

CBT versus supportive counselling: post-treatment (within/at 26 weeks)

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other considera-tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	ADDINGTON2011 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 2, N = 123	0.004 [-0.32, 0.40]	Low[1, 2]	Appendix 14a (16.1)
Positive symptoms (SMD)	ADDINGTON2011 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 4, N = 489	-0.12 [-0.30, 0.06]	Low[1, 2]	Appendix 14a (16.2)
Sensitivity analysis: positive symptoms (SMD)[b]	ADDINGTON2011 MORRISON2011 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 3, N = 319	-0.11 [-0.33, 0.11]	-	Appendix 14a (16.3)
Negative symptoms (SMD)	ADDINGTON2011 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 2, N = 123	0.17 [-0.19, 0.53]	Low[1, 2]	Appendix 14a (16.4)
General symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity) (SMD)	-							-	-	-	-
Completer analysis: depression (SMD)	ADDINGTON2011 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 4, N = 478	0.13 [-0.20, 0.47]	Low[1, 2]	Appendix 14a (16.5)
Sensitivity analysis: depression	ADDINGTON2011 MORRISON2011 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 3, N = 308	0.27 [0.15, 0.69]	-	Appendix 14a (16.6)

(SMD)[b]											
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 (16.7)
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 (16.8)
Social functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life (SMD)	MORRISON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 3, N = 383	0.01 [-0.19, 0.21]	Low[1, 2]	Appendix 14a (16.9)
Sensitivity analysis: quality of life (SMD)[b]	MORRISON2011 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 2, N = 213	0.01 [-0.26, 0.28]	-	Appendix 14a (16.10)
Completer analysis: transition to psychosis (RR)	ADDINGTON2011* MORRISON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 4, N = 591	0.62 [0.29, 1.31]	Low[1,2]	Appendix 14a (16.11)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	ADDINGTON2011* MORRISON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	K = 4, N = 612	0.66 [0.40, 1.08]	-	Appendix 14a (16.12)
Leaving the study early for any reason (RR)	ADDINGTON2011 MORRISON2011 PHILLIPS2009	RCT	Serious[1]	Serious[3]	No serious indirectness	Serious[2]	None	K = 3, N = 411	1.01 [0.75, 1.36]	Low[1,3]	Appendix 14a (17.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[b] The sensitivity analysis excluded VANDERGAAG2012.
*15 weeks during treatment.
[1]Serious risk of bias (including unclear sequence generation, trial registration could not be found, missing data).
[2] OIS (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: 52 weeks' follow-up

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other consider-ations	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	ADDINGTON2011 MORRISON2004 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 3, N = 154	0.05 [-0.27, -0.37]	Low[1, 2]	Appendix 14a (18.1)
Completer analysis; positive symptoms (SMD)	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 5, N = 493	-0.17 [-0.35, 0.01]	Moderate[1,]	Appendix 14a (18.2)
Sensitivity analysis: positive symptoms (SMD)[b]	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 4, N = 342	-0.27 [-0.49, -0.06]*	-	Appendix 14a (18.3)
Negative symptoms (SMD)	ADDINGTON2011 MORRISON2004 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 3, N = 154	0.11 [-0.21, 0.43]	Low[1, 2]	Appendix 14a (18.4)
General symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Completer analysis: depression (SMD)	ADDINGTON2011 MORRISON2011 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 3, N = 385	-0.05 [-0.25, 0.15]	Low[1, 2]	Appendix 14a (18.5)
Sensitivity analysis: depression (SMD)[b]	ADDINGTON2011 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 2, N = 234	-0.01 [-0.26, 0.25]	-	Appendix 14a (18.6)
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 (18.7)
Psychosocial	ADDINGTON2011	RCT	Serious[1]	No serious	No serious	Serious[2]	None	K = 2,	-0.10	Low[1, 2]	Appendix

functioning (SMD)	MORRISON2011			inconsistency	indirectness			N = 240	[-0.36, 0.15]		14a (18.8)
Social functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Completer analysis: quality of life (SMD)	MORRISON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 3, N = 329	-0.01 [-0.23, 0.21]	Low[1, 2]	Appendix 14a (18.9)
Sensitivity analysis: quality of life (SMD)[b]	MORRISON2011 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 2, N = 178	-0.05 [-0.35, -0.25]	-	Appendix 14a (18.10)
Completer analysis: transition to psychosis (RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 5, N = 645	0.54 [0.34, 0.86]*	Moderate[2]	Appendix 14a (18.11)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 5, N = 672	0.64 [0.44, 0.93]*	-	Appendix 14a (18.12)
Leaving the study early for any reason (RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 5, N = 665	1.03 [0.82, 1.30]	Low[1, 2]	Appendix 14a (19.1)

Note.[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[b]The sensitivity analysis excluded VANDERGAAG2012.
*Favours CBT.
[1]Serious risk of bias (including unclear sequence generation, trial registration could not be found, missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

CBT versus supportive counselling: follow-up of 78 weeks or more

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other considera-tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	ADDINGTON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 1, N = 51	-0.04 [-0.59, 0.51]	Low[1,2]	Appendix 14a (20.1)
Positive symptoms (SMD)	ADDINGTON2011 PHILLIPS2009 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 3, N = 256	-0.17 [-0.42, 0.07]	Low[1,2]	Appendix 14a (20.2)
Sensitivity analysis: positive symptoms (SMD)[b]	ADDINGTON2011 PHILLIPS2009	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 2, N = 116	-0.14 [-0.50, 0.23]	-	Appendix 14a (20.3)
Negative symptoms (SMD)	ADDINGTON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 1, N = 51	-0.10 [-0.65, 0.45]	Low[1,2]	Appendix 14a (20.4)
General symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Global state (severity) (SMD)	-	-	-	-	-	-	-	-	-	-	-
Depression (SMD)	ADDINGTON2011 MORRISON2011 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 3, N = 352	-0.11 [-0.36, 0.13]	Low[1,2]	Appendix 14a (20.5)
Sensitivity analysis: depression (SMD)[b]	ADDINGTON2011 MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 2, N = 112	-0.05 [-0.46, 0.37]	-	Appendix 14a (20.6)
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 (20.7)
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 (20.8)
Social functioning (SMD)	-	-	-	-	-	-	-	-	-	-	-
Quality of life	MORRISON2011	RCT	Serious[1]	No serious	No serious	Serious[2]	None	K = 2, N =	0.18 [-0.10,	Low[1,2]	Appendix

(SMD)	VANDERGAAG2012			inconsistency	indirectness			188	0.47]		14a (20.9)
Sensitivity analysis: quality of life (SMD)[b]	MORRISON2011	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 1, N = 48	0.40 [-0.17, 0.98]	-	Appendix 14a (20.10)
Completer analysis: transition to psychosis (RR)	ADDINGTON2011M ORRISON2011 MORRISON2004 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 4, N = 570	0.63 [0.40, 0.99]	Low[1,2]	Appendix 14a (20.11)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	ADDINGTON2011M ORRISON2011 MORRISON2004 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 4, N = 595	0.55 [0.25, 1.19]	-	Appendix 14a (20.12)
Leaving the study early for any reason (RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 VANDERGAAG2012	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	K = 4, N = 593	1.09 [0.88, 1.35]	Low[1,2]	Appendix 14a (21.1)

Note.[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
[1]Serious risk of bias (including unclear sequence generation, trial registration could not be found, missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Integrated psychotherapy versus supportive counselling: 52 weeks post-treatment

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other considera-tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Positive symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Negative symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
General symptoms (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 = 125	0.19 [0.04, 0.81]*	Very low[1,2,3]	Appendix 14a (22.1)

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 (23.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
*Favours integrated psychological therapies.
[1] Serious risk of bias (missing data).
[2] OIS (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: 104 weeks' follow-up

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprec-ision	Other considera-tions	Number of studies / participants	Effect estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
Positive symptoms (SMD)							-	-	-	-	-
Negative symptoms (SMD)	-	-	-	-	-	-	-	-	-	-	-
General symptoms (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 = 125	0.32 [0.11, 0.92]*	Very low[1,2,3]	Appendix 14a (24.1)
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 (25.1)

Note.[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 in the full guideline for further detail.
*Favours integrated psychological therapy.
[1] Serious risk of bias (missing data).
[2] OIS (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).

ECONOMIC EVIDENCE PROFILES

Study and country	Limitations	Applicability	Other comments	Incremental cost (£)[1]	Incremental effect (quality adjusted life years [QALYs])	Incremental cost-effectiveness ratio (ICER) (£/QALY)	Uncertainty
Valmaggia *et al.*, 2009, UK	Potentially serious limitation [2]	Partially applicable[3]	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	None reported for the findings from health sector perspective.
Phillips *et al.*, 2009, Australia	Potentially serious limitations[4]	Partially applicable[5]	Cost minimisation study conducted alongside a randomised controlled trial (RCT) Transition probability to psychosis, Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Brief Psychiatric Rating Scale (BPRS), BPRS-Psychotic Subscale (BPRS-P), Scale for the Assessment of Negative Symptoms (SANS), Young Mania Rating Scale (YMRS), Quality of Life Scale (QLS), Global Assessment of Functioning (GAF)	0-6 months: £955 6-12 months: £600 12-36 months: - £9,621	Transition probability to psychosis, HAM-A, HAM-D, BPRS-P, SANS, YMRS, QLS, GAF: No significant difference	Dominant	Not applicable

Note. [1] Incremental costs uplifted to 2011 prices using Hospital and Community Health Services inflation index.
[2] The time duration of the model is short to capture lifelong characteristics of psychosis and the data used are not from RCTs.
[3] Second year costs are not discounted.
[4]Cost implication study, no treatment outcomes measured.
[5] Cost implication study, no treatment outcomes measured, £3% discount rate used and Australian healthcare system not exactly similar to the UK.