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APPENDIX 13a: RECOGNITION AND AT RISK MENTAL STATES OF PSYCHOSIS IN CHILDREN AND YOUNG PEOPLE: INCLUDED STUDY CHARACTERISTICS

Study ID	**MCGLASHAN2003**
Bibliographic reference	McGlashan, T. H., Zipursky, R. B., Perkins, D., *et al.* (2003) The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis: I. Study rationale and design. Schizophrenia Research, 61, 7-18.
General info	Funding source: Eli Lilly Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Last observation carried forward Blindness: Participants, providers and outcome assessors blind. Duration: Length of follow-up – 104 weeks Duration: No. weeks of treatment – 52 weeks Raters: Independent of treatment Design: Multiple sites RCT in the US - Yale University, New Haven CT; University of Toronto, Canada; University of North Carolina, Chapel Hill, NC; and University of Calgary, Canada. Number of people screened, excluded and reasons: 71 consented, 11 were excluded (6 did not meet inclusion criteria, 1 was not prodromal, 4 met psychosis criteria, and 1 had an IQ <80, 4 withdrew consent, 1 did not return), 60 were randomised. Notes about study methods: N/A
Participants	Diagnosis: At risk mental state Diagnostic tool: The Criteria of Prodromal Syndromes (COPS). Inclusion criteria: Treatment-seeking outpatients. 12 to 45 years old Meeting a definition of prodromal syndrome Exclusion criteria: Meeting criteria for past or current DSM-IV psychotic disorder Judged clinically to suffer from a treatable psychiatric disorder (for example, mania, depression, attention deficit/ hyperactivity disorder) that could account for the inclusion symptoms Judged clinically to be at suicidal or homicidal risk too serious to risk randomisation to placebo

	Presenting with inclusion symptoms occurring primarily as sequelae to drug or alcohol use IQ <80 Took non protocol psychotropic medications within 1 week of randomisation. Total sample size: No. randomised 60 Gender: 65% male Age: Mean: 17.8 years (range 12 to 36) Ethnicity: 67% Caucasian Setting: A specialist outpatient clinic for prodromal patients called the 'Prevention through Risk Identification Management and Education (PRIME) clinic.
Interventions	Intervention – group 1: Olanzapine 8 mg/day for 52 weeks, N = 31. Intervention – group 2: Placebo for 52 weeks, N = 29. Notes about the interventions: Individual and family psychosocial interventions with supportive and psycho educational components were available to each participant.
Extractable outcomes	Transition to psychosis (presence of psychosis scale): Number of people Mental state: SOPS, PANSS, YMRS, MADRS Global state: CGI-S Psychosocial functioning: GAF Side effects: Blood pressure, pulse, weight, SAS, AIMS, BARNES Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Unclear risk Allocation Concealment: Unclear risk Participants blinded: Low risk Providers blinded: Low risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: Unclear risk Other bias: Low risk
Related publications	McGlashan, THZ (2006) Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *American Journal of Psychiatry*, 163, 790-799. Woods, SWB (2003) Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. *Biological Psychiatry*, 54, 453-464.

Study ID	MCGORRY2002
Bibliographic reference	McGorry, P. D., Yung, A. R., Phillips, L. J. *et al.* (2002) Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Archives of General Psychiatry*, *59*, 921–928.
General info	Funding source: The Commonwealth Government of Australia Research and Development Grants Advisory Committee and Janssen- Cilag Pharmaceuticals. Funding for the follow-up component was provided by an Australian Rotary Health Research Fund. Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT Blindness: 'Designed as a single-blind RCT with research interviewers intended to be blind to the interventions received. However, this was difficult to achieve because the two intervention groups were treated by different clinicians, a feature that was difficult to conceal from raters.' Duration: Length of follow-up – 156 to 208 weeks Duration: No. weeks of treatment – 26 weeks Raters: Independent of treatment Design: Single site RCT, Melbourne, Australia. Number of people screened, excluded and reasons: 522 individuals were referred to the PACE clinic, 135 met study criteria, 43 refused research participation, 92 agreed to participation. 59 participants were randomised. Notes about study methods: N/A
Participants	Diagnosis: At risk mental state Diagnostic tool: Not reported Inclusion criteria: • Aged 14 to 30 years • Lived in the Melbourne metropolitan area • Met criteria for 1 or more of 3 operationally defined UHR groups. Exclusion criteria: • A previous psychotic or manic episode • Previous treatment with an antipsychotic or mood stabilising agent • A substance induced psychotic disorder • IQ <70 • An inadequate command of the English language. Total sample size: No. randomised - 59 Gender: 58% male Age: Mean 20 (range 14 to 28) years

	Ethnicity: Not reported Setting: Specialist clinic – PACE (Personal Assessment and Crisis Evaluation) Clinic, an extension of the Early Psychosis Prevention and Intervention Centre (EPPIC).
Interventions	Intervention – group 1: Specific Preventative intervention (SPI) – Risperidone 1.3 mg/day + CBT for 26 weeks, N = 31. Intervention – group 2: Needs based intervention (NBI) for 26 weeks, N = 28. Notes about the interventions: N/A SPI: Involved all elements of NBI and 2 additional treatment components – risperidone and CBT. Cognitive behaviour therapy was conducted according to a manual. The overall aims were to develop an understanding of the symptoms experienced, to learn strategies to enhance control of these symptoms, and to reduce associated distress. The following modules were offered flexibly: Stress Management, Depression/Negative Symptoms, Positive Symptoms, and Other Comorbidity (including substance abuse, obsessive-compulsive features, and social anxiety). NBI: Focused on the presenting symptoms and problems already manifest. Patients assigned to this group received needs-based supportive psychotherapy primarily focusing on pertinent issues such as social relationships and vocational and family issues. Therapists also performed a case management role, providing assistance with accommodation, education or employment, and family education and support. Although patients in this group did not receive antipsychotic medication, they could receive antidepressants (sertraline hydrochloride) if moderate to severe depression was present or benzodiazepines for insomnia (usually temazepam).
Extractable outcomes	Transition to psychosis: Number of people Mental state: HAM-D, HAM-S, BPRS, SANS, YMRS Psychosocial functioning: GAF Quality of life: QLS Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Unclear risk Allocation Concealment: Unclear risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: High risk Missing outcome data: High risk Selective outcome reporting: Unclear risk Other bias: High risk
Related publications	Phillips, LJM (2007) Medium term follow-up of a randomized controlled trial of interventions for young people at ultra high risk of psychosis. *Schizophrenia Research*, 96, 25–33.

Study ID	PHILLIPS2009
Bibliographic reference	Phillips, L. J., Nelson, B., Yuen, H. P., *et al.* (2009) Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: Study design and baseline characteristics. *Australian and New Zealand Journal of Psychiatry*, *43*, 818–829.
General info	Funding source: Janssen-Cilag Pharmaceuticals Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT – multiple imputation was used to impute missing values. Blindness: Research interviewers and psychiatrists involved with the study were blind to treatment group. Psychologists were blind to treatment group as far as the design would allow (obviously to the pharmacological but not to the psychological intervention). Duration: Length of follow-up – 104 weeks Duration: No. weeks of treatment – 52 weeks Raters: Independent of treatment Design: Single site RCT, Melbourne, Australia. Number of people screened, excluded and reasons: 1428 referred to PACE clinic, 464 met study criteria, 225 agreed to research participation, 30 entered a lithium trial, 2 were subsequently found not to meet criteria for randomisation. 115 participants were randomised, 78 refused randomisation but agreed to research assessment and follow-up. Notes about study methods: The 78 people who formed the monitoring group were excluded from this systematic review owing to the absence of randomisation.
Participants	Diagnosis: At risk mental state Diagnostic tool: CAARMS Inclusion criteria: • Aged between 14 and 30 years. • Living in the Melbourne metropolitan area. • Meeting criteria for one or more of three UHR groups. Exclusion criteria: • History of a previous psychotic or manic episode (treated or untreated) • History of a medical condition that may account for symptoms leading to initial referral (for example, epilepsy) • Clinically relevant neurological, biochemical or haematological abnormalities • Serious coexisting illnesses • Previous use of neuroleptic medication (greater than the equivalent of 5 mg of haloperidol for 3 weeks or longer) • Any previous or current use of mood stabilising medication • History of severe drug allergy • Intellectual disability (IQ <70)

	• Pregnant or lactating • Insufficient English language skills to participate in research interviews or psychological treatment without assistance from an interpreter. Total sample size: No. randomised – 115 Gender: 39% male Age: Mean 18 (range not reported) years Ethnicity: Not reported Setting: Specialist clinic – PACE (Personal Assessment and Crisis Evaluation) Clinic, an extension of the Early Psychosis Prevention and Intervention Centre (EPPIC).
Interventions	Intervention – group 1: CBT (35 sessions was aimed at) + risperidone 2 mg/day), for 52 weeks, N = 43. Intervention – group 2: CBT (35 sessions was aimed at) + placebo, for 52 weeks, N = 44. Intervention – group 3: Supportive counselling (35 sessions was aimed at) + placebo, N = 28. Notes about the interventions: CBT Provided by trained clinical psychologists using a manualised program consisting of 4 modules: stress management, depression/ negative symptoms, positive symptoms and other comorbidities. Supportive Counselling: Was provided by the same clinical psychologists and aimed to provide the patient with emotional and social support, as well as basic problem solving, stress management and psycho education about psychosis.
Extractable outcomes	Transition to psychosis (CAARMS): Number of participants Mental state: BPRS, SOPS, HAM-D Psychosocial functioning: GAF Quality of life: QLS Side effects: UKU Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Low risk Allocation Concealment: Low risk Participants blinded: Low risk Providers blinded: Low risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: Unclear risk Other bias: High risk
Related publications	McGorry, PD, Nelson, B, Phillips, LJ et al (unpublished) Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: 12-month outcome. Yung, ARP (2011) Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis.

	Journal of Clinical Psychiatry, 72, 430–440.

Study ID	**AMMINGER2010**
Bibliographic reference	Amminger, G. P., Schäfer, M. R., Papageorgiou, K., *et al.* (2010) Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Archives of General Psychiatry*, *67*, 146–154.
General info	Funding source: Stanley Medical Research Institute Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT Blindness: Participants, providers and outcome assessors were blind. Duration: Length of follow-up – 52 weeks Duration: No. weeks of treatment – 12 weeks Raters: Independent of treatment Design: Single site RCT, Vienna, Austria. Number of people screened, excluded and reasons: 256 individuals assessed for eligibility, 175 excluded (150 did not meet inclusion criteria or met exclusion criteria and 25 refused to participate). 81 participants were randomised. Notes about study methods: N/A
Participants	Diagnosis: At risk mental state Diagnostic tool: PANSS Inclusion criteria: • Aged 13 to 25 years • Meeting criteria for 1 or more of 3 operationally defined and well-validated groups of risk factors for psychosis. Exclusion criteria: • A history of a previous psychotic disorder or manic episode (both treated or untreated) • Substance-induced psychotic disorder • Acute suicidal or aggressive behaviour • A current DSM-IV diagnosis of substance dependence (except cannabis dependence). • Neurological disorders (for example, epilepsy). • IQ <70 • Structural brain changes apparent on magnetic resonance imaging, except for enlargement of the ventricles or sulci or other minor abnormalities without pathological relevance (for example, white matter lucencies or temporal horn asymmetry). • Previous treatment with an antipsychotic or mood-stabilising agent (>1week).

	• Having taken ω-3 supplements within 8 weeks of being included in the trial. • Laboratory values more than 10% outside the normal range for transaminases, thyroid hormones, C-reactive protein, or bleeding parameters. • Another severe intercurrent illness that may have put the person at risk or influenced the results of the trial or affected their ability to take part in the trial. Total sample size: No. randomised – 81 Gender: 33% male Age: Mean 16 years (range not reported) Ethnicity: Not reported Setting: Specialist clinic – Psychosis detection unit of the Department of Child and Adolescent Psychiatry, Medical University of Vienna.
Interventions	Intervention – group 1: long-chain ω-3 fatty acids (fish oil), 1200 mg per day for 12 weeks, N = 41. Intervention – group 2: Placebo (coconut oil), N = 40. Notes about the interventions: Placebo capsules were carefully matched in appearance and flavour with the active treatment; they also contained the same amount of vitamin E as the ω-3 capsules and 1% fish oil to mimic taste.
Extractable outcomes	Transition to psychosis (DSM-IV): Number of participants. Mental state: PANSS, SANS, SAPS, MADRS Psychosocial functioning: GAF Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Low risk Allocation Concealment: Low risk Participants blinded: Low risk Providers blinded: Low risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: High risk Other bias: High risk
Related publications	Marshall, M and Rathbone, J (2011) Early intervention for psychosis. *Cochrane Database of Systematic Reviews*, 6.

Study ID	ADDINGTON2011A
Bibliographic reference	Addington, J., Epstein, I., Liu, L., *et al.* (2011) A randomized controlled trial of cognitive bevioural therapy for individuals at clinical high risk of psychosis. *Schizophrenia Research*, *125*, 54-61.
General info	Funding source: Ontario Mental Health Research Foundation Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Not reported Blindness: Only raters blind Duration: Length of follow-up – 78 weeks Duration: No. weeks of treatment – 26 weeks Raters: Independent of treatment Design: A single site RCT, Toronto, Canada. Number of people screened, excluded and reasons: 562 individuals referred, 302 assessed suitable after phone screen, 112 met COPS criteria, 37 refused any study, 19 refused but consented to a non-treatment study, 56 consented. 51 participants were then randomised. Notes about study methods: Recruitment of participants was sought from a variety of sources including family physicians, student counsellors, and community mental health teams and practitioners. Recruitment and ascertainment methods included advertisement on radio, public transit and local newspaper.
Participants	Diagnosis: At risk mental state Diagnostic tool: The Criteria of Prodromal Syndromes (COPS). Inclusion criteria: • Aged 14 and 30 • Meet the Criteria of Prodromal States Exclusion criteria: • Met criteria for any current or lifetime axis I psychotic disorder • Prior history of treatment with an antipsychotic • IQ <70 • Past or current history of a clinically significant central nervous system disorder which may confound or contribute to prodromal symptoms. Total sample size: No. randomised - 51 Gender: 71% male Age: Mean 20.9 years (range not reported). Ethnicity: 57% Caucasian Setting: Specialist centre - PRIME (Prevention through Risk Identification, Management and Education) clinic

Interventions	Intervention – group 1: CBT - up to 20 sessions within 26 weeks, N = 27. Intervention – group 2: Supportive counselling - up to 20 sessions within 26 weeks, N = 24. Notes about the interventions:
Extractable outcomes	Transition to psychosis (DSM-IV): Number of participants Mental state: SOPS, CDSS Functioning: GAF, SAS, SIAS Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Low risk Allocation Concealment: Unclear risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: Unclear risk Other bias: High risk
Related publications	N/A

Study ID	**BECHDOLF2012**
Bibliographic reference	Bechdolf, A., Wagner, M., Ruhrmann, S., *et al.* (2012) Preventing progression to first-episode psychosis in early initial prodromal states. *British Journal of Psychiatry*, *200*, 22–29.
General info	Funding source: German Federal Ministry for Education and Research BMBF Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT Blindness: Participants, providers and raters were not blind - "Although ratings were mainly carried out by people, who were not involved in treatment, raters could have been aware of the treatment allocation, which raises the possibility that rating bias could have influenced the results." Duration: Length of follow-up – 104 weeks Duration: No. weeks of treatment – 52 weeks Raters: Independent of treatment. Design: Multi-site RCT, at four Early Detection and Intervention Centres located at the Departments of Psychiatry and Psychotherapy at the Universities of Cologne, Bonn, Dusseldorf and Munich. Number of people screened, excluded and reasons: 1597 individuals assessed, 232 met early initial prodromal state (EIPS) inclusion criteria, and 168 were eligible for randomisation. 128 participants were randomised (22 refused research participation, 15

	refused treatment, 2 were lost during assessment and 1 developed psychosis). Notes about study methods: N/A
Participants	Diagnosis: At risk mental state Diagnostic tool: Early Recognition Inventory (ERIraos) Inclusion criteria: • Self-experienced cognitive thought and perception deficits • One or more of the following basic symptoms in the last 3 months several times a week: - Thought interferences - Thought perseveration - Thought pressure - Thought blockages - Disturbances of receptive language, either heard or read - Decreased ability to discriminate between ideas and perception, fantasy and true memories - Unstable ideas of reference (subject-centrism) - Derealisation - Visual perception disturbances (blurred vision, transitory blindness, partial sight, hypersensitivity to light, etc.) - Acoustic perception disturbances (hypersensitivity to sounds or noise, acoasms, etc.) - and/or • Reduction in the Global Assessment of Functioning Score (DSM IV) of at least 30 points (within the past year) and at least one of the following risk factors (GR/D): - First-degree relative with a lifetime-diagnosis of schizophrenia or a schizophrenia spectrum disorder - Pre- or perinatal complications Exclusion criteria: • Attenuated or brief limited intermittent psychotic symptoms • Present or past diagnosis of a schizophrenic, schizophreniform, schizoaffective, delusional or bipolar disorder according to DSM IV. • Present or past diagnosis of a brief psychotic disorder according to DSM IV with a duration of more than 1 week or within the last 4 weeks regardless of its duration. • Diagnosis of delirium, dementia, amnestic or other cognitive disorder, mental retardation, psychiatric disorders due to a somatic factor or related to the consumption of psychotropic substances according to DSM IV. • Alcohol or drug dependence within the last 3 months prior to inclusion according to DSM IV. • Organic brain disease (inflammatory, traumatic, epilepsy, etc.) • Previous treatment with antipsychotics. • Acute suicidality.

	• Aged below 17 years and above 35 years. Total sample size: No. randomised - 128 Gender: 66% male Age: Mean 25.8 years (range not reported) Ethnicity: Not reported Setting: Specialist early detection and intervention centres - (specialised out-patient departments designed to provide a low-threshold, non stigmatising environment).
Interventions	Intervention – group 1: Integrated Psychological Therapies (IPT), delivered weekly or bi-weekly for 52 weeks, N = 63. Intervention – group 2: Supportive Counselling, a maximum of 30 session over 52 weeks, N = 65. Notes about the interventions: IPT 25 individual CBT sessions 15 group therapy sessions 12 cognitive remediation therapy sessions 3 information and counselling of relatives sessions. Supportive Counselling Designed to provide a minimal level of support for individuals who were seeking help and were clearly in need of support as a result of psychiatric symptoms or concerns relating to functional domains. Basic assessment, basic psychoeducation about the at-risk mental state and counselling in a supportive, warm, genuine, empathic and unstructured style were delivered.
Extractable outcomes	Transition to psychosis (PANSS, DSM-IV): Number of participants. Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Low risk Allocation Concealment: Low risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: High risk Other bias: High risk
Related publications	Bechdolf, A, Wagner, M, Veith, V, et al (2007) Randomized controlled multicentre trial of cognitive behaviour therapy in the early initial prodromal state: effects on social adjustment post treatment. *Early Intervention in Psychiatry*, 1, 71–78

Study ID	MORRISON2004
Bibliographic reference	Morrison, A. P., French, P., Walford, L. *et al.* (2004) Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. *The British Journal of Psychiatry*, *185*, 291–297.
General info	Funding source: North West NHS Research and Development Executive and the Stanley Foundation. Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT Blindness: The Early Detection and Intervention Evaluation (EDIE) trial was designed as a pragmatic, single-masked (rater), randomised controlled trial. Assessors were intended to be masked to the condition to which the patient was allocated; however, this proved difficult in practice because the participants often divulged information about their therapist, or used language that suggested they were receiving cognitive therapy. Duration: Length of follow-up – 156 weeks Duration: No. weeks of treatment – 26 weeks Raters: Independent of treatment. Design: Single site RCT, Manchester, United Kingdom. Number of people screened, excluded and reasons: 134 individuals referred for assessment, 14 did not attend and 14 refused participation, therefore 106 were assessed for eligibility. 46 individuals were excluded (27 did not meet inclusion criteria, 3 refused participation, 12 had an untreated first episode of psychosis and 4 were receiving antipsychotic medication) and 60 participants were randomised. Notes about study methods: N/A
Participants	Diagnosis: At risk mental state Diagnostic tool: PANSS, GAF Inclusion criteria: • Brief limited intermittent psychotic symptoms (BLIPS) or attenuated (subclinical) psychotic Or • Trait plus state risk factors -operationally defined by the presence of an at risk mental state – defined for the purposes of this study as scoring for caseness on the General Health Questionnaire and/or a recent deterioration in function of 30 points or more on the Global Assessment of Functioning – plus either a family history, indicated by a first-degree relative with a history of any psychotic disorder, or a diagnosis of schizotypal personality disorder in the participant. • Aged 16 to 36 years old. Exclusion criteria: • Current or past receipt of antipsychotic medication. Total sample size: No. randomised - 60 Gender: 67% male

	Age: Mean 22 (range 16 to 36) years. Ethnicity: Not reported Setting: Recruitment of participants was sought from a variety of sources, including primary care teams (general practitioners, practice nurses, and psychological therapists), student counselling services, accident and emergency departments, specialist services (for example, community drug and alcohol teams, child and adolescent psychiatry and adult psychiatry services), and voluntary sector agencies (such as carers' organisations).
Interventions	Intervention – group 1: Cognitive therapy + monitoring, a maximum of 26 sessions over 26 weeks, N = 37. Intervention – group 2: Monitoring, N = 23. Notes about the interventions: Cognitive therapy + monitoring: Followed the principles developed by Beck (1976). It was problem oriented, time-limited and educational; it encouraged collaborative empiricism, used guided discovery and homework tasks, and was based on a written manual. It was based on the cognitive model most appropriate to the disorder that was prioritised on a problem list agreed between the therapist and the patient. Monitoring: Both monitoring and therapy conditions incorporated elements of case management in order to resolve crises regarding social issues and mental health risks.
Extractable outcomes	Transition to psychosis (PANSS, DSM-IV): Number of participants. Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Low risk Allocation Concealment: Low risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: Low risk Other bias: High risk
Related publications	Morrison, APB (2002) Randomised controlled trial of early detection and cognitive therapy for preventing transition to psychosis in high-risk individuals. Study design and interim analysis of transition rate and psychological risk factors. *British Journal of Psychiatry*, 181, s78-s84. Morrison, APF (2007) Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. *Schizophrenia Bulletin*, 33, 682-687.

Study ID	MORRISON2011
Bibliographic reference	Morrison, A. P., Stewart, S. L., French, P., *et al.* (2011) Early detection and intervention evaluation for people at high-risk of psychosis-2 (EDIE-2): Trial rationale, design and baseline characteristics. *Early Intervention in Psychiatry*, *5*, 24-32.
General info	Funding source: Medical Research Council and the Department of Health. Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT Blindness: Only raters blind Duration: Length of follow-up – 104 weeks Duration: No. weeks of treatment – 26 weeks Raters: Independent of treatment. Design: Multi-site RCT, Manchester, Birmingham/ Worcestershire, Glasgow, Cambridgeshire and Norfolk, United Kingdom. Number of people screened, excluded and reasons: 634 individuals assessed for eligibility and 346 were excluded (321 due to not meeting entry criteria, 36 due to antipsychotic medication, 91 due to current psychosis as initial baseline, 29 due to current psychosis as second baseline, 110 due to being sub-threshold for ARMS, 45 due to not being help-seeking, 10 due to other reasons, 16 lost contact before assessment was complete and 9 declined involvement before assessment was complete). 288 participants were randomised. Notes about study methods: N/A
Participants	Diagnosis: At risk mental state Diagnostic tool: CAARMS Inclusion criteria: • Brief limited intermittent psychotic symptoms, attenuated symptoms or state-plus-trait factors. • Aged between 14 and 35 years, and seeking help for symptoms. Exclusion criteria: • Current or previous receipt of antipsychotic medication • Moderate to severe learning disability • Organic impairment • Insufficient fluency in English. Total sample size: No. randomised - 288 Gender: 63% male Age: Mean 20.7 (range 14 to 34) years Ethnicity: 88% Caucasian Setting: Variable as conducted over multiple sites.

Interventions	Intervention – group 1: Cognitive Therapy + Monitoring, sessions were offered on a weekly basis for up to a maximum of 26 weeks, plus up to 4 booster sessions in the subsequent 6 months, N = 144. Intervention – group 2: Monitoring, for 26 weeks, N = 144. Notes about the interventions: Both conditions were in addition to treatment as usual, which will have been highly variable and dependent on local service configurations and specific source of referral to the trial; therefore, randomisation was stratified by site in an attempt to control for this variation. Cognitive Therapy + Monitoring: Cognitive therapy requires an individualised, problem-orientated approach and incorporates a process of assessment and formulation, which is manualised. The specific interventions depend on individual goals and formulations, but the range of permissible interventions is described in the manual. Key ingredients of the approach are the development of a problem and goal list, early formulation (both longitudinal and maintenance), a focus upon normalising psychotic-like experiences, and an active therapy stance utilising behavioural experiments and evaluation of appraisals. Monitoring: Incorporating a CAARMS assessment from a research assistant, which represents an enhancement over routine care since it aimed to provide warm, empathic and non judgmental face-to-face contact, supportive listening, signposting to appropriate local services for unmet needs and crisis management when required (usually by referral to a local crisis team, early intervention service or psychiatric liaison within emergency departments). Monitoring ensured that all participants had a General Practitioner who they were encouraged to stay in regular contact with and a personalised "crisis card," which provided contact details for local sources of help in a psychiatric emergency.
Extractable outcomes	Transition to psychosis (CAARMS): Number of participants. Mental state: CAARMS-severity, BDI-PC, Social Interaction Anxiety Scale (SIAS). Quality of life: Manchester Short Assessment of Quality of Life (MANSA). Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Low risk Allocation Concealment: Low risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: Low risk Other bias:
Related publications	Morrison, APF (2012) Early detection and intervention evaluation for people at risk of psychosis: Multisite randomised controlled trial. *BMJ* (Online), 344.

Study ID	VANDERGAAG2012
Bibliographic reference	van der Gaag, M., Nieman, D., Rietdijk, J., Dragt, S., Ising-Echergui, H., Klaassen, R., *et al.* (in press) Cognitive behavioural therapy for subjects at ultra-high risk for developing psychosis: a randomised controlled trial. *Schizophrenia Bulletin*, published online: 1 September 2012. DOI: 10.1093/schbul/sbs105.
General info	Funding source: Netherlands Health Research Council Published or unpublished data: Published
Method	Type of study: Multi-site randomised controlled trial Type of analysis: ITT analyses on primary outcomes, analyses on secondary outcomes were based on 164 patients that did not make a transition to psychosis in the study period. Blindness: Only outcome assessors blind Duration: Length of follow-up 18 months Duration: Each patient was treated for 6 months Raters: Only outcome assessors blind Design: Multi-site RCT. Participants were recruited at 4 sites in the Netherlands, (Mental Health Centre PsyQ Haaglanden, the Hague, Academic Medical Centre and Mental Health Centre PsyQ, Amsterdam, Mental Health Centre Rivierduinen, Leiden and surroundings, and Mental Health Institute Friesland in the province of Friesland). Number of people screened, excluded and reasons: Discrepancy in reporting of number of individuals screened (5800 in flow diagram and5705 in text). 5497 excluded (4841 did not meet initial PQ criteria, 373 did not meet criteria for ultra high risk, 104 had psychosis, 8 had history of psychosis, 16 used antipsychotic medication, 50 scored too high on the SOFAS, 3 not in age range, 1 died, 57 refused to participate, 22 lost contact, 22 'other 'reasons, up to 102 participants not accounted for due to discrepency in reporting number screened). 201 participants were randomised. Notes about study methods: N/A
Participants	Diagnosis: At risk mental state Diagnostic tool: CAARMS Inclusion criteria: • Age 14 to 35 years • A genetic risk or CAARMS scores in the range of the ARMS • An impairment in social functioning (a score on the SOFAS of 50 or less, and/or a reduction by 30% on the SOFAS for at least 1 month in the past year) Exclusion criteria: • Current or previous use of antipsychotic medication • Severe learning impairment • Problems due to an organic condition

	• Insufficient competence in the Dutch language • History of psychosis Total sample size: No. randomised = 201 Gender: 49% male Age: Mean 22.74 years (range not reported) Ethnicity: Not reported Setting: Mental health centres (Multi-site)
Interventions	Intervention group (CBTuhr): CBT + psychoeducation on dopamine and cognitive biases + TAU were offered on a weekly basis for up to a maximum of 26 weeks. The mean number of sessions was 10. N = 98. Control group: TAU. N = 103 Notes about the interventions: Both conditions were in addition to treatment as usual, which will have been highly variable and dependent on local service configurations and specific source of referral to the trial; therefore, randomisation was stratified by site in an attempt to control for this variation. CBTuhr: The CBT component of the intervention involved using the French and Morrison protocol; a CBT protocol designed for use with people at high risk of developing psychosis. The protocol was enriched with education on dopamine supersensitivity, explaining how this affects perception and thinking. Excercises were also added to experience cognitive biases; becoming aware of cognitive biases may lead to corrected secondary appraisals. TAU: Both the experimental and the control group were treated with evidence-based active treatment for the axis 1 or 2 disorder from which they were suffering.
Extractable outcomes	Transition to psychosis (CAARMS): Number of participants. Severity of psychosis, if transition had taken place: PANSS. Mental state: BDI-2, CDS, SIAS Quality of life: MANSA Social functioning: SOFAS Personal beliefs about illness: PBIQ-R Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Low risk Allocation Concealment: Low risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: Low risk Other bias:

Related publications	Rietdijk., J., Dragt, S., Klaassen, R., Ising, H., Nieman, D., Wunderink, L., et al. (2010). A single blind randomized controlled trial of cognitive behavioural therapy in a help-seeking population with an At Risk Mental State for psychosis: the Dutch Early Detection and Intervention Evaluation (EDIE-NL) trial. Trials, 11:30.

APPENDIX 13b: PSYCHOLOGICAL THERAPY AND PSYCHOSOCIAL INTERVENTIONS IN THE TREATMENT AND MANAGEMENT OF PSYCHOSIS AND SCHIZOPHRENIA IN CHILDREN AND YOUNG PEOPLE: INCLUDED STUDIES CHARACTERISTICS

Study ID	**APTER1978**
Bibliographic reference	Apter, A., Sharir, I., Tyano, S., *et al.* (1978) Movement therapy with psychotic adolescents. *British Journal of Medical Psychology*, *51*, 155-159.
General info	Funding source: Not reported Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Not reported Blindness: Only raters blind Duration: Length of follow-up – 12 weeks. Duration: No. weeks of treatment - 12 weeks. Raters: Only raters blind Design: Single site RCT, unclear location – "The work was carried out while the authors were at Geha Psychiatric Hospital, Patah-Tiqvah, Israel." Number of people screened, excluded and reasons: Not reported – 30 randomised. Notes about study methods: The unit is designed for the treatment of severely disturbed patients in a 'closed' setting. In addition to biological treatment (psychotropic drugs and ECT) there is a very active milieu programme which includes large and small group therapies, psychodrama, occupational and recreational therapies and in the last 2 years, movement therapy.
Participants	Diagnosis: Acute psychosis (BP not specified) Diagnostic tool: Not reported Inclusion criteria: • Aged 13 to 18. • Admission to the closed inpatient ward. Exclusion criteria: Not reported Total sample size: No. randomised - 30

	Gender: 50% male Age: Not reported Ethnicity: Not reported Setting: Acute inpatient unit
Interventions	Intervention – group 1: Individual movement therapy, 1 hour three times a week, N = 10. Intervention – group 2: Group movement therapy, 1 hour three times a week, N = 10. Intervention – group 3: Group non-specific dance therapy and gymnastic activities in the ward, N = 10. Notes about the interventions: Movement Therapy: The idea of movement therapy is that the patient becomes 'aware' of their body, is able to know the full limits of their physical potential and is able to realise their potential completely. The main foci of attention are body stability, improving body image, coordination, expression of body energy, organisation and planning of body movements and non-verbal communication and expression.
Extractable outcomes	None
Quality	Sequence generation: Unclear risk Allocation Concealment: Unclear risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: Unclear risk Selective outcome reporting: High risk Other bias: Low risk
Related publications	N/A

Study ID	**EDWARDS2011**
Bibliographic reference	Edwards, J. Cocks, J. Burnett, P., *et al.* (2011) Randomized controlled trial of clozapine and CBT for first-episode psychosis with enduring positive symptoms: A pilot study. *Schizophrenia Research and Treatment*, *2011*, 8 pp., Article ID: 394896. DOI: 10.1155/2011/394896.
General info	Funding source: Victorian Government's Health Promotion Foundation (Australia) and NOVARTIS Published or unpublished data: Published
Method	Type of study: Single-blind randomised trial Type of analysis: ITT Blindness: Single-blind (unclear if participants, providers or outcome assessors are blind) Duration: Length of follow-up 24 weeks Duration: No. weeks of treatment 12 weeks

	Raters: Not reported Design: Single site RCT, Melbourne, Australia. Number of people screened, excluded and reasons: 1456 individuals were referred to the EPICC (Early Psychosis Prevention and Intervention Centre) clinic, 89 met study criteria, 41 refused research participation, 48 agreed to participation. 48 participants were randomised. Notes about study methods: 64.3% of CLZ group were male compared to 90.9% of CLZ+CBT group.
Participants	Diagnosis: FEP patients with enduring positive symptoms Diagnostic tool: DSM-IV Inclusion criteria: • FEP patients meeting the DSM-IV criteria for a diagnosis of schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified. • Aged 15 to 29 • Patients continuing to experience moderate to severe positive symptoms defined as a score ≥4 on at least one of the hallucinations, unusual thought content, and conceptual disorganisation items of the expanded version of the brief psychiatric rating scale (BPRS), with a score of not less than 3 on these items for a period of 14 consecutive days or more during the preceding 12 weeks. • Participants were sourced from consecutive admissions to the Early Psychosis Prevention and Intervention Centre (EPPIC) at the Orygen Youth Health Centre for Youth Mental Health in Melbourne, Australia. Exclusion criteria: • An organic mental disorder • Pregnancy or lactation • Requiring antidepressant medication • A mood stabiliser or ECT • A history of drug-induced granulocytopenia Total sample size: No. randomised - 48 Gender: 71% male Age: Mean 21.4 years (range not reported) Ethnicity: NR Setting: Early Psychosis Prevention and Intervention Centre (EPPIC).
Interventions	Intervention – group 1: Clozapine (CLZ) 12.5 mg/day titrated up to a maximum dose of 300 mg/day for 12 weeks, N = 14. Intervention – group 2: Clozapine (CLZ) 12.5 mg/day titrated up to a maximum dose of 300 mg/day + CBT (the manualised program STOPP) for 12 weeks, N = 11. Notes about the interventions: Data was extracted for 2 out of 4 treatment arms, as thioridazine is not included in the research protocol.

	Average daily dose of clozapine was 44.8 mg/day higher in the CLZ only group than the CLZ+CBT group. For CBT, a manualised CBT program, the systematic treatment of persistent psychosis (STOPP) was used. Therapy was conducted twice weekly for 12 weeks, with a minimum attendance of 15 sessions required. All participants received routine clinical care, including access to a 24-hour mobile assessment and treatment team, inpatient service, case management, and psychiatric review. Patients were seen weekly by a psychiatrist/psychiatry registrar for the duration of the trial. All participants not receiving CBT attended weekly case management sessions.
Extractable outcomes	Mental state: BPRS-P, BDI, SANS, CGI Social functioning: SOFAS Quality of life: QLS Leaving the study early: Not reported.
Quality	Sequence generation: Unclear risk Allocation Concealment: Unclear risk Participants blinded: Unclear risk Providers blinded: Unclear risk Outcome Assessors blinded: Unclear risk Missing outcome data: Low risk Selective outcome reporting: Unclear risk Other bias: High risk
Study ID	**GLEESON2009**
Bibliographic reference	Gleeson, J. F., Cotton, S. M., Alvarez-Jimenez, M., *et al.* (2009) A randomized controlled trial of relapse prevention therapy for first-episode psychosis patients. *Journal of Clinical Psychiatry*, *70*, 477-486.
General info	Funding source: Eli Lilly, Colonial Foundation, National Health and Medical Research Council of Australia and Marques de Valdecilla Public Foundation. Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT with last observation carried forward Blindness: Only raters blind Duration: Length of follow-up - 30.33 weeks Duration: No. weeks of treatment- 30.33 weeks Raters: Independent of treatment Design: Single centre RCT – Early Psychosis Prevention and Intervention Centre (EPPIC): Melbourne, Australia. Number of people screened, excluded and reasons: 399 assessed for eligibility, 127 refused to participate, 186 did not meet inclusion criteria and 4 did not meet inclusion criteria at baseline. Notes about study methods: N/A

Participants	Diagnosis: First episode psychosis (4% bipolar) in remission. Diagnostic tool: DSM-IV (Automated in clinic). Inclusion criteria: • DSM-IV diagnosis of first episode psychotic disorder • <6 months of prior treatment with antipsychotic medication • Age 15 to 25 years • Remission on positive symptoms (defined as 4 weeks or more of scores of 3 (mild) or below on the subscale items hallucinations, unusual thought disorder, conceptual disorganisation, and suspiciousness on the expanded version of the BPRS. Exclusion criteria: • Ongoing active positive symptoms of psychosis • Severe intellectual disability • Inability to converse in English • Participation in previous CBT trials. Total sample size: No. randomised - 82 Gender: 63% male Age: 20.1 years (range not reported) Ethnicity: Not reported Setting: Specialist centre (EPPIC)
Interventions	Intervention – group 1: Combined individual and family CBT for relapse prevention + EPPIC TAU, mean(sd) number of individual therapy sessions completed was 8.51(4.87) and family sessions 10.2 (4.6), N = 41. Intervention – group 2: EPPIC Treatment as usual (TAU), N = 41. Notes about the interventions: Combined individual and family CBT for relapse prevention Key difference with TAU: Shared written individualised formulation regarding relapse risk; systematic and phase approach to relapse prevention via a range of CBT interventions; the parallel individual and family sessions focused on relapse prevention and supervision focused on relapse prevention. EPPIC TAU Participants had access to home-based treatment and a range of psychosocial interventions. At entry to the service, all families were routinely offered access to a brief family psychoeducation group, and EPPIC families had access to a family peer support service.
Extractable outcomes	Relapse (BPRS): Number of people Relapse (BPRS): Time in days Mental state: BPRS, SANS, MADRS.

	Quality of life: World Health Organisation Quality of Life Assessment Social Functioning: Social and Occupational Functioning Assessment Scale. Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Low risk Allocation Concealment: Unclear risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: Low risk Selective outcome reporting: Low risk Other bias: Low risk
Related publications	N/A

Study ID	**HADDOCK2006**
Bibliographic reference	Haddock, G., Lewis, S., Bentall, R., *et al.* (2006) Influence of age on outcome of psychological treatments in first-episode psychosis. *The British Journal of Psychiatry*, *188,* 250-254.
General info	Funding source: UK Medical Research Council Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT Blindness: Only raters blind Duration: Length of follow-up – 78 weeks Duration: No. weeks of treatment – 5 weeks Raters: Only raters blind Design: Multi-site RCT, Manchester/Salford, Liverpool and north Nottinghamshire, England Number of people screened, excluded and reasons: 433 individuals screened, 63 ineligible, 370 eligible. 45 refused randomisation, 10 unable to consent, 315 randomised, 6 excluded within 7 days owing to diagnostic change. Notes about study methods: 71 participants were aged≤ 21 and 238 were aged >21. Baseline data were compared according to age using a cut-off point of age 21 years (that is, 'over 21' and '21 years and under'). This cut-off was considered to be a pragmatic developmental point at which to divide the groups. It also allowed sufficient numbers of participants in both groups to ensure that the appropriate comparisons could be made.
Participants	Diagnosis: schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder or psychosis not otherwise

	specified. Diagnostic tool: DSM-IV Inclusion criteria: • Either first or second admission (within 2 years of a first admission) to inpatient or day-patient unit for treatment of psychosis • DSM–IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder or psychosis not otherwise specified • Positive psychotic symptoms for 4 weeks or more; a score of 4 or more on PANSS target item for either delusions (P1) or hallucinations (P3); neither Exclusion criteria: • Substance misuse or organic disorder judged to be the main cause of psychotic symptoms. Total sample size: No. randomised – 309 Gender: 70% male (77% male aged ≤ 21 years) Age: 27.4 (19.6 aged ≤ 21) years Ethnicity: 85% Caucasian Setting: Inpatient/ day patient
Interventions	Intervention – group 1: CBT plus routine care, 15 to 20 hours within 5 weeks, N = 101. Intervention – group 2: Supportive counselling plus routine care, 15 to 20 hours within 5 weeks, N = 106. Intervention – group 3: Routine care, N = 102. Notes about the interventions: CBT: Manual-based and conducted by one of five therapists trained in CBT in psychosis, supervised by experienced cognitive therapists. The design of the delivery was to aim for 15–20 hours within a 5-week treatment envelope, plus 'booster' sessions at a further 2 weeks and 1, 2 and 3 months. SC: A comparison intervention to control for non-specific elements of therapist exposure. It was delivered in the same 5-week format with three boosters, with the aim of matching the duration of total therapist contact time to that in the CBT arm. The supportive counselling was also manual-based and supervised by an experienced counsellor. The same five research therapists administered both CBT and supportive counselling interventions, according to randomisation. Routine care: Not reported
Extractable Outcomes	None
Quality	Sequence generation: Unclear risk Allocation Concealment: Unclear risk Participants blinded: High risk

	Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: Unclear risk Selective outcome reporting: Unclear risk Other bias: High risk
Related publications	Lewis, S., Tarrier, N., Haddock, G. et al, (2002) Randomised controlled trial of cognitive behavioural therapy in early schizophrenia: acute-phase outcomes. *British Journal of Psychiatry*, suppl.43, s91–97.

Study ID	**JACKSON2008**
Bibliographic reference	Jackson, H. J., McGorry, P. D., Killackey, E., *et al.* (2008) Acute-phase and 1-year follow-up results of a randomized controlled trial of CBT versus befriending for first-episode psychosis: the ACE project. *Psychological Medicine*, *38*, 725-735.
General info	Funding source: NH and MRC project grant. Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Missing values in each of the outcome measures for any individual at time points subsequent to baseline were assumed to have occurred at random, given observed pre-treatment scores. Ten multiply imputed datasets were generated using the PAN package in the R statistical software program to deal with these missing responses. Blindness: Only raters blind Duration: Length of follow-up – 52 weeks Duration: No. weeks of treatment – 14 weeks Raters: Independent of treatment Design: Single centre RCT – Early Psychosis Prevention and Intervention Centre (EPPIC): Melbourne, Australia. Number of people screened, excluded and reasons: 427 people screened, 316 were eligible. 126 could not be approached within 4 weeks (for example, no response to telephone calls/letters, non-attendance at appointments) and were excluded because the trial required therapy commencement within 6 weeks of admission. Therefore, 190 individuals were approached for inclusion in the study, but 128 people refused participation. 62 were randomised. Notes about study methods: 5% of the sample had received ECT
Participants	Diagnosis: First episode psychosis (21% bipolar). Diagnostic tool: NR (automated in clinic). Inclusion criteria: • First episode psychosis • Aged 15 to 25 Exclusion criteria:

	• Inability to speak English; • Intellectual disability (IQ <70) • Psychosis due to a medical condition • Change to a non-psychotic diagnosis • Left the EPPIC catchment area • Treatment from a private psychiatrist/psychologist • Participating in a first-episode mania trial • Exhibiting violent behaviour • Being incarcerated. Total sample size: No. randomised - 62 Gender: 73% male Age: 22.3 years (range not reported) Ethnicity: Not reported Setting: Specialist centre (EPPIC)
Interventions	Intervention – group 1: Active Cognitive Therapy for Early Psychosis (ACE), a maximum of 20 sessions over 14 weeks, N = 31. Intervention – group 2: Befriending, a maximum of 20 sessions over 14 weeks, N = 31. Both in addition to EPPIC TAU: A comprehensive treatment service for 15- to 25-year-olds experiencing a first episode of psychosis. It includes a 16-bed inpatient unit, an outpatient case management system, family work, accommodation, prolonged recovery programmes and tailored group programmes. Medication is administered in line with a low-dose protocol. Notes about the interventions: ACE: Assessment of the presenting psychotic and non-psychotic complaints followed by a formulation of the relationship between these complaints and the participant's life history. Problems were prioritised according to a flowchart that directed the ACE therapy. Each area of difficulty was treated from a broadly cognitive behavioural perspective. Befriending: Aimed to control for time in therapy, participant expectations and positive experiences of therapy. Based on the Befriending therapy used by Sensky et al. (2000), Befriending consisted of talking about neutral topics that interested the participant, such as music, sport, books, cooking and pets. If the participant found verbal interaction difficult, the participant and therapist engaged in activities such as board games, walking, or playing sport, with a view to using the activity as a tool to engage the participant in further neutral conversation during and after the activity.
Extractable outcomes	Mental State: BPRS, SANS. Social Functioning: Social and Occupational Functioning Assessment Scale (SOFAS). Number of hospitalisations. Mortality: Number of people who committed suicide.

	Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Low risk Allocation Concealment: Unclear risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: Low risk Selective outcome reporting: Unclear risk Other bias: Low risk
Related publications	N/A

Study ID	**JACKSON2009**
Bibliographic reference	Jackson, C., Trower, P., Reid, I., *et al.* (2009) Improving psychological adjustment following a first episode of psychosis: A randomised controlled trial of cognitive therapy to reduce post psychotic trauma symptoms. *Behaviour Research and Therapy*, *47*, 454-462.
General info	Funding source: The Department of Health Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case analysis Blindness: Only raters blind Duration: Length of follow-up – 52 weeks Duration: No. weeks of treatment – 26 weeks Raters: Independent of treatment Design: Multiple site RCT – 4 mental health services across the West Midlands, Great Britain. Number of people screened, excluded and reasons: 357 individuals were screened, 166 patients met the inclusion criteria. Of these, 60 (37%) refused consent; 25 could not be contacted and 11 were thought to be unsuitable to be contacted by their care teams at the time of the study. This left a sample of 70 consenting to randomisation. One person then withdrew their consent, two were deported and one person no longer fulfilled the criteria for the trial (i.e. their diagnosis was changed). In total 66 people were randomised to the two conditions. Notes about study methods: No changes were made to medication regimes in either the experimental or control conditions. The majority of patients in CBT and treatment as usual (90% versus 92%, respectively) were prescribed atypical neuroleptic medication.

Participants	Diagnosis: First episode psychosis (excluding bipolar) Diagnostic tool: ICD-10 Inclusion criteria: • A first episode of psychosis within the previous 6–18 months. • Aged between 16 and 35 years old. Exclusion criteria: • Unable to speak English. • Unable to give informed consent. Total sample size: No. randomised – 70 Gender: 74% male Age: Mean 23.3 years (range: 16 to 38) Ethnicity: 71% Caucasian Setting: Not reported
Interventions	Intervention – group 1: Cognitive therapy based recovery intervention (CRI) + TAU, a maximum of 26 sessions over 26 weeks, N = 36. Intervention – group 2: Treatment as usual (TAU) from their local mental health services, N = 30. Notes about the interventions: CRI There were three key components: (a) engagement and formulation; (b) trauma processing; and (c) appraisals of psychotic illness (shame, loss and entrapment). The intervention was not just designed for those who could be described as 'traumatised' by their experiences of psychosis but was intended to be helpful for all first episode patients adjusting to and recovering from a first episode of psychosis. TAU Although the TAU interventions across the four sites were not standardised, they were closely monitored and documented. In both conditions (control and CRI), TAU usually consisted of a combination of case management and antipsychotic medication.
Extractable outcomes	Mental state: CDSS Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Low risk Allocation Concealment: Unclear risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: Unclear risk

	Other bias: Unclear risk
Related publications	N/A

Study ID	**LINSZEN1996**
Bibliographic reference	Linszen, D., Dingemans, P., Van der Does, J. W., *et al.* (1996) Treatment, expressed emotion and relapse in recent onset schizophrenic disorders. *Psychological Medicine*, 26, 333-342.
General info	Funding source: Not reported Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Not reported Blindness: Only raters blind Duration: Length of follow-up – 5 years Duration: No. weeks of treatment – 65.8 weeks. Mean number of weeks of inpatient treatment: 13.8 and outpatient treatment: 52 Raters: Independent of treatment. Design: Single centre RCT– psychiatric inpatient: Amsterdam, The Netherlands. Number of people screened, excluded and reasons: Not reported. Notes about study methods: Randomisation of participants to the specific outpatient intervention was performed on completion of inpatient treatment.
Participants	Diagnosis: Schizophrenia (55%), schizoaffective disorders (21%), schizophreniform disorder (13%) and other psychotic disorders (for example, delusional disorder and atypical psychosis; 11 % Diagnostic tool: DSM-III-R Inclusion criteria: • Confirmed diagnosis of schizophrenia or a related disorder • In need of continuous antipsychotic medication • Between 15 and 26 years and living with parents or other relatives or in close contact with them. Exclusion criteria: • Patients with primary alcohol or drug dependence or brief drug-related psychoses who needed detoxification Total sample size: No. randomised -76 Gender: 70% male Age: Mean 20.6 years (range not reported). Ethnicity: Not reported Setting: Inpatient and outpatient
Interventions	Intervention – group 1: Inpatient psychosocial and behavioural family intervention (IPFI), 18 family therapy sessions over a

	maximum of 12 months, N = 37. Intervention – group 2: Inpatient psychosocial intervention (IPI), 18 sessions over a maximum of 12 months, N = 39. Notes about the interventions: IPFI A behavioural family intervention was added to the inpatient psychosocial intervention. The family treatment was based on the behavioural family management approach as developed by Falloon et al. (1984). Psychoeducation, communication training and the development of problem solving skills were the main components; the methods include instruction, role rehearsal and modelling. IPI Acted as a control condition. As during inpatient treatment, patients were taught about their illness including recognizable psychotic, negative, affective and residual symptoms and prodromal signs. Patients were also supported with respect to seeking employment, education and financial support.
Extractable outcomes	Relapse (BPRS): Number of people Leaving the study early: Leaving due to any reason
Quality	Sequence generation: Unclear risk Allocation Concealment: Unclear risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: Unclear risk Selective outcome reporting: High risk Other bias: Low risk
Related publications	Lenior, M., Dingemans, P., Linszen, D *et al.* (2001). Social functioning and the course of early-onset schizophrenia: five-year follow-up of a psychosocial intervention. *BJP*, *179*, 53–58. Linszen, D., Dingemans, P., Scholte, W., *et al.* (1998). Early recognition, intensive intervention and other protective and risk factors for psychotic relapse in patients with first psychotic episodes in schizophrenia. *International Clinical Psychopharmacology*, *13* (Suppl. 1), S7–S12. Nugter, A., Dingemans, P., Van der Does, J., Linszen, D & Gersons, B (1997). Family treatment, expressed emotion and relapse in recent onset schizophrenia. *Psychiatry Research*, *72*, 23–31.

Study ID	MAK2007
Bibliographic reference	Mak, G. K. L., Li, F. W. S. & Lee, P. W. H. (2007) A pilot study on psychological interventions with Chinese young adults with schizophrenia. *Hong Kong Journal of Psychiatry*, *17*, 17-23.
General info	Funding source: Zee Foundation Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case Blindness: Only raters blind Duration: Length of follow-up – 65 weeks Duration: No. weeks of treatment – 39 weeks Raters: Independent of treatment. Design: Single-site RCT, Hong Kong, China. Number of people screened, excluded and reasons: 53 patients interviewed and screened. 48 patients randomised. Notes about study methods: N/A
Participants	Diagnosis: Schizophrenia Diagnostic tool: DSM-IV Inclusion criteria: • Schizophrenia according to DSM-IV criteria • Aged 15 to 32 years • Cantonese speaking • Willing to participate in the study and attend the specified follow-up treatments. • Consent to continue seeing their psychiatrist for ongoing psychiatric treatment. • The absence of any other psychiatric and medical comorbidity. Exclusion criteria: Not reported Total sample size: No. randomised – 48. Gender: 56% male Age: Mean 24 years (range 15 to 32). Ethnicity: Not reported Setting: Non-specified psychiatric setting.
Interventions	Intervention – group 1: Psychotherapy over 65 weeks, N = 23. Intervention – group 2: Waitlist over 65 weeks, N = 13. Notes about the interventions: Psychotherapy: Psychological treatment was based on clinical assessments of the subjects' presenting problems and needs; the orientation being

	cognitive-behavioural. The 2 project psychologists had periodic case consultations with each other to ensure their therapy coverage and approach were compatible. Each patient was seen at least once (about 1 hour) every 2 weeks during the treatment period. Patients with extra needs were allocated more treatment sessions, after the basic psychological treatment package.
Extractable outcomes	None
Quality	Sequence generation: Unclear risk Allocation Concealment: Unclear risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: High risk Other bias: Low risk
Related publications	N/A

Study ID	**POWER2003**
Bibliographic reference	Power, P. J., Bell, R. J., Mills, R., *et al.* (2003) Suicide prevention in first episode psychosis: The development of a randomised controlled trial of cognitive therapy for acutely suicidal patients with early psychosis. *Australian and New Zealand Journal of Psychiatry*, *37*, 414-420.
General info	Funding source: Commonwealth Department of Health and Family Services. Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Not reported Blindness: Only raters blind Duration: Length of follow-up – 6 months Duration: No. weeks of treatment – 10 weeks Raters: Independent of treatment Design: Single centre RCT – Early Psychosis Prevention and Intervention Centre (EPPIC): Melbourne, Australia. Number of people screened, excluded and reasons: 92 people were referred and meeting criteria for the trial, 36 refused to participate and the remaining 56 were randomised. Notes about study methods: N/A
Participants	Diagnosis: Acutely suicidal first episode psychosis (bipolar not specified). Diagnostic tool: Automated in clinic Inclusion criteria:

	• First episode psychosis • Aged 15 to 29 years old • All patients at EPPIC who were rated between 4 and 7 on the Expanded Version 4 of the BPRS suicidality subscore were referred for consideration of LifeSPAN Therapy. A score of 4 equates to 'suicidal thoughts frequent, without intent or plan' and 7 equated to a 'specific suicidal plan and intent or suicide attempt'. Exclusion criteria: Not reported Total sample size: No. randomised – 56 Gender: Not reported Age: Estimated mean 22 years (inclusion range 15 to 29) Ethnicity: Not reported Setting: Specialist centre (EPPIC)
Interventions	Intervention – group 1: life span therapy (cognitive orientated therapy for suicide behaviour)+ EPPIC TAU, eight to ten individual sessions, over 10 weeks, N = 31. Intervention – group 2: EPPIC Treatment as usual (TAU), N = 25. Notes about the interventions: Life span therapy Draws on the experience at EPPIC with Cognitive Oriented Therapy for Early Psychosis (COPE) [and suicide prevention manuals such as Choosing to live and Cognitive therapy of suicide behaviour: A manual for treatment. There were four phases: initial engagement; suicide risk assessment/formulation; cognitive modules; and a final closure/handover. EPPIC TAU An early intervention program for young people(aged 15–29) presenting with first episode psychosis. The Early Psychosis Prevention and Intervention Centre's services include an early detection and crisis assessment team, an acute inpatient unit, an outpatient group program, assertive follow-up teams and an intensive outreach mobile support team. Approximately 250 new patients are accepted into the EPPIC service each year. Treatments are provided via an integrated bio-psychosocial model with a strong emphasis on low-dose medication, cognitive-orientated individual, group and family therapies. Follow-up is provided for 18 months.
Extractable outcomes	Mortality: No people committing suicide Quality of life: Quality of life scale Leaving the study early: Leaving due to any reason
Quality	Sequence generation: Unclear risk Allocation Concealment: Unclear risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk

	Missing outcome data: High risk Selective outcome reporting: High risk Other bias: Low risk
Related publications	

APPENDIX 13ci: INITIAL TREATMENT WITH ANTIPSYCHOTIC MEDICATION: INCLUDED STUDIES CHARACTERISTICS

Study ID	ARANGO2009
Bibliographic reference	Arango, C., Robles, O., Parellada, M., *et al.* (2009) Olanzapine compared to quetiapine in adolescents with a first psychotic episode. *European Child and Adolescent Psychiatry*, *18*, 418-428.
General information	Funding source: AstraZeneca Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: LOCF Blindness: None (open label trial) Duration: Length of follow-up 26 weeks Duration: No. weeks of treatment 26 weeks Raters: Clinical evaluations were performed by one of the four adolescent psychiatrists participating in the research study Design: Single centre (Adolescent Unit of Hospital General Universitario Gregorio Maran ˜o´n), open label, RCT: Madrid Spain Number of people screened, excluded and reasons: 53 screened; 3 excluded (refused to participate in the study) Notes about study methods: • Inaccuracies exist in reporting of dropout rates and number of participants assessed. • During the run-in/wash-out period all participants were prescribed risperidone 2 to 6 mg (flexible dose at the discretion of the clinician) between 3and 5 days prior to randomisation.
Participants	Diagnosis: FEP Diagnostic tool: K-SADS-PL; DSM-IV Inclusion criteria: • First episode of psychosis before 18 years, lasting less than 1 year after onset of first symptom • 12 to 18 years old Exclusion criteria: • Psychotic symptoms appeared to result from acute intoxication or withdrawal • Meeting DSM-IV criteria for any substance abuse, learning disabilities, or pervasive developmental disorder • Suffered from any organic central nervous system disorder • History of traumatic brain injury with loss of consciousness • Pregnant or breast feeding • Taking olanzapine or quetiapine before enrolment

	Total sample size: No. Randomised: 50 Gender: 77.5% male Age: Mean 15.9 years (range not reported) Ethnicity: 78.1% Caucasian Setting: General Hospital Mean duration of disorder: NR Mean age of onset: NR Prior antipsychotic use: 50% participants were antipsychotic naïve prior to inclusion.
Interventions	Intervention – group 1: Quetiapine, mean dose 438.8 mg/day (variable dose), over 26 weeks, N = 24. Intervention – group 2: Olanzapine, mean dose 12.11 mg/day (variable dose), over 26 weeks, N = 26. Notes about the interventions: Doses were administered at the discretion of the clinician. Mean treatment time for quetiapine and olanzapine was 143.75 (68) and 144.1 (62.5) days, respectively.
Extractable outcomes	Symptoms: PANSS (Total, General, Positive, Negative) Depression: HAM-D Mania: YMRS Global State: CGI Psychosocial functioning: GAF Leaving the study early: Leaving due to any reason. Side effects: Tremor, akathisia, tachycardia (BPM), weight (kg), fasting total cholesterol (mg per dl), fasting high-density lipoprotein cholesterol level (mg per dl)
Quality	Sequence generation: Unclear Allocation Concealment: High Participants blinded: High Providers blinded: High Outcome Assessors blinded: High Missing outcome data: Unclear Selective outcome reporting: High Other bias: Low
Related publications	ROBLES2011
NR – Not reported	

Study ID	BERGER2008
Bibliographic reference	Berger, G. E., Proffitt, T. M., McConchie, M., *et al.* (2008) Dosing quetiapine in drug-naive first-episode psychosis: A controlled, double-blind, randomized, single-center study investigating efficacy, tolerability, and safety of 200 mg/day vs. 400 mg/day of quetiapine fumarate in 141 patients aged 15 to 25 years. *Journal of Clinical Psychiatry*, *69*, 1702-1714.
General information	Funding source: AstraZeneca Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case Blindness: Participants, providers and raters blind during Part 1. In Part 2 only raters blind. Duration: Length of follow-up 12 weeks Duration: No. weeks of treatment Part 1: 4 weeks fixed dose; Part 2: 8 weeks flexible dose. Raters: Independent of treatment Design: Single centre ('ORYGEN' Research Centre), RCT: Melbourne, Australia Number of people screened, excluded and reasons: 443 screened, 302 excluded (ineligible: n = 97; refused to participate: n = 55; other reasons: n = 150) Notes about study methods: Part 1: randomised, double-blind study administering either 200 mg day or 400 mg per day of quetiapine of 4 weeks duration. Part 2: single-blind, naturalistic flexible dose study (participants remain in randomised groups) of 8 weeks duration.
Participants	Diagnosis: FEP Diagnostic tool: SCID DSM-IV Inclusion criteria: • 15 to 25 years old • FEP (one or more of the following symptoms, each present for at least 1 week on a daily basis according to the manual of the extended BPRS, version 4: somatic concerns (>6), guilt (>6), suspiciousness (>5), hallucinations (>5), unusual thought content (>4), and/or conceptual disorganisation (>4) and meeting one of the following DMS-IV diagnoses: schizophreniform psychosis, schizophrenia, schizoaffective disorder, delusional disorder, major depression with psychotic features, or psychosis not otherwise specified. Exclusion criteria: • Previous treatment with antipsychotic medication • Presence of concurrent manic syndrome, learning disabilities (IQ<70) • Organic disorders presenting with a psychotic syndrome • Epilepsy • A clinically significant physical illness • History of brain surgery or infarct

	• Concomitant medications that prolong QT interval • 20% deviation from normal range laboratory values at baseline • Participation in other studies involving investigational or marketed products concomitantly or within 30 days prior to entry into the study • Having donated blood, or blood products within 4 weeks prior to start of study drug • Pregnant or lactating women, or women of child bearing potential not using an acceptable method of contraception Total sample size: No. Randomised: 141 Gender: 67.5% male Age: Mean 19.3 (range 15 to 24) years Ethnicity: NR Setting: Inpatients and outpatients in a specialist clinic Mean duration of disorder: NA Mean age of onset: NA Prior antipsychotic use: 100% participants were antipsychotic naïve prior to inclusion.
Interventions	Intervention – group 1: Quetiapine 200 mg/day over 4 weeks, flexible dose over following 8 weeks, N = 69 Intervention – group 2: Quetiapine 400 mg/day over 4 weeks, flexible dose over following 8 weeks, N = 72 Notes about the interventions: In the both groups receiving (quetiapine 200 mg: 100-mg tablet b.i.d; quetiapine 400 mg: 100 mg tablet in the morning/300 mg tablet at night, each tablet equally sized) the protocol allowed for patients to be started on 200 mg, however most psychiatrists titrated the dose up to 200 mg, typically from a starting dose of 25 to 50 mg. The titration period was never longer than 7 days.
Extractable outcomes	Symptoms: BPRS; Response (defined as a 20% reduction in BPRS and a CGI global improvement rating of at least minimal improvement); Remission (defined as a score of <3 on the BPRS; a CGI-severity rating of mild or less and a CGI global improvement rating of at least minimal improvement). Depression: CDSS Mania: YMRS Global State: CGI Psychosocial functioning: GAF Social functioning: SOFAS Side effects: Udvalg for Kliniske Undersogelser (UKU) Neurologic Subscale Total Score, Weight (kg)
Quality	Sequence generation: Low Allocation Concealment: Low Participants blinded: Part 1: Low; Part 2: High Providers blinded: Part 1: Low; Part 2: High

	Outcome Assessors blinded: Low Missing outcome data: Low Selective outcome reporting: High Other bias: Low
Related Publications	None
NR – Not reported	

Study ID	**LIEBERMAN2003**
Bibliographic reference	Lieberman, J. A., Tollefson, G., Tohen, M., *et al.* (2003) Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *The American Journal of Psychiatry*, *160*, 1396-1404.
General information	Funding source: Lilly research laboratories Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case (study reports LOCF) Blindness: Unclear. Study reports 'double blind' conditions, but it is not clear if this refers to the participants, providers or raters. Duration: Length of follow-up 92 weeks Duration: No. weeks of treatment 104 weeks Raters: Unclear Design: Multicentre (14 academic medical centres in North America and Western Europe), RCT. Number of people screened, excluded and reasons: NR Notes about study methods: The study was divided into a 12-week acute phase and a 92-week continuation phase (the difference between the two phases was the difference in dose ranges of study medications administered).
Participants	Diagnosis: FEP Diagnostic tool: SCID DSM-IV Inclusion criteria: • 16 to 40 years • Onset of psychotic symptoms before age 35 years • Met DSM-IV diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder as assessed by using the Structured Clinical Interview for DSM-IV Research Version • Experienced psychotic symptoms for at least 1 month but not more than 60 months • Scored ≥4 on at least two PANSS psychosis items (P1, P2, P3, P5, or P6) or scored ≥5 on one psychosis item

	• Had a Clinical Global Impression (CGI) severity score ≥4 (moderately ill) • Required treatment with antipsychotic drugs on a clinical basis • Has a level of understanding sufficient to communicate with the research staff and to cooperate with all tests and examinations • Understood the nature of the study and signed an informed consent document (required of each patient or the patient's authorised legal representative) • Female patients of childbearing potential had to have been using a medically accepted means of contraception. Exclusion criteria: • Previously received antipsychotic drug treatment for more than 16 cumulative weeks • Had been treated with clozapine at anytime in their lifetime, or had been treated with an injectable depot neuroleptic within less than three dosing intervals before study entry • Pregnant or nursing • Serious, unstable medical illnesses or findings from a medical examination that suggested a contraindication to antipsychotic drug treatment • A history of allergic or severe adverse reactions to study medications • Met the DSM-IV criteria for substance dependence within 1 month before the first visit • Judged clinically to be at suicidal risk too serious to be included in this study • Required treatment with anticonvulsants, benzodiazepines (except as allowed for agitation and control of extrapyramidal signs), antidepressants, psycho-stimulants, or other antipsychotic drugs concurrently with study medications beyond those permitted as concomitant treatments • Had contraindications for neuro-imaging per current regulations of the local regulatory agency • Had a past history of any DSM-IV psychotic disorder with recovery (Recovery, although based on the clinical impression of the patient's history, was defined as the cessation of positive and negative symptoms and return of functioning for 6 months or longer. • Premorbid IQ of ≤70 • Had received ECT within 1 month (30 days) before study entry. Total sample size: No. Randomised: 263 Gender: 81.8% male Age: Mean 23.8 years (range not reported) Ethnicity: 52.9% Caucasian Setting: Inpatients and outpatients in a specialist clinic Mean duration of disorder: 62.5 weeks Mean age of onset: NR

	Prior antipsychotic use: 26% participants were antipsychotic naïve at baseline.
Interventions	Intervention – group 1: Olanzapine, mean (range) dose: 10.2 (5 to 20) mg per day, over 104 weeks, N = 131 Intervention – group 2: Haloperidol, mean (range) dose: 4.82 (2 to 20) mg per day, over 104 weeks, N = 132 Notes about the interventions: • During the 12-weeks acute phase the initial dose titration ranges for the first 6 weeks were 5 to 10 mg/day for olanzapine and 2 to 5 mg/day for haloperidol. • In the second 6 weeks of the acute phase and for the entire continuation phase, the allowed doses were 5 to 20 mg/day of olanzapine and 2 to 20 mg/day of haloperidol.
Extractable outcomes	Symptoms: PANSS (Total, General, Positive, Negative) Depression: MADRS Global State: CGI Leaving the study early: Leaving due to any reason. Side effects: Weight (kg), Prolactin level (mg/dl)
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: Unclear Providers blinded: Unclear Outcome Assessors blinded: Unclear Missing outcome data: Low Selective outcome reporting: High Other bias: Low
Related Publications	GREEN2006
NR – Not reported	

Study ID	**MCEVOY2007**
Bibliographic reference	McEvoy, J. P., Lieberman, J. A., Perkins, D. O., *et al*. (2007) Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: A randomized, double-blind 52-week comparison. *The American Journal of Psychiatry*, *164*, 1050-1060.
General information	Funding source: AstraZeneca Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Efficacy analyses used a modified intent-to-treat population (defined as patients who were randomly assigned to a treatment and returned for at least one post-randomisation assessment). Continuous side effect outcomes were analyzed using

	mixed model similar to the efficacy outcomes. Dichotomous side effect outcomes were analyzed using logistic regression. Blindness: Unclear. Study reports 'double blind' conditions, but it is not clear if this refers to the participants, providers or raters. Duration: Length of follow-up 52 weeks Duration: No. weeks of treatment 52 weeks Raters: Unclear Design: Multicentre (US and Canada), RCT Number of people screened, excluded and reasons: 400 screened, exclusions NR. Notes about study methods: • It is not clear if baseline outcome measures administered before randomisation • 8% of participants discontinued in the quetiapine and the risperidone group due to administrative causes. Greatest drop out for this reason observed in quetiapine and risperidone groups • Following case-by-case discussions with site investigators nine participants who had been ill for more than 60 months, seven patients who were over 40 years of age, and 16 patients who had taken antipsychotics for more than 16 weeks were also enrolled into the study.
Participants	Diagnosis: FEP Diagnostic tool: SCID DSM-IV Inclusion criteria: • 16 to 40 years of age • Met DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder • First episode of their psychotic illness and had to have been continuously ill for at least 1 month and no more than 5 years. • A score ≥4 on at least one PANSS psychosis item (delusions, conceptual disorganisation, hallucinatory behaviour, grandiosity, or suspiciousness/persecution) • A score ≥4 (moderately ill) on the severity item of the CGI at the point of maximum severity of illness to date. • Female participants of childbearing potential had to be using a medically acceptable form of contraception. Exclusion criteria: • A prior psychotic episode had remitted for 3 months or more • Prior antipsychotic drug treatment for more than 16 cumulative weeks. • Not English speaking • History of learning disabilities • Pregnant or nursing • Had a serious, unstable medical illness • Had a known allergy to one of the study medications • Were at serious risk of suicide

	• Had participated in an investigational drug trial within 30 days before the first treatment visit. Total sample size: No. Randomised: 400 Gender: 73% male Age: Mean 24.5 (range 16 to 40) years Ethnicity: 51.3% Caucasian Setting: Inpatient and outpatient clinic Mean duration of disorder: NR Mean age of onset: 23.5 years Prior antipsychotic use: 96% participants were antipsychotic naïve at baseline.
Interventions	Intervention – group 1: Quetiapine, mean (range) dose: 506 (100 to 800) mg/day, over 52 weeks, N = 134 Intervention – group 2: Olanzapine, mean (range) dose: 11.7 (2.5 to 20) mg/day, over 52 weeks, N = 133 Intervention – group 2: Risperidone, mean (range) dose: 2.4 (0.5 to -4) mg/day, over 52 weeks, N = 133 Notes about the interventions: • On days 1 and 2, each patient received one capsule of olanzapine (2.5 mg), quetiapine (100 mg), or risperidone (0.5 mg) in the evening. At the treating physician's discretion, the dose could be increased by one capsule every other day. • Anticholinergic medications for acute extrapyramidal side effects were permitted for up to a total of 2 weeks over the course of the trial. Clinicians were encouraged to lower the dose of antipsychotic to relieve extrapyramidal side effects. Adjunctive medications and concomitant medications could be used without restriction.
Extractable outcomes	Symptoms: PANSS (Total, Positive, Negative) Depression: CDSS Global State: CGI Quality of Life: Heinrichs-Carpenter Quality of Life Scale - Social and Vocational subscales Leaving the study early: Leaving due to any reason. Side effects: Weight (kg), BMI (kg/m^2), fasting triglycerides (mg/dl), fasting serum glucose level (mg/dl), fasting total cholesterol (mg/dl), high-density lipoprotein cholesterol level (mg/dl), systolic and diastolic blood pressure (mm Hg), prolactin level (mg/dl)
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: Unclear Providers blinded: Unclear Outcome Assessors blinded: Unclear Missing outcome data: Unclear Selective outcome reporting: Unclear Other bias: Low
Related publications	YUNG2011

	KEEFE2007 PERKINS2008 PATEL2009
NR – Not reported	

Study ID	ROBINSON2006
Bibliographic reference	Robinson, D. G., Woerner, M. G., Napolitano, B., *et al.* (2006) Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. *The American Journal of Psychiatry*, *163*, 2096-2102.
General information	Funding source: Non-industry Published or unpublished data: Published and unpublished
Method	Type of study: Individual randomised trial Type of analysis: Available case Blindness: Only raters were blinded Duration: Length of follow-up 156 weeks (extractable outcome data during treatment 16 weeks) Duration: No. weeks of treatment Acute treatment: 16 weeks, continuation: 156 weeks Raters: Independent of treatment Design: Single centre (The Zucker Hillside Hospital), open-label, RCT: US, New York Number of people screened, excluded and reasons: 474 screened, 354 excluded (Ineligible: n = 282; refused to participate: n = 64; other reasons: n = 8) Notes about study methods: Unclear reporting of number of participants analyzed when drop out taken into consideration Patients were stratified by sex, current DSM-IV-defined substance abuse or dependence (excluding nicotine and caffeine) and site so it is likely that baseline measures were obtained prior to randomisation.
Participants	Diagnosis: FEP Diagnostic tool: K-SADS-PL DSM-IV Inclusion criteria: • Current diagnosis of DSM-IV schizophrenia, schizophreniform disorder, or schizoaffective disorder • 16 to 40 years • Less than 12 weeks of lifetime antipsychotic medication treatment • Current positive symptoms evidenced by a rating of 4 or more on the severity of delusions, hallucinations, or thought disorder items of the SADS-C with psychosis and disorganisation items or current negative symptoms demonstrated by a rating of 4 or more on the affective flattening, alogia, avolition, or anhedonia global items of the Hillside Clinical Trials version of the SANS

	• For females, a negative pregnancy test and agreement to use a medically accepted method of birth control • Competent and willing to sign informed consent. Exclusion criteria: • Meeting DSM-IV criteria for a current substance induced psychotic disorder, psychotic disorder due to a general medical condition, or learning disabilities • Medical condition/treatment known to affect the brain • Any medical condition requiring treatment with a medication with psychotropic effects • Medical contraindications to treatment with olanzapine or risperidone • Significant risk of suicidal or homicidal behaviour. Total sample size: No. randomised 120 Gender: 70% male Age: 23.3 years Ethnicity: 20% Caucasian Setting: General Hospital Mean duration of disorder: 16.5 months Mean age of onset: 20.7 years Prior antipsychotic use: 78% participants were antipsychotic naïve at study entry
Interventions	Intervention – group 1: Olanzapine, mean (range) dose: 11.8 (2.5 to 20) mg/day, over 156 weeks, N = 60 Intervention – group 2: Risperidone, mean (range) dose: 3.9 (1 to 6) mg/day, over 156 weeks, N = 60 Notes about the interventions: • Variable doses. The initial daily dose was 2.5 mg for olanzapine and 1 mg for risperidone. An increasing titration schedule was used: after week 1, dose increases occurred at intervals of 1 to 3 weeks until the subject improved or reached a maximum daily dose of 20 mg or 6 mg of risperidone • Mean length of study participation for participants treated with olanzapine and risperidone was 11.5 and 12.1 weeks.
Extractable outcomes	Symptoms: A rating of mild or better on the SADS-C with psychosis, disorganisation items and positive symptom items plus a CGI rating of much improved or very much improved, maintained for two consecutive visits Leaving the study early: Leaving due to any reason. Side effects: Parkinsonism, BMI (kg/m^2)
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: High Providers blinded: High Outcome Assessors blinded: Low Missing outcome data: Unclear

	Selective outcome reporting: High Other bias: Low
Related publications	SEVY2011
NR – Not reported	

Study ID	SCHOOLER2005
Bibliographic reference	Schooler, N., Rabinowitz, J., Davidson, M., *et al.* (2005) Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *The American Journal of Psychiatry*, *162*, 947-953.
General information	Funding source: Johnson and Johnson Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case Blindness: Unclear Duration: Length of follow-up NR Duration: No. weeks of treatment 206 weeks Raters: Unclear Design: Multiple centres, RCT. Number of people screened, excluded and reasons: NR Notes about study methods: Three patients assigned to risperidone and one patient assigned to haloperidol did not receive study medication and were therefore excluded from the analysis.
Participants	Diagnosis: FEP Diagnostic tool: K-SADS-PL DSM-IV Inclusion criteria: • 16 to 45 years old • Met SCID DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder for no more than 1 year during which period they had no more than two psychiatric hospitalisations for psychosis • Less than 12 weeks of cumulative exposure to antipsychotics and required antipsychotic treatment upon enrolment into the trial. Exclusion criteria: • Met DSM-IV criteria for another axis I diagnosis, including substance dependence or abuse • Needed another non-antipsychotic psychotropic medication at enrolment • Serious or unstable medical illness.

	Total sample size: No. randomised 559 Gender: 71.3% male Age: Mean 25.5 years (range not reported) Ethnicity: 74.4% Caucasian Setting: NR Mean duration of disorder: NR Mean age of onset: 24.4 years Prior antipsychotic use: 46.7% participants were antipsychotic naïve at baseline
Interventions	Intervention – group 1: Risperidone, mean (range) dose: 3.3 (NR) mg/day, over 206 weeks, N = 281 Intervention – group 2: Haloperidol mean (range) dose: 2.9 (NR) mg/day, over 206 weeks, N = 278 Treatment of side effects: Concomitant psychotropic medications addressing extrapyramidal signs and symptoms; chloral hydrate, zolpidem, or flurazepam for sleep; and lorazepam for agitation. Notes about the interventions: • Variable doses: participants in both treatment groups started with a once daily dose of 1 mg that could be increased to 2 mg/day on day 4 and thereafter by 1 mg/day each week, up to a maximum daily dose of 4 mg. • In exceptional cases (insufficient response with not more than mild extrapyramidal signs and symptoms observed at 4 mg/day), dose could be increased further by 1 mg a week up to a maximum daily dose of 8 mg.
Extractable outcomes	Symptoms: PANSS (Total, General, Positive, Negative) Global State: CGI Leaving the study early: Leaving due to any reason. Side effects: Extrapyramidal Symptoms Rating Scale, Weight (kg), Prolactin level (mg/dl)
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: Unclear Providers blinded: Unclear Outcome Assessors blinded: Unclear Missing outcome data: Unclear Selective outcome reporting: Low Other bias: High (it is unclear at what time point data reported was obtained)
Related publications	EMSLEY2007
NR – Not reported	

Study ID	SIKICH2008 (Treatment of Early Onset Schizophrenia Spectrum Disorders Study [TEOSS])
Bibliographic reference	Sikich, L., Frazier, J. A., McClellan, J., *et al.* (2008) Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. *The American Journal of Psychiatry*, 165, 1420-1431.
General information	Funding source: Non-industry sponsors Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: LOCF Blindness: Participants, providers and raters blind Duration: Length of follow-up 52 weeks Duration: No. weeks of treatment 8 weeks' acute phase plus 44-week double-blind maintenance phase for responders. Raters: Clinicians blind to treatment Design: Multiple center (University of North Carolina, McLean Harvard Medical School, University of Washington, and Case Western Reserve University), RCT; US Number of people screened, excluded and reasons: 478 screened, 285 not enrolled in study (reasons not provided). Of 193 enrolled in the study, 74 were excluded (did not meet diagnostic criteria: n = 46; prior treatment with study medication: n = 17; clinical or safety reasons: n = 6; withdrew consent: n = 5) Notes about study methods: Random assignment to olanzapine was discontinued towards the end of the recruitment phase by NIMH's data and safety monitoring board following their review of the interim data, which showed a greater increase in weight with olanzapine than molidone or risperidone, without evidence of greater efficacy. Participants being treated with olanzapine continued their participation and the integrity of the study blind was maintained.
Participants	Diagnosis: FEP (93%) Diagnostic tool: SCID DSM-IV Inclusion criteria: • 8 to 19 years old (no more than 30% of subjects 16 to 19 years) • Score of at least moderate severity on 1 of the positive psychotic symptom ratings of the PANSS or BPRS-C • Met DSM-IV criteria for schizophrenia, schizophreniform, or schizoaffective disorder • No depot antipsychotic medication for at least 6 months • Good physical health • Able to provide informed consent/assent for the study and have a guardian who gives informed written consent Exclusion criteria: • History of an adequate trial of risperidone, olanzapine, or molindone (defined as at least 8 weeks of treatment with the dose during the final 2 weeks of treatment >risperidone 6 mg/day, olanzapine 20 mg/day, or molindone 140 mg/day)

	during current psychotic episode • History of non response to an adequate trial of study drug during a prior episode • History of intolerance to risperidone, olanzapine, or molindone • Bipolar disorder, primary posttraumatic stress disorder, primary personality disorder, or psychosis NOS diagnosed by clinician and confirmed by KID-SCID Current major depressive episode • Active substance abuse or dependence • Premorbid diagnosis of learning disabilities • Endocrinological or neurological conditions that confound the diagnosis or are a contraindication to treatment • Pregnancy or refusal to practice contraception during the study Total sample size: No. randomised 119 Gender: 65% male Age: Mean 13.8 (range 8 to 19) years Ethnicity: 64% Caucasian Setting: 90% out-patients, 10% inpatients Mean duration of disorder: NR Mean age of onset: NR Prior antipsychotic use: 33% antipsychotic naïve at baseline
Interventions	Intervention – group 1: Risperidone, mean (range) 2.8 (0.5 to 6) mg/day, over 8 weeks, N = 41 Intervention – group 2: Olanzapine, mean (range) 11.4 (2.5 to 20) mg/day, over 8 weeks, N = 35 Treatment of side-effects: NR Notes about the interventions: • Molindone was the third arm of this trial (n = 40), however as it was discontinued by its sole supplier, Endo Pharmaceuticals, on January 13, 2010 only data for risperidone and olanzapine are used in this guideline • Dose schedules were variable. Medications were initiated at the lowest dose within the range and typically increased to the middle of the dose range within 10 days for those participants aged 12 years and older and within 14 days for those participants aged 8 to 11 years according to age specific schedules. • When TEOSS began, no antidepressants or mood stabilizers were permitted during the acute treatment phase, however, the protocol changed twice in 2003 in response to safety and enrolment concerns. All of the subjects randomised to molindone received prophylactic benztropine to reduce the risk of extra-pyramidal side effects and to protect the blind. Participants randomised to either olanzapine or risperidone received placebo. Study clinicians were allowed to add thymoleptic agents during the maintenance phase.
Extractable outcomes	Symptoms: PANSS (Total, Positive, Negative), BPRS-C Global State: CGI, CAFAS

	Leaving the study early: Leaving the study early for any reason Side Effects: Extra-pyramidal side effects (AIMS, BARS, SAS), Weight (kg), BMI (kg/m^2), Fasting total cholesterol (mg/dl), Fasting triglycerides (mg/dl), Fasting high- and low-density lipoprotein cholesterols (mg/dl), P rolactin level (µg/l), Fasting insulin (mU/L), QT interval (msec), Sitting pulse (beats/msec), Systolic and diastolic blood pressure (mm Hg).
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: Low Providers blinded: Low Outcome Assessors blinded: Low Missing outcome data: Low Selective outcome reporting: High Other bias: Low
Related publications	MCCLELLAN2007 FINDLING2010 FRAIZER2007
NR – Not reported	

Study ID	**SWADI2010**
Bibliographic reference	Swadi, H. S., Craig, B. J., Pirwani, N. Z., *et al.* (2010) A trial of quetiapine compared with risperidone in the treatment of first onset psychosis among 15- to 18-year-old adolescents. *International Clinical Psychopharmacology*, 25, 1-6.
General information	Funding source: AstraZeneca Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: LOCF Blindness: Only raters were blinded Duration: Length of follow-up 6 weeks Duration: No. weeks of treatment 6 weeks Raters: Independent of treatment Design: Single-centre (The Princess Margaret Hospital), open-label, RCT: New Zealand: Christchurch Number of people screened, excluded and reasons: 176 screened, 154 excluded (non-psychotic disorder: n = 149; substance-

	induced psychosis: n = 3; informed consent refusal: n = 2) Notes about study methods: In the ITT, last measures were taken either at discontinuation or at completion and taken as the final data for comparison. Patients who discontinued because of the need to increase dosage beyond the level stipulated in the protocol after 3 weeks was included in the analysis. Four patients treated with quetiapine had to exceed the maximum 800 mg dose after the third week and had to exit the study. Their data at the point of the exit were included in the analysis.
Participants	Diagnosis: FEP Diagnostic tool: DSM-IV (format NR) Inclusion criteria: 19 years First onset psychotic disorder or a mood disorder with psychotic features according to the criteria of DSM-IV Exclusion criteria: Alcohol or substance dependence not in full remission Earlier treatment with atypical antipsychotic drugs. Total sample size: No. randomised 22 Gender: NR Age: NR Ethnicity: NR Setting: Inpatient clinic Mean duration of disorder: NR Mean age of onset: NR Prior antipsychotic use: NR (however, participants who had earlier treatment with atypical antipsychotic drugs were excluded).
Interventions	Intervention – group 1: Quetiapine, mean (range) dose: 607 (100 to 800) mg/day, over 5 weeks, N = 11 Intervention – group 2: Risperidone mean (range) dose: 2.9 (1.5 to 5) mg/day, over 6 weeks, N = 11 Treatment of side effects: NR Notes about the interventions: • Doses were variable • Four patients treated with quetiapine had to exceed the maximum 800 mg dose after the third week and had to exit the study • Cognitive behavioural therapy, family work and activity-based interventions (part of the clinic's usual treatment programme) were allowed.
Extractable outcomes	Symptoms: PANSS (Total), BPRS Depression: HAM-D Mania: YMRS

	Global State: CGI Leaving the study early: Leaving due to any reason. Side effects: AIMS, BARS, SAS, Weight (kg), Prolactin level (mg/l)
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: High Providers blinded: High Outcome Assessors blinded: Low Missing outcome data: Low Selective outcome reporting: High Other bias: Low
Related publications	None
NR – Not reported	

Study ID	**VANBRUGGEN2003**
Bibliographic reference	van Bruggen, J., Tijssen, J., Dingemans, P., *et al.* (2003) Symptom response and side-effects of olanzapine and risperidone in young adults with recent onset schizophrenia. *International Clinical Psychopharmacology*, *18*, 341–346.
General information	Funding source: Eli Lily and non-industry sponsors Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case Blindness: Blinding NR Duration: Length of follow-up 6 to 10 weeks Duration: No. weeks of treatment 6 to 10 weeks Raters: NR Design: Single centre (University of Amsterdam), RCT: Amsterdam, The Netherlands Number of people screened, excluded and reasons: NR Notes about study methods: • Continuous data is reported dichotomously • Duration of untreated psychosis was much longer in the olanzapine group (24.9 months) compared to the risperidone group (8.8months) • Duration of prior antipsychotic use was much greater in the risperidone groups (45.5 weeks) than the olanzapine group (15.9 weeks)

	• Participants who achieved remission (defined using the PANSS) after 6 weeks were discharged from the psychiatric ward and endpoint data was obtained. Participants who were still actively symptomatic at 6 weeks remained on the psychiatric ward for further treatment by switching medication and endpoint data was obtained. Participants who achieved partial remission based on the clinical judgment of their treating psychiatrist, continued study medication for another 4 weeks after which endpoint data was obtained. It is not clear how many participants were considered to have achieved remission at 6 weeks; how many participants were considered to be actively symptomatic at 6 weeks and switched medication, or how many participants were considered to have achieved partial remission and continued treatment for a further 4 weeks.
Participants	Diagnosis: First and second episode psychosis (FEP 89% and 85% in the risperidone and olanzapine treated groups respectively) Diagnostic tool: SDSM-IV (format not specified) Inclusion criteria: • Age 16 to 28 years • First or second psychotic episode according to DSM-IV criteria of schizophrenia, schizophreniform or schizoaffective disorder Exclusion criteria: • Epilepsy • Toxic psychosis or infectious disorder • Primary diagnosis of substance abuse • Learning disabilities • Pregnant or lactating female patients • Concomitant use of other antipsychotic agents • Treatment with an injectable depot neuroleptic less than one dosing interval before study entry • Narrow-angle glaucoma • Known hypersensitivity to any ingredient of the tablets containing olanzepine or risperidone • Insufficient knowledge of the Dutch language Total sample size: No. randomised 44 Gender: 79.6% male Age: Mean 20.8 years (range not reported) Ethnicity: NR Setting: Inpatient clinic Mean duration of disorder: Mean age of onset: 17.9 years Prior antipsychotic use: NR
Interventions	Intervention – group 1: Risperidone, mean (range) dose: 4.4 (1 to 8) mg/day), over 6 to 10 weeks, N = 26 Intervention – group 2: Olanzapine, mean (range) 15.6 (5 to 30) mg/day, over 6 to 10 weeks, N = 18

	Notes about the interventions: • The olanzapine treatment regimen started with 10 mg/day with a flexible titration of 5 mg increments or decrements/day during the first 2 weeks. • The risperidone treatment regimen started with 1 mg/day increased to 2 mg/day after 3 days with a flexible titration of 1 mg increments or decrements/day with the allowed dose range during the first 2 weeks. • The mean (SD) length of treatment in the risperidone and olanzapine groups was 9.8 (6.7) weeks and 6.7 (3.4) weeks, respectively.
Extractable outcomes	Symptoms: PANSS (Total, Positive, Negative, General, Depression) Leaving the study early: Leaving the study early for any reason Side Effects: Akathesia, Parkinsonism, Weight (kg)
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: High Providers blinded: High Outcome Assessors blinded: High Missing outcome data: High Selective outcome reporting: High Other bias: High
Related publications	None
NR – Not reported	

APPENDIX 13cii: ANTIPSYCHOTICS IN THE TREATMENT OF THE ACUTE EPISODE: INCLUDED STUDIES CHARACTERISTICS

Study ID	**AstraZenecaD1441C00112**
Bibliographic reference	AstraZeneca D1441C00112 (unpublished) A 6-week, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase IIIb study of the efficacy and safety of quetiapine fumarate (SEROQUEL™) immediate-release tablets in daily doses of 400 mg and 800 mg compared with placebo in the treatment of adolescents with schizophrenia. Available from: www.astrazenecaclinicaltrials.com/_mshost800325/content/clinical-trials/resources/pdf/8579471 [accessed 6 November 2012].
General information	Funding source: AstraZeneca Published or unpublished data: Unpublished
Method	Type of study: Individual randomised trial Type of analysis: Available case (study reports LOCF) Blindness: Participants, providers and assessors blind Duration: Length of follow-up 6 weeks Duration: No. weeks of treatment 6 weeks Raters: Independent of treatment Design: Multiple centre (43 international, inpatient and outpatient sites), RCT. Number of people screened, excluded and reasons: 268 screened, 46 excluded (adverse events: 4.3%; eligibility criteria not fulfilled: 91.3%; lack of study drug: 2.2%; sponsor directive 2.2%) Notes about study methods: A medication washout period of 1 to 28 days based on the current medications at screening preceded the study Results are currently unpublished
Participants	Diagnosis: Schizophrenia Diagnostic tool: K-SADS-PL DSM-IV Inclusion criteria: • Provision of written informed consent by one or both parents or by legal guardian prior to any study procedure and have a parent or legal guardian available to accompany the patient at each scheduled study visit, providing reliable information, and responsible for receiving and dispensing study medication; and provision of written assent by the patient prior to any study procedure • Aged 13 to 17 years • If female and of childbearing potential, must have used a reliable method of contraception. All female patients needed to have the absence of pregnancy confirmed by a negative β-human chorionic gonadotropin (β-hCG) before randomisation

	• DSM-IV criteria for schizophrenia • Patients with an SCQ score of ≥15 and who otherwise met entrance criteria must have had a documented history of delusions or hallucinations • PANSS score of ≥60 and a score of 4 or greater on at least 1 of the following items; delusions (P1), conceptual disorganisations (P2), or hallucinations (P3) at both screening and randomisation (Day 1) • Willingness to agree not to harm self • Willingness to adhere to the schedule of assessments Exclusion criteria: • Secondary DSM-IV Axis I diagnoses of Bipolar Disorders • Premorbid intelligence quotient (IQ) <70 or diagnosis of learning disabilities • Psychosis judged to be the direct physiological consequence of a medical condition or treatment. • Psychosis judged to be the direct physiological effect (for example, intoxication, withdrawal) of an abused medication or substance • History of any serious suicide attempt that required medical intervention or current suicidal risk that could not be safely managed as determined by the clinical judgment of the investigator • Serious homicidal risk or homicidal behaviours within the past 3 months that resulted in adjudication • Known intolerance for or lack of response to quetiapine, as judged by the investigator • Contraindications as detailed in country-specific prescribing information for quetiapine • For female patients, pregnancy or lactation • Substance abuse or dependence including alcohol, as defined in DSM-IV within 1 month prior to screening • Inability to discontinue psychoactive medications prior to randomisation • Use of haloperidol decanoate, fluphenazine decanoate, or risperidone microspheres within 1 dosing interval prior to randomisation • Electroconvulsive therapy (ECT) within 30 days prior to screening • Use of potent cytochrome P450 (children and young people) 3A4 inhibitors or Use of potent children and young people 3A4 inducers in the 14 days preceding randomisation • Thyroid-stimulating (TSH) hormone concentration more than 10% above the upper limit of the normal range • Laboratory test results outside the reference range and considered by the investigator to be clinically significant • Baseline QTc interval (Fridericia formula) ≥450 milliseconds at baseline • Renal, cardiovascular, hepatic, hematologic, endocrinologic, ophthalmologic, or other disease or clinical finding that was unstable or that in the opinion of the investigator would be negatively affected by study medication or that would affect study medication • Unstable Diabetes Mellitus (DM) with a baseline glycosylated haemoglobin (HbA1c)≥8.5; admission to a hospital for

	treatment of diabetes or diabetes-related illness in past 12 weeks; not under the care of a physician responsible for the patient's DM care; DM which is clinically unstable in the opinion of the physician responsible for the patient's diabetes management at the time of baseline; physician responsible for the patient's DM care had not approved the patient's participation in the study • The patient had not been on the same dose of oral hypoglycaemic drug(s) and/or diet for the 4 weeks prior to randomisation • For patients taking insulin whose daily dose on one occasion in the past 4 weeks was more than 10% above or below their mean dose in the preceding 4 weeks • Patient's complete blood count (CBC) with white blood cell (WBC) differential showed an absolute neutrophil count (ANC) <1.0 x 109/L 24 hours after testing • Medical condition that would affect absorption, distribution, metabolism, or excretion of study medication • History of seizure disorder, except febrile convulsions • Use of experimental drug within 30 days of randomisation • Previous participation in this study • Significant medical illness which could prevent patient from completing double-blind treatment Total sample size: No. randomised 222 Gender: 58.6% male Age: Mean 15.4 years (range: 13 to 17 years) Ethnicity: 61.4% Caucasian Setting: Inpatient and outpatient Mean duration of disorder: NR Mean age of onset: NR Prior antipsychotic use: NR
Interventions	Intervention – group 1: Quetiapine, mean (range) dose: 400 (NR) mg/day, over 6 weeks, N = 73 Intervention – group 2: Quetiapine, mean (range) dose: 800 (NR) mg/day, over 6 weeks, N = 74 Control –group 3: Placebo (mean dose n/a), over 6 weeks, N = 75 Notes about the interventions: Study treatment was given twice daily and began with an initial dose of 50 mg of quetiapine or matching placebo on the evening of Day 1. Patients randomised to the 400 mg/day group reached the target dose of quetiapine or matching placebo by Day 5.
Extractable outcomes	Symptoms: PANSS (Total, Positive, Negative) Depression: Positive and Negative Syndrome Scale-Depressive Symptoms Global State: CGI Psychosocial functioning: CGAS Leaving the study early: Leaving due to any reason.

	Side effects: Tremor, Akathesia, Dyskinesia, Extra pyramidal disorder, Tachycardia (bpm), QT Interval (msec), Fasting serum glucose Level (mg/dl), Insulin (μU/L), Weight (kg), Fasting Total Cholesterol (mg/dl), Fasting High-Density Lipoprotein Cholesterol Level (mg/dl), Fasting Low-Density Lipoprotein Cholesterol Level (mg/dl), Fasting triglycerides, Prolactin Level, Standing Pulse (beats/min), Sitting Pulse (beats/min), Systolic Blood Pressure (mm Hg), Diastolic Blood Pressure (mm Hg), BMI (kg/m^2)
Quality	Sequence generation: Unclear Allocation Concealment: Low Participants blinded: Low Providers blinded: Low Outcome Assessors blinded: Low Missing outcome data: High Selective outcome reporting: High (unpublished data) Other bias: Low
Related publications	AstraZenecaD1441C00150
NR – Not reported	

Study ID	**FINDLING2008A**
Bibliographic reference	Findling, R. L., Robb, A., Nyilas, M., *et al.* (2008) A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. *The American Journal of Psychiatry*, *165*, 1432-1441.
General information	Funding source: Otsuka Pharmaceuticals Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case (study reports LOCF) Blindness: Unclear Duration: Length of follow-up 6 weeks Duration: No. weeks of treatment 6 weeks Raters: Unclear Design: Multiple centre, RCT: United States, Europe, South America, Asia, the Caribbean, and South Africa Number of people screened, excluded and reasons: NR Notes about study methods: Participants who were deemed appropriate candidates by their treating physicians were screened for eligibility within 4 weeks of baseline.
Participants	Diagnosis: Schizophrenia Diagnostic tool: K-SADS-PL DSM-IV

	Inclusion criteria: • male or female • Age 13 to 17 years inclusive • DSM-IV (22) axis I primary diagnosis of schizophrenia and confirmation of the schizophrenia diagnosis by an adequately trained clinician (for example, child psychiatrist) at the time of screening by means of the K-SADS-PL (23) and a baseline PANSS score of 70 or higher Exclusion criteria: • Psychiatric comorbidity requiring pharmacotherapy • Evidence of suicide risk • History of current diagnosis of schizoaffective disorder • Learning disabilities • Major depressive episodes • Neuroleptic malignant syndrome • Any neurologic disorder other that Tourette's Syndrome • Severe head trauma • Any unstable medical condition Total sample size: No. randomised 302 Gender: 57% male Age: Mean 15.5 years (range not reported) Ethnicity: 37% Caucasian Setting: Inpatient and outpatient clinics Mean duration of disorder: 1.4 years Mean age of onset: 14.1 years Prior antipsychotic use: 51.7% participants were antipsychotic naïve before the study
Interventions	Intervention – group 1: Aripiprazole, mean (range) dose: 10 (2 to 10) mg/day, over 6 weeks, N = 100 Intervention – group 2: Aripiprazole, mean (range) dose: 30 (2 to 30) mg/day, over 6 weeks, N = 102 Intervention – group 3: Placebo (mean dose n/a), over 6 weeks, N = 100 Notes about the interventions: • Aripiprazole was administered according to a forces titration schedule. One group started on 2 to 5 mg/day, followed by an increase after day 3 to the target dose of 10 mg/day by day 5. The second group started on 2 mg/day, which was increased every 2 days to 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day and finally the target dose of 30 mg/day by day 11. • Target doses were maintained for at least 2 weeks

	• Participants who experienced unacceptable tolerability problems before day 25 were removed from the study • After day 25 a dose reduction was permitted, after which point a return to the target dose was not permitted • Participants were permitted to receive benzodiazepine or anticholinergic medications for relief of transient symptoms.
Extractable outcomes	Symptoms: (PANSS Total, Positive, Negative Psychosocial functioning: CGAS Global State: CGI Quality of Life: Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire Leaving the study early: Leaving the study early for any reason Side effects: Akathesia, dyskinesia, parkinsonism, dystonia, weight (kg), BMI (kg/m^2), Fasting serum glucose levels (mg/dl), Fasting total cholesterol (mg/dl), Fasting triglycerides (mg/dl), Fasting high-density lipoprotein cholesterol level (mg/dl), Prolactin level (µg/l), QT interval (msec), Mortality.
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: Unclear Providers blinded: Unclear Outcome Assessors blinded: Unclear Missing outcome data: Low Selective outcome reporting: Low Other bias: Low
Related publications	ROBB2010
NR – Not reported	

Study ID	**HAAS2009**
Bibliographic reference	Haas, M., Eerdekens, M., Kushner, S., *et al.* (2009a) Efficacy, safety and tolerability of two dosing regimens in adolescent schizophrenia: double-blind study. *The British Journal of Psychiatry*, *194*, 158-164.
General information	Funding source: Johnson and Johnson Published or unpublished data: Published and unpublished
Method	Type of study: Individual randomised trial Type of analysis: Available case (study reports LOCF) Blindness: Unclear Duration: Length of follow-up 8 weeks Duration: No. weeks of treatment 8 weeks Raters: Unclear

	Design: Multicentre, RCT: Belgium, Bulgaria, Czech Republic, Estonia, Germany, Poland, Romania, US Number of people screened, excluded and reasons: 343 screened, 86 excluded (ineligible: n = 51; withdrew consent: n = 7; 'other': n = 5; lost to follow-up: n = 1; following a protocol amendment children under the age of 13 years and those with a schizophreniform disorder: n = 22) Notes about study methods: Reported as a double blind trial, however "During the consent process, the difference in the two doses was explained to the patients and their caregivers. It was explained that the lower dose although expected to have some activity, might be an ineffective treatment" Side effect data was not reported in sufficient detail to allow extraction and analysis.
Participants	Diagnosis: Schizophrenia disorder Diagnostic tool: K-SADS-PL DSM-IV Inclusion criteria: • male and female • Age 13 to 17 years • DSM-IV diagnosis of schizophrenia • Currently hospitalised for an acute episode (PANSS total score between 60 and 120, inclusive) • Negative pregnancy test • Inpatients and outpatients experiencing an acute episode with a total Positive and Negative Syndrome Scale (PANSS) score of 60 to 120, inclusive. Exclusion criteria: • Significant risk for suicide or violent behaviour during the study • History of neuroleptic malignant syndrome • Tardive dyskinesia • Known or suspected seizure disorder • BMI<5th percentile or >95th percentile using standardised percentile curves for children and adolescents Total sample size: No. randomised 279 Gender: 56.6% male Age: Mean 15.6 (range 13 to 17) years Ethnicity: 84.6% Caucasian Setting: Inpatient and outpatient clinics Mean duration of disorder: 1.8 years Mean age of onset: 13.9 years Prior antipsychotic use: 32% participants were antipsychotic naïve before the study
Interventions	Intervention – group 1: Risperidone 0.15 to 0.6 mg/day (participants >50 kg: 0.15 to 0.6 mg/day; patients <50 kg: 0.003 to

	0.012 mg/kg/day), over 8 weeks, N = 132 Intervention – group 2: Risperidone 1.5 to 6 mg/day (participants >50 kg: 1.5 to 6 mg/day; patients <50 kg: 0.03 to 0.12 mg/kg/day), over 8 weeks, N = 125 Notes about the interventions: • Administered as an oral solution once or twice daily. • For participants in intervention 1, starting dose was 0.5 mg/day for participants weighing >50 kg or 0.01 mg/kg/day for participants weighing <50 kg. • For participants in intervention 2, starting dose was 0.05 mg/day for participants weighing >50 kg or 0.001 mg/kg/day for participants weighing <50 kg. • Upwards titration schedules were adjusted up to the maximum tolerated dose over a period of 12 days. • Dose remained stable during the last 4 weeks of the treatment period
Extractable Outcomes	Symptoms: PANSS (Total, Positive, Negative) Global State: CGI Leaving the study early: Leaving the Study Early for any reason Side effects: Akathesia, Dyskinesia, Dystonia, Parkinsonism, Tremor, Weight (kg), Fasting total cholesterol (mmol/L), Fasting triglycerides (mmol/l), Fasting glucose (mmol/l), Prolactin level (ng/ml), Tachycardia (bpm).
Quality	Sequence generation: Low Allocation Concealment: Unclear Participants blinded: Unclear Providers blinded: Unclear Outcome Assessors blinded: Unclear Missing outcome data: Low Selective outcome reporting: High Other bias: Low
Related publications	None
NR – Not reported	

Study ID	**HAAS2009B**
Bibliographic reference	Haas, M., Unis, A. S., Armenteros, J., *et al.* (2009b) A 6-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of risperidone in adolescents with schizophrenia. *Journal of Child and Adolescent Psychopharmacology*, *19*, 611-621.
General information	Funding source: Johnson and Johnson Published or unpublished data: Published
Method	Type of study: Individual randomised trial

	Type of analysis: LOCF Blindness: Unclear Duration: Length of follow-up 6 weeks Duration: No. weeks of treatment 6 weeks Raters: Unclear Design: Multicentre (23 sites), RCT: India, Russia, Ukraine, United States Number of people screened, excluded and reasons: 178 screened, 18 excluded (ineligible: n = 16; withdrew consent: n = 2) Notes about study methods: None
Participants	Diagnosis: Schizophrenia Diagnostic tool: DSM-IV (interview format NR) Inclusion criteria: • Male and female • Aged 13 to 17 years • DSM-IV diagnosis of schizophrenia • Inpatients and outpatients experiencing an acute episode with a total Positive and Negative Syndrome Scale (PANSS) score of 60 to 120 (inclusive) • Good physical health • Negative pregnancy test Exclusion criteria: • Subjects who met DSM-IV criteria for dissociative disorder, bipolar disorder, major depressive disorder, schizoaffective disorder, schizophreniform disorder, autistic disorder or primary substance-induced psychotic disorder at screening • Mild, moderate or severe learning disabilities (intelligence [IQ] <70) • Known or suspected substance dependence diagnosed by DSM-IV criteria in the 3 months preceding screening • Significant risk of suicide or violent behaviour • Subjects failing to respond to adequate treatment with two or more typical or atypical antipsychotics (including risperidone) during the current psychotic episode • Exhibited hypersensitivity or intolerance to risperidone • History of neuroleptic malignant syndrome or any severe drug allergy or hypersensitivity • Depot antipsychotic treatment (within two treatment cycles before baseline) • Electroconvulsive therapy (in the 4 weeks before baseline) • Clozapine (within 2 months before baseline) • Use of prohibited concomitant medications that could not be discontinued per the investigator's judgement • Use of insight-oriented or cognitive-behavioural psychotherapy during the study; however could receive a limited

	supportive psychotherapy or psychoeducation Total sample size: No. randomised 160 Gender: 64% male Age: Mean 15.6 (range 13 to 17) years Ethnicity: 53% Caucasian Setting: Inpatient and outpatient clinics Mean duration of disorder: 2.5 years Mean age of onset: 13.1 years Prior antipsychotic use: NR
Interventions	Intervention – group 1: Risperidone 1 to 3 mg/day, over 6 weeks, N = 55 Intervention – group 2: Risperidone 4 to 6 mg/day, over 6 weeks, N = 51 Intervention – group 2: Placebo (mean dose n/a), over 6 weeks, N = 54 Notes about the interventions: • Treatment administered once daily • Doses administered by forced titration from minimum within assigned target ranges by day 7, further increases within the assigned dose range were made by day 14 to maximum tolerated dosage level. • After day 14, doses were maintained at maximally tolerated level for the remainder of the study • Treatment of side effects included β-adrenergic blocker for treatment-emergent akathesia and anti-parkinsonism medications • Participants were allowed to receive limited supportive psychotherapy or psychoeducation
Extractable outcomes	Symptoms: PANSS (Positive, Negative) Psychosocial functioning: CGAS Leaving the study early: Leaving the study early for any reason Side effects: Extra-pyramidal (AIMS, SAS), Extra-pyramidal disorder, Prolactin level (µg/l), Tachycardia (bpm), Mortality.
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: Unclear Providers blinded: Unclear Outcome Assessors blinded: Unclear Missing outcome data: Low Selective outcome reporting: Low Other bias: Low
Related publications	None

Study ID	JENSEN2008
Bibliographic reference	Jensen, J. B., Kumra, S., Leitten, W., *et al.* (2008) A comparative pilot study of second-generation antipsychotics in children and adolescents with schizophrenia-spectrum disorders. Journal of Child and Adolescent Psychopharmacology, 18, 317-326.
General information	Funding source: AstraZeneca Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case (reports LOCF) Blindness: Open-label trial Duration: Length of follow-up 12 weeks Duration: No. weeks of treatment 12 weeks Raters: Not independent of study Design: Single centre (University of Minnesota Medical Centre), open-label, RCT: US, Minnesota Number of people screened, excluded and reasons: 67 screened, 37 excluded (ineligible: n = 37; refused to participate: n = 10) Notes about study methods: To enhance treatment adherence and/or alleviate side effects, the dosing strategy could be modified to twice daily (rather than once daily) based on the discretion of the study physician
Participants	Diagnosis: Schizophrenic disorder Diagnostic tool: K-SADS-PL DSM-IV Inclusion criteria: • Male and female • Aged 10 to 18 years • Diagnosis of schizophrenia, schizoaffective disorder, schizophreniform, or psychotic disorder not otherwise specified • At least one positive or negative symptom associated with schizophrenia, present throughout the past 2 weeks of moderate or greater severity on the Positive and Negative Syndrome Scale (PANSS). • (Past diagnosis of OCD, past history or substance abuse or dependence or pervasive developmental disorder were allowed to participate only if their psychotic symptoms were not better accounted for by the comorbid disorder) Exclusion criteria: • Learning disabilities • Affective disorder (major depressive disorder or bipolar disorder) with psychotic features • Current alcohol or drug dependence or abuse • History of serious adverse reactions or non-response to an adequate trial of any of the proposed treatments • Pregnant or refused to practice contraception • Serious or unstable medical condition • PTSD if the majority of psychotic symptoms were related to the PTSD

	Total sample size: No. randomised 30 Gender: 66.7% male Age: Mean 15.2 (range 10 to 18) years Ethnicity: 60% Caucasian Setting: Inpatient and outpatient clinics Mean duration of disorder: NR Mean age of onset: NR Prior antipsychotic use: 76.7% participants antipsychotic naïve at study entry
Interventions	Intervention – group 1: Risperidone, mean (range) dose: 3.4 (1 to 6) mg/day, over 12 weeks, N = 10 Intervention – group 2: Quetiapine, mean (range) dose: 611 (100 to 800) mg/day, over 12 weeks, N = 10 Intervention – group 3: Olanzapine, mean (range) dose: 14 (5 to 20) mg/day over 12 weeks, N = 10 Notes about the interventions: • The risperidone dose started at 0.5 mg/day and could be increased in 0.5 to 1 mg increments every two to three days to a maximum dose of 6 mg/day. • The quetiapine dose started at 100 mg/day and could be increased in 100 mg increments every two to three days to a maximum dose of 800 mg/day. • The olanzapine dose started at 5 mg/day and could be increased in 5 mg increments every three days to a maximum dose of 20 mg/day. • Study medications could be adjusted on the basis of participant response and emergence of treatment-related side effects at the discretion of the study physician. Slower increases in medication were used if the participant had significant side effects. • Diphenhydramine (up to 100 mg/day) was provided if clinically significant side effects were experienced. Lorazepram (0.5 to 2 mg/day) was provided to treat insomnia or to decrease agitation and anxiety. • Psychoeducation and dietary counselling was provided. • Inpatients received routine group, recreational and family therapies.
Extractable outcomes	Symptoms: PANSS (Total, General, Positive, Negative) Psychosocial functioning: CGAS Global State: CGI Leaving the study early: Leaving the study early for any reason Side effects: Akathesia, Extra-pyramidal (AIMS, SAS), weight (kg), BMI (m^2/kg)
Quality	Sequence generation: Low Allocation Concealment: Unclear Participants blinded: High Providers blinded: High

	Outcome Assessors blinded: High Missing outcome data: Low Selective outcome reporting: High Other bias: Low
Related publications	None
NR – Not reported	

Study ID	**KRYZHANOVSKAYA2009B**
Bibliographic reference	Kryzhanovskaya, L., Schulz, S. C., McDougle, C., *et al.* (2009) Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*, 60-70.
General information	Funding source: Eli Lilly and Company Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case for side effect outcomes, LOCF for efficacy outcomes Blindness: Participants blind, providers not blind, unclear blinding of raters Duration: Length of follow-up 6 weeks Duration: No. weeks of treatment 6 weeks Raters: Unclear Design: Multiple centres (20 sites), RCT: US and Russia Number of people screened, excluded and reasons: 115 screened, 8 excluded (reasons not reported) Notes about study methods: It is not clear if baseline measures were administered before or after randomisation Patients were excluded if they had a previous non-response to an adequate dose/duration of olanzapine treatment Variance associated with mean scores on primary outcomes is not reported
Participants	Diagnosis: Schizophrenia Diagnostic tool: K-SADS-PL DSM-IV Inclusion criteria: • 13 to 17 years • Met DSM-IV-TR diagnosis of schizophrenia • Total score of >35 on the anchored version of the BPRS-C with a score of >3 or higher on at least one of the following BPRS-C items at enrolment and randomisation: hallucinations, delusions, or peculiar fantasies. Exclusion criteria:

	• Previous participation in a clinical trial of oral olanzapine • Treatment within 30 days of the trial with a drug without regulatory approval for any indication • Documented olanzapine allergic reaction • Previous non-response to an adequate dose/duration of olanzapine treatment • Potential safety concerns • For females; pregnancy, nursing or refusal to practice acceptable contraception • Acute/unstable medical conditions • Current/expected use of any concomitant psychotropic medication (except for certain benzodiazepines and anticholinergics) • >200ng/ml of baseline prolactin • Clinically significant laboratory abnormalities • DSM-IV-TR substance dependence within 30 days (except nicotine and caffeine) • Current DSM-IV-TR diagnosis of a comorbid psychiatric or developmental disorder Total sample size: No. randomised 107 Gender: 70.1% male Age: Mean 16.7 years (range not reported) Ethnicity: 72% Caucasian Setting: Inpatients and outpatients Mean duration of disorder: 3.2 years Mean age of onset: 13 years Prior antipsychotic use: 56.5% participants antipsychotic naïve at baseline
Interventions	Intervention – group 1: Olanzapine, mean (range) 11.1 (2.5 to 20) mg/day, over 6 weeks, N = 72 Intervention – group 2: Placebo (mean n/a), over 6 weeks, N = 35 Notes about the interventions: • Starting dose of olanzapine was 2.5 or 5 mg/day at the discretion of the investigator and could be increased (to a maximum of 20 mg/day) or decreased by an increment of 2.5 or 5 mg/day at the investigator's discretion. The dose was titrated to least 10 mg/day by the third week (providing there were not tolerability concerns). Doses were increase to the highest tolerated dose if there were not concerns. Dose adjustments were allowed at any time in any number of increments/decrements. • Patients who were unable to tolerate the minimum dose (2.5 mg/day) were discontinued from the study. • Patients who did not respond to therapy (<20% decrease in BPRS-C and CGI-S score >3 after at least 3 weeks of treatment) were able to receive open-label olanzapine without completing the double blind period. • Benzodiazepines and anticholinergics allowed.

Extractable outcomes	Symptoms: BPRS-C, PANSS (Total, General, Positive, Negative) Global State: CGI Leaving the study early: Leaving the study early for any reason Side effects: Weight (kg), BMI (m^2/kg), fasting triglycerides (mg/dl), fasting glucose (mg/dl), fasting total cholesterol (mg/dl), fasting high-density lipoprotein cholesterol level (mg/dl), fasting low-density lipoprotein cholesterol level (mg/dl), QT interval (ms), prolactin level (µg/l)
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: Low Providers blinded: High Outcome Assessors blinded: Unclear Missing outcome data: Low Selective outcome reporting: Other bias: High
Related publications	None
NR – Not reported	

Study ID	**MOZES2006**
Bibliographic reference	Mozes, T., Ebert, T., Michal, S. E., *et al.* (2006) An open-label randomized comparison of olanzapine versus risperidone in the treatment of childhood-onset schizophrenia. *Journal of Child and Adolescent Psychopharmacology*, *16*, 393-403.
General information	Funding source: NR Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: LOCF Blindness: Open-label trial, unclear is raters were blinded Duration: Length of follow-up 12 weeks Duration: No. weeks of treatment 12 weeks Raters: Unclear Design: Single centre (Ness Ziona Mental Health Center), open-label, RCT: Ness Ziona, Israel Number of people screened, excluded and reasons: NR Notes about study methods: Population included co morbid obsessive compulsive disorder (n = 3); attention-deficit/hyperactivity disorder (n = 3); grand mal epilepsy (n = 2); neurofibromatosis (n = 1); familial Mediterranean fever (n = 1); chronic motor tic disorder (n = 1).
Participants	Diagnosis: Schizophrenic disorder

	Diagnostic tool: K-SADS-PL DSM-IV Inclusion criteria: NR Exclusion criteria: Learning disabilities Total sample size: No. randomised 25 Gender: 40% male Age: Mean 11.1 (range 9 to 14) years Ethnicity: NR Setting: Inpatient unit Mean duration of disorder: 2.1 years Mean age of onset: 9 years Prior antipsychotic use: NR
Interventions	Intervention – group 1: Risperidone, mean (range) 1.62 (0.25 to 4.5) mg/day, over 12 weeks, N = 13 Intervention – group 2: Olanzapine, mean (range) 8.18 (2.5 to 20) mg/day, over 12 weeks, N = 12 Notes about the interventions: Dosing of either intervention was determined according to clinical response and side effects
Extractable outcomes	Symptoms: PANSS (Total, General, Positive, Negative), BPRS Psychosocial functioning: CGAS Leaving the study early: Leaving the study early for any reason Side effects: Extra-pyramidal (SAS, BARS), tremor, weight (kg).
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: High Providers blinded: High Outcome Assessors blinded: Unclear Missing outcome data: Low Selective outcome reporting: Low Other bias: High
Related publications	None
NR – Not reported	

Study ID	**PAILLIERE-MARTINOT1995**
Bibliographic reference	Paillère-Martinot, M. L., Lecrubier, Y., Martinot, J. L., *et al.* (1995) Improvement of some schizophrenic deficit symptoms with low

	doses of amisulpride. *The American Journal of Psychiatry*, *152*, 130-133.
General information	Funding source: Laboratories Synthèlabo (now Sanofi-Aventis) Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: LOCF Blindness: Available case Duration: Length of follow-up 6 weeks Duration: No. weeks of treatment 6 weeks Raters: Unclear Design: Single centre (Hospital de la Salpetriere), RCT: Paris, France Number of people screened, excluded and reasons: NR Notes about study methods: Baseline ratings were performed after a pre-treatment period of eight days. Side effect outcome data was not reported in sufficient detail for extraction Significant sex difference between groups existed, with only 1 female in the amisulpride group and 6 in the placebo group (p=0.03)
Participants	Diagnosis: Schizophrenic disorder Diagnostic tool: DSM-III-R (Interview schedule not reported) Inclusion criteria: • Male and female • Important negative schizophrenic symptoms defined as mean items rating of 3 on at least two subscales of the Scale for the Assessment of Negative Symptoms (SANS) • Short disease course, assessed as time since onset of DSM-III-R prodromal symptoms and neuroleptic–naive condition or lifetime neuroleptic treatment shorter than 1 month Exclusion criteria: • Organic brain disorder • Somatic disease • Alcohol or drug abuse • Prominent positive symptoms or depression Total sample size: No. randomised 27 Gender: 74% male Age: Mean 20 years (range not reported) Ethnicity: NR Setting: Inpatient and outpatient clinics Mean duration of disorder: 34 months

	Mean age of onset: 17 years Prior antipsychotic use: NR
Interventions	Intervention – group 1: Amisulpride, mean (range) dose: NR (50 to 100) mg/day, over 6 weeks, N = 14 Intervention – group 2: Placebo (mean dose n/a), over 6 weeks, N = 13 Notes about the interventions: During the first 3 weeks each patient received one 50 mg tablet a day. On day 21, if the patient was not improved, the dose was increased to two tablets per day for three more weeks.
Extractable outcomes	Symptoms: PANSS (Positive, Negative) Depression: Depressive Retardation Rating Scale, MADRS Leaving the study early: Leaving due to any reason.
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: Unclear Providers blinded: Unclear Outcome Assessors blinded: Unclear Missing outcome data: Low Selective outcome reporting: High Other bias: High
Related publications	None
NR – Not reported	

Study ID	**POOL1976**
Bibliographic reference	Pool, D., Bloom, W., Mielke, D. H., *et al.* (1976) A controlled evaluation of loxitane in seventy-five adolescent schizophrenic patients. Current therapeutic research, clinical and experimental, 19, 99-104.
General information	Funding source: Public Health Service Grant MH-03701-16 (Psychopharmacology Research Branch, NIMH) Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case Blindness: Participants and raters blind, provider blinding not reported Duration: Length of follow-up 4 weeks Duration: No. weeks of treatment 4 weeks Raters: Independent of study Design: Single centre, RCT: United States

	Number of people screened, excluded and reasons: Not reported Notes about study methods: Patients who failed to complete 4 weeks of daily medication because of voluntary withdrawal or for administrative reasons were not included in the analyses of efficacy ratings and were replaced by new patient. Withdrawal of patients by the investigator because of side effects or inadequate response to study medication were included in the analysis of efficacy ratings.
Participants	Diagnosis: Schizophrenia Diagnostic tool: NR Inclusion criteria: • 13 to 18 years • Undisputed diagnosis of schizophrenia associated with a gross disorder of thought associations and/or hallucinations at the time of admission Exclusion criteria: • Not a danger to self or others • DSM-IV diagnosis other than schizophrenia; substance dependence (DSM-IV criteria) in 3 months preceding screening • History of seizure, neuroleptic malignant syndrome, encephalopathic syndrome, tardive dyskinesia, insulin-dependent diabetes mellitus; and any significant or unstable systemic disease • Increased risk for torsade de pointes or sudden death (investigator's assessment) • Had received either clozapine in the 2 months before, depot antipsychotic therapy within two treatment cycles before, or electroconvulsive therapy in the 3 months before baseline visit • (For females) Pregnant, planning to become pregnant, or nursing Total sample size: No. randomised 75 Gender: 94.7% male Age: Mean 15.5 years (range not reported) Ethnicity: NR Setting: Inpatient (adolescent hospital) Mean duration of disorder: NR Mean age of onset: NR Prior antipsychotic use: NR
Interventions	Intervention – group 1: Haloperidol mean dose 9.8 mg/day, over 4 weeks, N = 25 Intervention – group 2: Loxapine mean dose 87.5 mg/day, over 4 weeks, N = 26 Intervention – group 3: Placebo (mean dose n/a), over 4 weeks, N = 24 Notes about the interventions: • The capsule unit for haloperidol was 2 mg: dose schedule was: one capsule h.s. for days 1 and 2; one capsule b.i.d. for day 3; 2 capsules daily through days 4 to 7; five capsules daily for days through 8 to 10. On days 11 to 14 the patient received 6

	capsules daily and 8 capsules if necessary on days 15 to 28. • Dosage could be adjusted in the event of troublesome side effects of if the patient showed an excellent response and it was felt advisable to continue at that level. After the patient reached a dosage of 3 capsules b.i.d. by day 15, the dosage regimen was then made flexible and could be regulated according to individual patient response.
Extractable outcomes	Side effects: Number of people experiencing an extra-pyramidal side effect.
Quality	Sequence generation: Unclear Allocation Concealment: Unclear Participants blinded: Low Providers blinded: High Outcome Assessors blinded: Low Missing outcome data: High Selective outcome reporting: High Other bias: High
Related publications	None
NR – Not reported	

Study ID	**SIKICH2004**
Bibliographic reference	Sikich, L., Hamer, R. M., Bashford, R. A., *et al.* (2004) A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. *Neuropsychopharmacology*, *29*, 133-145.
General information	Funding source: Eli Lily, Janssen and non-industry sponsors Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case (study reports LOCF) Blindness: Participants blind. Provider and rater blinding unclear. Duration: Length of follow-up 8 weeks Duration: No. weeks of treatment 8 weeks Raters: Unclear Design: Multiple centre (UNC Healthcare system and Dorothea Dix Hospital as well as the practices of other psychiatrists), RCT: North Carolina, US Number of people screened, excluded and reasons: 160 screened, 109 excluded (ineligible: n = 20; lived too far away: n = 15; refused to participate: n = 74) Notes about study methods:

	None
Participants	Diagnosis: Psychosis, including schizophrenia spectrum disorders (52%) and affective disorders (48%) Diagnostic tool: SCID DSM-IV Inclusion criteria: • At least one positive psychotic symptom of moderate or greater severity on the BPRS-C which had been present • throughout the past 2 weeks • Full scale IQ >69 • Permitted primary diagnoses were Psychosis NOS, Schizophreniform Disorder, Schizophrenia, Schizoaffective Disorder, Delusional Disorder, Major Depression with Psychotic Features, and Bipolar Affective Disorder with Psychotic Features • Exclusion criteria: • Psychotic symptoms that appeared to result from acute substance intoxication or withdrawal • History of serious adverse reactions or non-response to an adequate trial of any of the study medications during this psychotic episode • Prior diagnosis of a pervasive developmental disorder • Serious medical or neurological disorder • (For females) pregnancy or refusal to practice contraception • Imminent risk in current setting to harm self or others. • Individuals with comorbid diagnoses of posttraumatic stress disorder (PTSD) were permitted only if the majority of psychotic symptoms appeared unrelated to the PTSD. • Individuals with a current or recent diagnosis of attention deficit hyperactivity disorder, Tourette's syndrome, or obsessive compulsive disorder, or with a past history of substance abuse or dependence were allowed to participate only if their psychotic symptoms were not better accounted for by the comorbid disorder. Total sample size: No. randomised 51 Gender: 60% male Age: Mean 14.8 years (range not reported) Ethnicity: 60% Caucasian Setting: Inpatient and outpatient services Mean duration of disorder: 2.4 years Mean age of onset: 12.4 years Prior antipsychotic use: 24% antipsychotic naïve at baseline
Interventions	Intervention – group 1: Risperidone, mean (range) 4 (0.5 to 6) mg/day, over 8 weeks, N = 20 Intervention – group 2: Olanzapine, mean (range) 12.3 (2.5 to 20) mg/day, over 8 weeks, N = 16 Intervention – group 2: Haloperidol, mean (range) 5 (1 to 8) mg/day, over 8 weeks, N = 15 Notes about the interventions:

	• Doses were titrated to a moderate dose (risperidone 0.5 to 3 mg/day in 0.5 mg increments; olanzapine 2.5 to 12.5 mg/day in 2.5 mg increments; and haloperidol 1 to 5 mg/day in 1 mg increments) over 1 to 2 weeks. • Titration was determined by participant response. Slower titration was used if participants had significant side effects. Participants with intolerable side effects were withdrawn. • Doses were maintained below target if participants demonstrated marked improvement at a lower dose; or if participants continued to show significant psychotic symptoms after 2 weeks, the dose could be titrated upwards to a maximum of 6 mg/day (risperidone); 20 mg/day (olanzapine); 8 mg/day (haloperidol) • Psychoeducation and supportive psychotherapy were provided to all participants and their families during the course of the study • Inpatients also received routine group, recreational and occupational therapies
Extractable outcomes	Symptoms: BPRS-C, CPRS (Total, Positive, Negative) Global State: CGI Leaving the study early: Leaving the study early for any reason Side Effects: Weight (kg), BMI (kg/m^2), SAS, prolactin level (ng/ml)), QT interval (msec)
Quality	Sequence generation: Low Allocation Concealment: High Participants blinded: Low Providers blinded: Unclear Outcome Assessors blinded: Unclear Missing outcome data: Low Selective outcome reporting: Unclear Other bias: Low
Related publications	None

Study ID	**SINGH2011**
Bibliographic reference	Singh, J., Robb, A., Vijapurkar, U., *et al.* (2011) A randomized, double-blind study of paliperidone extended-release in treatment of acute schizophrenia in adolescents. *Biological Psychiatry*, *70*, 1179-1187.
General information	Funding source: Johnson and Johnson Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case for side effect outcomes, LOCF for efficacy outcomes Blindness: Participants, providers and raters blind Duration: Length of follow-up 6 weeks

	Duration: No. weeks of treatment 6 weeks Raters: Independent of study Design: Multiple centre (35 centres), RCT: Russia, India, Ukraine, United States, Romania Number of people screened, excluded and reasons: 228 screened, 27 excluded (adverse event: n = 1; 'other': n = 25; withdrew for unknown reasons: n = 1) Notes about study methods: Duration of exposure (days) was higher in the paliperidone extended-release medium- treatment and high-treatment groups than in placebo and paliperidone extended-release low-treatment groups.
Participants	Diagnosis: Schizophrenia Diagnostic tool: K-SADS-PL DSM-IV Inclusion criteria: • 12 to 17 years (inclusive) • Weighing at least 29 kg • Diagnosed with schizophrenia (DSM-IV criteria) for at least 1 year before screening • Positive and Negative Syndrome Scale (PANSS) total score between 60 and 120 (inclusive) at screening and baseline (indicative of an acute, symptomatic episode of schizophrenia) • History of at least one adequate antipsychotic trial Exclusion criteria: • Not a danger to self or others • DSM-IV diagnosis other than schizophrenia; substance dependence (DSM-IV criteria) in 3 months preceding screening • History of seizure, neuroleptic malignant syndrome, encephalopathic syndrome, tardive dyskinesia, insulin-dependent diabetes mellitus; and any significant or unstable systemic disease • Increased risk for torsade de pointes or sudden death (investigator's assessment) • Had received either clozapine in the 2 months before, depot antipsychotic therapy within two treatment cycles before, or electroconvulsive therapy in the 3 months before baseline visit • (For females) Pregnant, planning to become pregnant, or nursing Total sample size: No. randomised 201 Gender: 59% male Age: Mean 15.4 years (range not reported) Ethnicity: 68% Caucasian Setting: Inpatient and outpatient clinics Mean duration of disorder: 2.5 years Mean age of onset: 12.9 years Prior antipsychotic use: 36% and 60% atypical and typical antipsychotic naïve at baseline, respectively.

Interventions	Intervention – group 1: Paliperidone 1.5 mg/day, over 6 weeks, N = 54 Intervention – group 2: For patients <51 kg: paliperidone 3 mg/day; or for patients >51 kg: paliperidone 6 mg/day); over 6 weeks, N = 48 Intervention – group 3: For patients <51 kg: paliperidone 6 mg/day; or for patients >51 kg: paliperidone 12 mg/day); over 6 weeks, N = 47 Intervention – group 4: Placebo (mean dose n/a), over 6 weeks, N = 51 Notes about the interventions: • Participants who did not respond to treatment or whose symptoms worsened (defined as >20% increase in PANSS total score from baseline) were discontinued on the basis of the clinical judgment of the investigator • Patients could also be withdrawn for safety reasons • Benzodiazepines were allowed as rescue medication when clinically indicated (except for 8 hours before any behavioural assessment), during the screening and washout phase and up to day 21 of the double-blind treatment phase • Beta-adrenergic blocker were allowed throughout the double-blind phase for the relief of treatment-emergent akathesia and EPS
Extractable outcomes	Symptoms: PANSS (Total, Positive, Negative) Depression: Positive and Negative Syndrome Scale - Anxiety and Depression symptoms Global State: CGI Psychosocial functioning: CGAS Leaving the study early: Leaving the study early for any reasons Side effects: Extra-pyramidal side effects (AIMS, SAS, BARS), Weight (kg), Prolactin level (µg/l), Tachycardia (bpm), QT interval (msec)
Quality	Sequence generation: Low Allocation Concealment: Low Participants blinded: Low Providers blinded: Low Outcome Assessors blinded: Low Missing outcome data: Unclear Selective outcome reporting: Unclear Other bias: High
Related publications	None
NR – Not reported	

Study ID	XIONG2003/KENNEDY2012[1]
Bibliographic reference	Kennedy, E., Kumar, A., Datta, S. S. (2012) Antipsychotic medication for childhood-onset schizophrenia (review). *The Cochrane Library*, 2.
General information	Funding source: NR Published or unpublished data: Published
Method	Type of study: Randomised trial Type of analysis: Not reported by KENNEDY2012 Blindness: Unclear Duration: 8 weeks Duration: 8 weeks Raters: Unclear Design: Single centre (centre not reported), RCT: China Number of people screened, excluded and reasons: Not reported by KENNEDY2012 Notes about study methods: Unclear reporting of methods of blinding and no explicit description of randomisation methods
Participants	Diagnosis: Childhood-onset schizophrenia Diagnostic tool: CCMD-II-R Inclusion criteria: • Children with a diagnosis of schizophrenia according to the CCMD-II-R • 7 to 16 years Exclusion criteria: Physical problems or any organic neurological disease Total number randomised: 60 Gender: 57% male Age: Mean 13 years (range not reported) Ethnicity: Not reported by KENNEDY2012 Setting: Inpatient Mean duration of disorder: 9 to 9.5 years Mean age of onset: NR by KENNEDY2012
Interventions	Intervention – group 1: Risperidone, mean (range) dose: NR (0.5 to 5) mg/day, over 8 weeks, N = 30 Intervention – group 2: Chlorpromazine, mean (range) dose: NR (50 to 400) mg/day, over 8 weeks, N = 30 Notes about the interventions: No additional information provided by KENNEDY2012
Extractable outcomes	Symptoms: BPRS Side effects: Tremor (TESS)

Quality	Sequence generation: Unclear (not reported by KENNEDY2012) Allocation Concealment: Unclear (not reported by KENNEDY2012) Participants blinded: Unclear Providers blinded: Unclear Outcome Assessors blinded: Unclear Missing outcome data: Unclear (NR by KENNEDY2012) Selective outcome reporting: Unclear (NR by KENNEDY2012) Other bias: Unclear (NR by KENNEDY2012)
Related publications	NR by KENNEDY2012
NR - Not reported [1] Study characteristics and quality assessment has been derived from KENNEDY2012 (Cochrane Collaboration Review: ' Antipsychotic medication for childhood-onset schizophrenia')	

Study ID	**YAO2004/KENNEDY2012[1]**
Bibliographic reference	Kennedy, E., Kumar, A., Datta, S. S. (2012) Antipsychotic medication for childhood-onset schizophrenia (review). *The Cochrane Library*, 2.
General information	Funding source: NR Published or unpublished data: Published
Method	Type of study: Randomised trial Type of analysis: Not reported by KENNEDY2012 Blindness: Unclear Duration: 6 weeks Duration: 6 weeks Raters: Unclear Design: Single centre (centre not reported), RCT: China Number of people screened, excluded and reasons: Not reported by KENNEDY2012 Notes about study methods: Unclear reporting of methods of blinding and no explicit description of randomisation methods
Participants	Diagnosis: Childhood-onset schizophrenia Diagnostic tool: Not reported by KENNEDY2012 Inclusion criteria: Not reported by KENNEDY2012 Exclusion criteria: Not reported by KENNEDY2012 Total number randomised: 60

	Gender: 56% male Age: Mean 11 years (range not reported) Ethnicity: NR by KENNEDY2012 Setting: Inpatient and outpatient Mean duration of disorder: NR by KENNEDY2012 Mean age of onset: NR by KENNEDY2012
Interventions	Intervention – group 1: Risperidone, mean (range) dose: NR (0.25 to 3) mg/day, over 6 weeks, N = 30 Intervention – group 2: Haloperidol, mean (range) dose: NR (0.5 to 12) mg/day, over 6 weeks, N = 30 Notes about the interventions: No additional information provided by KENNEDY2012
Extractable outcomes	Symptoms: BPRS Side effects: EPS (TESS)
Quality	Sequence generation: NR by KENNEDY2012 Allocation Concealment: NR by KENNEDY2012 Participants blinded: Unclear Providers blinded: Unclear Outcome Assessors blinded: Unclear Missing outcome data: NR by KENNEDY2012 Selective outcome reporting: NR by KENNEDY2012 Other bias: NR by KENNEDY2012
Related publications	NR by KENNEDY2012
NR - Not reported [1] Study characteristics and quality assessment has been derived from KENNEDY2012 (Cochrane Collaboration Review: 'Antipsychotic medication for childhood-onset schizophrenia')	

APPENDIX 13ciii: ANTIPSYCHOTICS FOR CHILDREN AND YOUNG PEOPLE WHOSE ILLNESS HAS NOT RESPONDED ADEQUATELY TO TREATMENT: INCLUDED STUDIES CHARACTERISTICS

Study ID	**KUMRA1996**
Bibliographic reference	Kumra, S., Frazier, J. A., Jacobsen, L. K., *et al.* (1996) Childhood-onset schizophrenia: a double-blind clozapine-haloperidol comparison. *Archives of General Psychiatry*, *53*, 1090-1097.
General information	Funding source: NR Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: LOCF Blindness: Participants and providers blind, raters unblinded Duration: Length of follow-up 104 weeks Duration: No. weeks of treatment 6 weeks Raters: Publication authors Design: Single centre (Clinical Center of the National Institute of Health), RCT: Bethesda, MD Number of people screened, excluded and reasons: NR Notes about study methods: None
Participants	Diagnosis: Schizophrenia Diagnostic tool: K-SADS-PL DSM-III Inclusion criteria: Male and female, 6 to 18 years Diagnosis of schizophrenia (DSM-III) (documented psychotic symptoms by age 12 years, intolerance, non-response or both to at least 2 different neuroleptic drugs and full scale IQ>70) Exclusion criteria: Neurologic or medical disease Total sample size: No. randomised 21 Gender: 52.4% male Age: Mean 14.1 (range not reported) Ethnicity: NR Setting: Participants were identified though national recruitment via professional and patient advocacy organisations Mean duration of disorder: 4.1 years

	Mean age of onset: 10 years Definition of inadequate response: NR
Interventions	Intervention – group 1: Clozapine, mean (range) dose: 176 (25 to 125) mg/day, over 6 weeks, N = 10 Intervention – group 2: Haloperidol, mean (range) dose: 16 (7-27) mg/day, over 6 weeks, N = 11 Notes about the interventions: Starting dose of Clozapine was 6.25 to 25 mg/day. And for haloperidol 0.25 to 1 mg/day depending on the weight of the participant. Doses could be increased and three to four days by one to two times the starting dose, on an individual basis In addition to the study antipsychotic medication, participants prophylactically received benzotropin mesylate tablets up to 6 mg/day (haloperidol group) or identical placebo tablets (clozapine group)
Extractable outcomes	Symptoms: PANSS (Positive, Negative), BPRS Global State: CGI Psychosocial functioning: CGAS Leaving the study early: Leaving the study early for any reason Side effects: AIMS, SAS, Sinus tachycardia (bpm)
Quality	Sequence generation: Low Allocation Concealment: Unclear Participants blinded: Yes Providers blinded: Yes Outcome Assessors blinded: Unclear Missing outcome data: Low Selective outcome reporting: High Other bias: Low
Related publications	None
NR – Not reported	

Study ID	**KUMRA2008A**
Bibliographic reference	Kumra, S., Kranzler, H., Gerbino-Rosen, G., *et al.* (2008b) Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. *Biological Psychiatry*, *63*, 524-529.
General information	Funding source: NR Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT (method of analysis unclear) Blindness: Participants and providers blind, rater blinding unclear Duration: Length of follow-up 12 weeks

	Duration: No. weeks of treatment 12 weeks Raters: Unclear Design: Multiple centre (Bronx Children's Psychiatric Center; Sagamore Children's Psychiatric Center; Zucker-Hillside Hospital), CT: US Number of people screened, excluded and reasons: 248 screened, 208 excluded (ineligible: n = 191, refused to participate: n = 10; 'other: n = 7). Notes about study methods: The included population were not treatment-refractory to study medications (see eligibility criteria)
Participants	Diagnosis: Schizophrenic disorder Diagnostic tool: K-SADS-PL DSM-IV Inclusion criteria: • Aged between 10 and 18 years • Diagnosis of schizophrenia or schizoaffective disorder based on a structured interview (K-SADS-PL) • Meet study criteria for treatment-refractoriness that was defined as a documented treatment failure of at least two prior adequate antipsychotic trials and a baseline BPRS total score of at least 35 and a score of at least "moderate" on one or more psychotic item(s) on the BPRS (for example, conceptual disorganisation, suspiciousness, hallucinatory behaviour, and unusual thought content) Exclusion criteria: • Premorbid diagnosis of learning disabilities (IQ<70) • History of serious adverse reactions to the proposed treatments • (For females) pregnancy • Serious and unstable medical condition • Failed an adequate trial of clozapine (at least 12 weeks) at adequate doses (300 mg/day or higher) and/or had failed an adequate trial of olanzapine (at least 8 weeks) at high doses (20 mg/day or higher). • Total sample size: No. randomised 40 • Total sample size: ITT 39 (one participant was excluded owing to withdrawal of parental consent after randomisation but • before administration of first dose of study medication) Total sample size: no. randomised 39 Gender: 53.8% male Age: Mean 15.6 years (range not reported) Ethnicity: 20.5% Caucasian Setting: Inpatient and outpatient (35 of 39 began treatment as inpatients) Mean duration of disorder: 3.4 years Mean age of onset: 12.2 years

	Definition of inadequate response: Documented treatment failure of at least two prior adequate antipsychotic trials (not including clozapine or olanzapine) and a baseline BPRS total score of at least 35 and a score of at least "moderate" on one or more psychotic item(s) on the BPRS
Interventions	Intervention – group 1: Clozapine, mean (range) dose: 403.1 (25 to 900) mg/day, over 12 weeks, N = 18 Intervention – group 2: Olanzapine, mean (range) dose: 26.2 (5 to 30) mg/day, over 12 weeks, N = 21 Notes about the interventions: • Clozapine therapy started at a dose of 25 mg/day and could be increased in 25-mg or 50-mg increments every 3 days to a maximum dose of 900 mg/day • Olanzapine therapy was started at a dose of 5 mg/day up and could be increased in 5-mg increments every 3 days to a maximum of 30 mg/day • As study medications were being titrated, current medication therapies were tapered, as tolerated over the first 4 weeks of the trial to allow patients to achieve a therapeutic dosage of study medications. • Patients never received less than the same dosage of antipsychotic medication (in terms of chlorpromazine equivalents) than they had at study entry
Extractable outcomes	Symptoms: BPRS (Total, psychotic); PANSS (Negative) Global State: CGI Psychosocial functioning: CGAS Leaving the study early: Leaving the study early for any reason Side effects: BMI (kg/m^2), fasting serum glucose level (mg/dl), fasting triglycerides (mg/dl), fasting total cholesterol (mg/dl)
Quality	Sequence generation: Low Allocation Concealment: Unclear Participants blinded: Low Providers blinded: Low Outcome Assessors blinded: Unclear Missing outcome data: Unclear Selective outcome reporting: Low Other bias: High
Related publications	None
NR - Not reported	

Study ID	**SHAW2006**
Bibliographic reference	Shaw, P., Sporn, A., Gogtay, N., *et al.* (2006) Childhood-onset schizophrenia: A double-blind, randomized clozapine-olanzapine comparison. *Archives of General Psychiatry*, *63*, 721-730.

General information	Funding source: NR Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case (study reports LOCF) Blindness: Participants, providers and raters blind Duration: Length of follow-up 8 weeks (plus 104 weeks following medication switch) Duration: No. weeks of treatment 8 weeks double blind plus 104 weeks open label following medication switch Raters: Blind Design: Single centre (centre not reported), RCT: Bethesda, MD Number of people screened, excluded and reasons: Notes about study methods: 96 screened, 71 excluded (ineligible: n = 71; refused to participate: n = 4)
Participants	Diagnosis: Schizophrenia, resistant to antipsychotic medication Diagnostic tool: K-SADS-PL DSM-IV Inclusion criteria: • Diagnosis of schizophrenia with a definite onset of symptoms before 13 years of age. • IQ > 70 • No history of progressive neurological or medical disorders such as epilepsy • Failure to respond to 2 antipsychotic medications (typical or atypical) used at adequate doses (>100-mg chlorpromazine equivalents) and for adequate duration (>4 weeks unless terminated owing to intolerable adverse effects). Failure was defined as insufficient response with persistence of symptoms significantly impairing the child's functioning according to child, parental, medical, and school reports or intolerable adverse effects. Exclusion criteria: Non-response to an adequate trial of clozapine or olanzapine (an adequate trial for these medications was defined as 8 weeks of olanzapine at a dosage of 20 mg/day or of clozapine at a dosage of 200 mg/day) Total sample size: No. randomised 25 Gender: 60% male Age: Mean 12.3 (range 7 to 16) years Ethnicity: 56% Caucasian Setting: Inpatient Mean duration of disorder: 3.2 years Mean age of onset: 9.1 years Definition of inadequate response: Failure to respond to 2 antipsychotic medications (typical or atypical, not including clozapine or olanzapine) used at adequate doses (>100-mg chlorpromazine equivalents) and for adequate duration (>4 weeks unless terminated owing to intolerable adverse effects). Failure was defined as insufficient response with persistence of symptoms

	significantly impairing the child's functioning according to child, parental, medical, and school reports or intolerable adverse effects.
Interventions	Intervention – group 1: Clozapine, mean (range) dose: 327 (12.5 to 900) mg/day, over 8 weeks, N = 12 Intervention – group 2: Olanzapine, mean (range) dose: 18.1 (5 to 20) mg/day, over 8 weeks, N = 12 Notes about the interventions: • Doses were titrated from starting doses of 12.5 mg/day (clozapine) and 5 mg/day (olanzapine). Clozapine was increased every other day with the first increase of 12.5 mg/day and thereafter increments of 25 mg/day. When the clozapine dose reached 150 mg/day (typically day 12), olanzapine was increased to 10 mg/day. When the clozapine dose reached 300 mg/day (typically week 3) olanzapine was increased to 15 mg/day. Further increases were guided by clinical judgment to maximum doses. • After double blind treatment, participants were offered an open trial of the second medication if non response to the trial medication was evident.
Extractable outcomes	Symptoms: PANSS (Total, Positive, Negative); BPRS; Bunney Hamburg Psychosis Rating Scale Global State: CGI Leaving the study early: Leaving the study early for any reason Side effects: Weight (kg), BMI (kg/m²), Tachycardia (bpm)
Quality	Sequence generation: Low Allocation Concealment: Low Participants blinded: Low Providers blinded: Low Outcome Assessors blinded: Low Missing outcome data: Low Selective outcome reporting: High Other bias: High
Related publications	None
NR - Not reported	

APPENDIX 13civ: OBSERVATIONAL STUDIES – INCLUDED STUDY CHARACTERISTICS

Study ID	**AZD1441C00150**
Bibliographic reference	AstraZeneca D1441C00150 (unpublished) A 26-week, international, multicenter, open-label phase IIIb study of the safety and tolerability of quetiapine fumarate (SEROQUEL™) immediate-release tablets in daily doses of 400 mg to 800 mg in children and adolescents with bipolar I disorder and adolescents with schizophrenia. Available from: www.astrazenecaclinicaltrials.com/_mshost800325/content/clinical-trials/resources/pdf/8579486 [accessed 6 November 2012].
General info	Funding source: AstraZeneca Published or unpublished data: Unpublished
Method	Type of study: Open-label Phase IIIb Study Type of analysis: LOCF Blindness: None Duration: Length of follow-up 26 weeks Duration: No. weeks of treatment 26 weeks Raters: N/A Design: Multicentre (59 centres in the US and other countries) prospective cohort: International. Number of people screened, excluded and reasons: Of the 383 patients screened in this study, 207 bipolar I disorder patients were previously enrolled in acute feeder Study 149, and 176 schizophrenia patients were previously enrolled in acute feeder Study 112. Two bipolar I disorder patients were screen failures in Study 150 (1 patient did not fulfil eligibility criteria [willingness to adhere to schedule of assessments] and 1 patient was not willing to continue) and 1 schizophrenia patient discontinued before receiving study drug. Thus, of 381 enrolled patients, 380 were included in the safety population (205 patients with bipolar I disorder and 175 patients with schizophrenia). Notes about study methods: Data only extracted for schizophrenia patients.
Participants	Diagnosis: sSchizophrenia: 46.1%, bipolar: 53.9% Diagnostic tool: DSM-IV Inclusion criteria: • Provision of written informed consent by one or both parents or by legal guardian prior to any study procedure. • Provision of written assent by the patient prior to any study procedure • Prior participation in Study 149 or Study 112 for ≥14 days • Male or female, aged 13 to 17 years at randomisation of Study 112 or aged 10 to 17 years at baseline of Study 149. Patients who became 18 years of age after entering Study 112 or Study 149 were permitted to enter this open-label study.

	• If female and of childbearing potential, must have used a reliable method of contraception. Reliable methods included abstinence, hormonal contraceptives (for example, oral contraceptive or long-term injectable or implantable hormonal contraceptive), double-barrier methods (for example, condom and diaphragm, condom and foam, condom and sponge), intrauterine devices, and tubal ligation. • All female patients needed to have the absence of pregnancy confirmed by a negative serum β-human chorionic gonadotropin (β-hCG) before OL baseline • DSM-IV criteria for schizophrenia or bipolar I disorder, confirmed by the K-SADS-PL at entry into the preceding double-blind Study 149 or Study 112 • Willingness to agree not to harm self • Had a parent or legal guardian accompany the patient at each scheduled study visit, who provided reliable information and was responsible for receiving and dispensing study medication. • Willingness to adhere to the schedule of assessments. Exclusion criteria: • DSM-IV Axis I diagnoses of Schizophreniform Disorder, Schizoaffective Disorder, Psychotic Disorder Not Otherwise Specified (NOS), Bipolar II Disorder, Bipolar Disorder NOS • An interval greater than 7 days between the last double-blind study visit (OL baseline) and Day 1 • Premorbid intelligence quotient (IQ) <70 or diagnosis of mental retardation. • Psychosis judged to be the direct physiological consequence of a medical condition or treatment. These conditions included degenerative neurological conditions (for example, Parkinson's disease, Huntington's disease), cerebrovascular disease (for example, stroke), metabolic conditions (for example, vitamin B12 deficiency), autoimmune conditions (for example, systemic lupus erythematosus), viral or other infections (for example, hepatitis, mononucleosis, human immunodeficiency), and cancers. • Psychosis judged to be the direct physiological effect (for example, intoxication, withdrawal) of an abused medication or substance • History of any serious suicide attempt that required medical intervention, or current suicidal risk that could not be safely managed as determined by the clinical judgment of the investigator. • Serious homicidal risk or homicidal behaviour within the past 3 months that resulted in adjudication • Known intolerance for or lack of response to quetiapine, as judged by the investigator • Contraindications as detailed in country-specific prescribing information for quetiapine • For female patients, pregnancy or lactation • Substance abuse or dependence including alcohol (except for caffeine or nicotine dependence), as defined in DSM-IV, within 1 month prior to screening • Use of depot antipsychotics (for example, haloperidol decanoate, fluphenazine decanoate, or risperidone microspheres),

	within one dosing interval of the start of OL treatment • Electroconvulsive therapy (ECT) within 30 days before enrolment • Use of potent cytochrome P450 (children and young people) 3A4 inhibitors (for example, ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, and saquinavir) in the 14 days preceding enrolment • Use of potent children and young people 3A4 inducers (for example, phenytoin, carbamazepine, barbiturates, rifampin, glucocorticoids, Saint John's Wort) in the 14 days preceding enrolment • Thyroid-stimulating hormone (TSH) concentration more than 10% above the upper limit of the normal (ULN) range at OL baseline • Laboratory test results outside the reference range at OL baseline and considered by the investigator to be clinically significant • Baseline QTc interval (Fridericia formula; Puddu et al 1988) ≥450 milliseconds at OL baseline • Renal, cardiovascular, hepatic, hematologic, endocrinologic, ophthalmologic, or other disease or clinical finding that is unstable or that in the opinion of the investigator would be negatively affected by study medication or that would affect study medication • Unstable diabetes mellitus (DM) with an OL baseline HbA1c ≥8.5 • Patients admitted to a hospital for treatment of diabetes or diabetes-related illness in past 12 weeks • Not under the care of a physician responsible for the patient's DM care • Diabetes mellitus clinically unstable in the opinion of the physician responsible for the patient's diabetes management at the time of OL baseline • The physician responsible for the patient's DM care had not approved the patient's participation in the study • The patient had not been on the same dose of oral hypoglycaemic drug(s) and/or diet for the 4 weeks prior to OL baseline. For thiazolidinediones (glitazones) this period should not have been less than 8 weeks. • A patient taking insulin whose daily dose on one occasion in the past 4 weeks was more than 10% above or below their mean dose in the preceding 4 weeks • If the patient's complete blood count (CBC) with white blood cell count (WBC) differential showed an absolute neutrophil count (ANC) <1.0 x 109/L, the test was to be repeated within 24 hours. If it remained <1.0 x 109/L, the patient was to be excluded. • Medical condition that would affect absorption, distribution, metabolism, or excretion of study medication. • History of seizure disorder, except febrile convulsions • Use of experimental drug outside of a quetiapine study within 30 days of enrolment • Significant medical illness which could prevent patient from completing OL treatment. • Previous participation in this study.

	Total sample size: No. randomised 381 Gender: 60% male Age: Mean: 14.4 (range: not reported) years Ethnicity: 71% Caucasian Setting: Not reported Mean duration of disorder: Not reported Mean age of onset: Not reported Prior antipsychotic use: Not reported
Interventions	Intervention – group 1: Quetiapine (mean dose 400 to 800 mg/day), over 26 weeks, N = 381 Intervention – group 2: N/A Notes about the interventions: N/A
Extractable Outcomes	Metabolic symptoms: Weight, BMI, fasting serum glucose, total cholesterol, HDL, LDL, triglycerides. Neurological symptoms: AIMS, SAS, BARS, UKU. Hormonal symptoms: Prolaction, TSH. Cardiac symptoms: Blood pressure, QTc interval. Leaving the study early: Leaving due to any reason.
Related publications	Unpublished study: AZD1441C00112

Study ID	**CASTRO-FORNIELES2008**
Bibliographic reference	Castro-Fornieles, J., Parellada, M., Soutullo, C. A., *et al.* (2008). Antipsychotic treatment in child and adolescent first-episode psychosis: a longitudinal naturalistic approach. *Journal of Child and Adolescent Psychopharmacology*, *18*, 327-336.
General info	Funding source: Carlos III Institute of Health, Spanish Department of Health, Cooperative Research Thematic Network and from the Spanish Ministry of Health, Instituto de Salud Carlos III, CIBERSAM Network. Published or unpublished data: Published
Method	Type of study: Naturalistic, longitudinal Type of analysis: Available case Blindness: None Duration: Length of follow-up 26 weeks Duration: No. weeks of treatment 52 weeks Raters: N/A Design: Multicentre (6 university hospitals)prospective cohort: Spain Number of people screened, excluded and reasons: 116 individuals met the inclusion criteria. Six patients were excluded, three due to mental retardation and 3 due to parents' refusal to participate. The final sample comprised 110 children and adolescents.

	Notes about study methods: N/A
Participants	• Diagnosis: Schizophrenia type disorder: 39.1%, psychotic disorder NOS: 38.2%, • Depressive disorder with psychotic symptoms: 11.8%, • Bipolar disorder, manic episode with psychotic symptoms: 10.9% Diagnostic tool: DSM-IV Inclusion criteria: • Age between 7 and 17 years at the time of first evaluation • Presence of positive psychotic symptoms (within a psychotic episode) such as delusions or hallucinations of less than 6 months' duration. • Exclusion criteria: • Presence of a concomitant Axis I disorder at the time of evaluation that might account for the psychotic symptoms (such as substance abuse, autistic spectrum disorders, post traumatic stress disorder, or acute stress disorder) • Mental retardation according to DSM-IV criteria including not only an intelligence quotient (IQ) below 70 but also impaired functioning • Pervasive developmental disorder • Neurological disorders, • History of head trauma with loss of consciousness • Pregnancy. • Occasional substance use was not an exclusion criterion if positive symptoms persisted for more than 2 weeks after a negative urine drug test. Total sample size: No. randomised 110 Gender: 67% male Age: Mean 15.5 (range: 9 to 17) years Ethnicity: 86% Caucasian Setting: In- and out-patient psychiatric units Mean duration of disorder: Not reported Mean age of onset: Not reported Prior antipsychotic use: 51% antipsychotic naive
Interventions	Intervention – group 1: Olanzapine (mean dose 11.6 mg/day), over 26 weeks, N = 14 Intervention – group 2: Quetiapine (mean dose 405.1 mg/day), over 26 weeks, N = 15 Intervention – group 3: Risperidone (mean dose 3.3 mg/day), over 26 weeks, N = 31 Notes about the interventions: N/A
Extractable Outcomes	Metabolic symptoms: Weight

	Neurological symptoms: AIMS, SAS, BARS, UKU Leaving the study early: Leaving due to any reason.
Related publications	N/A

Study ID	**CROCQ2007**
Bibliographic reference	Crocq, M. A., Guillon, M. S., Bailey, P. E., *et al.* (2007). Orally disintegrating olanzapine induces less weight gain in adolescents than standard oral tablets. *European Psychiatry*, *22*, 453-454.
General info	Funding source: Not reported Published or unpublished data: Published
Method	Type of study: Open label, non-randomised, observational Type of analysis: Available case Blindness: None Duration: Length of follow-up 12 weeks Duration: No. weeks of treatment 12 weeks Raters: N/A Design: Single site prospective cohort: France Number of people screened, excluded and reasons: Screening information not reported. Data available for 52 hospitalised adolescents. Notes about study methods: N/A
Participants	Diagnosis: Schizophreniform disorder Diagnostic tool: DSM-IV Inclusion criteria: Not reported Exclusion criteria: Not reported Total sample size: No. randomised 52 Gender: Age: Mean 15.2 (range NR) years Ethnicity: 100% Caucasian Setting: Inpatient unit Mean duration of disorder: Not reported Mean age of onset: Not reported Prior antipsychotic use: 75% antipsychotic naive

Interventions	Intervention – group 1: Olanzapine standard tablet (mean dose 18 mg/day), over 12 weeks, N = 10. Intervention – group 2: Olanzapine orally disintegrating tablet (mean dose 16.6 mg/day), over 12 weeks, N = 16. Intervention – group 3: Risperidone (mean dose 2.8 mg/day), over 12 weeks, N = 26. Notes about the interventions: Subjects were hospitalised during the study period. Consequently, medication compliance was verified; also, all participants took part in the same sports activities and they were served the same meals. However, the quantity of food that was effectively eaten was not kept constant and depended on individual appetites.
Extractable Outcomes	Metabolic symptoms: Weight Leaving the study early: Leaving due to any reason.
Related publications	N/A

Study ID	**DITTMANN2008**
Bibliographic reference	Dittmann, R. W., Meyer, E., Freisleder, F. J., (2008). Effectiveness and tolerability of olanzapine in the treatment of adolescents with schizophrenia and related psychotic disorders: Results from a large, prospective, open-label study. *Journal of Child and Adolescent Psychopharmacology*, *18*, 54-69.
General info	Funding source: Lilly Deutschland Published or unpublished data: Published
Method	Type of study: Open label, prospective Type of analysis: LOCF Blindness: None Duration: Length of follow-up 24 weeks Duration: No. weeks of treatment 24 weeks Raters: N/A Design: : Multicentre (10 inpatient units) prospective open label study: Germany Number of people screened, excluded and reasons: 100 participants signed consent forms. Of these four dropped out prior to starting olanzapine because they did not meet all inclusion and exclusion criteria after baseline examination. Notes about study methods: After a 6 week treatment period participants were assessed using the BPRS. Responders (absolute BPRS improvement >30%) continued treatment as outpatients in an open label extension period of 18 weeks duration.
Participants	Diagnosis: Schizophrenia (84.3%), schizophreniform (9.4%), schizoaffective (6.3%). For the majority of participants (85.4%) this was their first episode. Diagnostic tool: DSM-IV Inclusion criteria:

	• Aged 12 to 21 years • Initial BPRS total score of at least 18 Exclusion criteria: • Previous participation in a study investigating olanzapine • Serious unstable illnesses • Uncorrected hypo- or hyperthyroidism • Narrow-angle glycoma • History of seizures • Agranulocytosis • Jaundice • Allergic reaction to study medication • Substance abuse • Recent pre-treatment with depot neuroleptics • Monoamine oxidase inhibitors • Other medications with primarily central nervous system activity • Pregnant or nursing Total sample size: No. randomised 100 Gender: 71% male Age: Mean 15.5 (range 12 to 19) years Ethnicity: 95% Caucasian Setting: Inpatients during Phase I (6 weeks); out-patients during Phase II (18 weeks) Mean duration of disorder: Not reported Mean age of onset: 15.5 years Prior antipsychotic use: 38 % antipsychotic naive
Interventions	Intervention – group 1: Olanzapine (mean dose 14 mg/day), over 24 weeks, N = 96 Notes about the interventions: 80 participants completed the 6 weeks acute period. 62.5% of enrolled patients were responders at week 6 and continued treatment into the 18 week extension period.
Extractable Outcomes	Metabolic symptoms: Weight Hormonal symptoms: Prolactin Leaving the study early: Leaving due to any reason.
Related publications	N/A

Study ID	KUMRA1998
Bibliographic reference	Kumra, S., Jacobsen, L. K., Lenane, M., *et al.* (1998) Case series: spectrum of neuroleptic-induced movement disorders and extrapyramidal side effects in childhood-onset schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry*, *37*, 221-227.
General info	Funding source: Not reported Published or unpublished data: Published
Method	Type of study: Open, controlled continuation of a 6 week double blind RCT Type of analysis: Blindness: None Duration: Length of follow-up: 104 to 208 weeks Duration: No. weeks of treatment: unclear Raters: N/A Design: Prospective open label Number of people screened, excluded and reasons: Not reported Notes about study methods: Participants recruited via professional and patient advocacy organisations.
Participants	Diagnosis: Schizophrenia – treatment resistant Diagnostic tool: DSM III Inclusion criteria: • aged 6 to 18 years • psychotic symptoms documented by age 12 years • failure of two prior typical neuroleptic treatment • IQ >70. Exclusion criteria: • significant unstable neurological or medical disorder • current serious risk of suicide • active alcohol/drug abuse. Total sample size: No. randomised 34 Gender: 56% male Age: Mean 14.15 (range NR) years Ethnicity: 32% Caucasian Setting: Not reported Mean duration of disorder: Not reported Mean age of onset: 10.31 years

	Prior antipsychotic use: 0% antipsychotic naïve – On average 22.35 months of neuroleptic exposure.
Interventions	Intervention – group 1: Clozapine (mean dose 176 mg/day), over 24 weeks, N = 10 Intervention – group 2: Haloperidol (mean dose 16 mg/day), over 24 weeks, N = 11 Intervention – group 3: Olanzapine (mean dose 17.5 mg/day), over 24 weeks, N = 8 Notes about the interventions: N/A
Extractable Outcomes	Extra pyramidal symptoms: Tardive dyskinesia
Related publications	Kumra, S., Jacobsen, L. K. & Rapoport, J. L. (1996) Childhood-Onset Schizophrenia - A Double-Blind Clozapine Trial. 149th.Annual Meeting of the American Psychiatric Association. New York, NY. 4 to 9 May, 1996.

Study ID	**ROSS2003**
Bibliographic reference	Ross, R. G., Novins, D., Farley, G. K., Adler, L. E. (2003) A 1-year open-label trial of olanzapine in school-age children with schizophrenia. *Journal of Child and Adolescent Psychopharmacology*, *13*, 301–309.
General info	Funding source: Veterans' Administration Research Services; Public Health Service; Eli Lilly Published or unpublished data: Published
Method	Type of study: Prospective, open-label, naturalistic trial Type of analysis: LOCF Blindness: None Duration: Length of follow-up 52 weeks Duration: No. weeks of treatment 52 weeks Raters: N/A Design: Single site prospective open label study: Colorado, US Number of people screened, excluded and reasons: Not reported Notes about study methods: N/A
Participants	Diagnosis: Schizophrenia or Schizoaffective disorder • Diagnostic tool: DSM-IVNo recent exposure and preferably naïve to olanzapine treatment; • Chronological age 6–15 years, with recruitment focused on children ages 6–12 years • Agreement by the current treating clinician that the child had either childhood-onset schizophrenia or schizoaffective disorder and that treatment with olanzapine was one of the treatment options currently being considered. • Lack of concurrent neurological disease (for example, seizures or tumour) • Lack of concurrent substance abuse • Lack of medical disease with which antipsychotic use might be contraindicated (for example, hepatitis). Exclusion criteria: Not reported

	Total sample size: No. randomised 20 Gender: 74% male Age: Mean: 10.5 (range: 6 to 15) years Ethnicity: 84% Caucasian Setting: Not reported Mean duration of disorder: Not reported Mean age of onset: <13 years old Prior antipsychotic use: 58% antipsychotic naive
Interventions	Intervention – group 1: Olanzapine (mean dose 7.7 mg/day), over 52 weeks, N = 20 Intervention – group 2: N/A Notes about the interventions: N/A
Extractable Outcomes	Metabolic symptoms: Weight, BMI. Extra pyramidal symptoms: (AIMS, SAS, BARS, UKU) Leaving the study early: Leaving due to any reason.
Related publications	N/A

Study ID	**SCHIMMELMANN2007**
Bibliographic reference	Schimmelmann, B. G., Mehler-Wex, C., Lambert, M., Schulze-zur-Wiesch, C., Koch, E., Flechtner, H. H., *et al.* (2007) A propesctive 12-week study of quetiapine in adolescents with schizophrenia spectrum disorders. *Journal of Child and Adolescent Psychopharmapathology*, *17*, 768–778.
General info	Funding source: AstraZeneca Published or unpublished data: Published
Method	Type of study: Prospective, longitudinal Type of analysis: LOCF Blindness: None Duration: Length of follow-up 12 weeks Duration: No. weeks of treatment 12 weeks Raters: N/A Design: Multicentre (six university and two non university affiliated departments) open label study: Germany. 2002–2004. Number of people screened, excluded and reasons: 61 individuals screened, 5 were excluded (4 didn't meet inclusion criteria and 1 refused to participate). 56 participants entered the study. Four participants discontinued in the first week, one withdrew consent and 3 needed impermissible medication. Therefore, 52 participants were included in the ITT analysis.

	Notes about study methods: N/A
Participants	Diagnosis: 76.8% schizophrenia, 12.5% schizophreniform, 10.7% schizoaffective disorder Diagnostic tool: DSM-IV Inclusion criteria: • Medically healthy subjects • Ages 12 to 17 years, meeting • DSM-IV criteria for schizophrenia, schizoaffective or schizophreniform disorder • A PANSS total score of 60 points Exclusion criteria: • Alcohol or drug dependency within 2 months before study • Clinically significant electrocardiogram, electroencephalogram or laboratory abnormalities. • Pregnant or lactating women as assessed prior to study entry • Women of childbearing potential not using an acceptable method of contraception • Concomitant medication not allowed by the protocol. Total sample size: No. randomised 56 Gender: 68% male Age: Mean: 15.9 (range: 12 to 17.9) years Ethnicity: 84% Caucasian Setting: 98% hospitalised Mean duration of disorder: Not reported Mean age of onset: Not reported Prior antipsychotic use: 77% antipsychotic naive
Interventions	Intervention – group 1: Quetiapine (mean dose 594.9 mg/day), over 52 weeks, N = 56 Intervention – group 2: N/A Notes about the interventions: N/A
Extractable Outcomes	Metabolic symptoms: Weight, BMI, total cholesterol. Extra pyramidal symptoms: (AIMS, SAS, BARS, UKU). Hormonal symptoms: Prolactin, TSH. Cardiac symptoms: Blood pressure. Leaving the study early: Leaving due to any reason.
Related publications	N/A

APPENDIX 13d: COGNITION, EMPLOYMENT AND EDUCATION: INCLUDED STUDIES CHARACTERISTICS

Study ID	EACK2009
Bibliographic reference	Eack, S. M., Greenwald, D. P., Hogarty, S. S., *et al.* (2009) Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. *Psychiatric Services*, *60*, 1468-1476.
General info	Funding source: National Institute of Mental Health Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT Blindness: Participants, providers and outcome assessors unblinded. Duration: Length of follow-up – 104 weeks Duration: No. weeks of treatment– 104 weeks Raters: Independent of treatment. Design: Single site RCT, Pittsburg, PA. Number of people screened, excluded and reasons: Not reported Notes about study methods: Although many participants had some college education (67%), most were not employed at baseline (74%).
Participants	Diagnosis: Schizophrenia (66%) or schizoaffective disorder (34%) Diagnostic tool: DSM-IV Inclusion criteria: • Those with schizophrenia, schizoaffective, or schizophreniform disorder whose illness had been stabilised on antipsychotic medication, who had experienced their first psychotic symptoms (including duration of untreated illness) within the past 8 years. • IQ ≥80 • Not been abusing substances for at least 2 months before study enrolment • Significant social and cognitive disability on the Cognitive Style and Social Cognition Eligibility Interview. Exclusion criteria: Not reported Total sample size: No. randomised - 58 Gender: 69% male Age: Mean 25.9 (range not reported) Ethnicity: 69% Caucasian

	Setting: Outpatient clinic
Interventions	Intervention – group 1: Cognitive Enhancement Therapy (CET), 60 hours of computer-assisted neurocognitive training and 45 social-cognitive group sessions, over 104 weeks, N = 31. Intervention – group 2: Enriched Supportive Therapy (EST), over 104 weeks, N = 27. Notes about the interventions: All participants received Food and Drug Administration–approved antipsychotic medications for the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorder as indicated by a study psychiatrist. Medication changes were allowed, although every effort was made to stabilize participants on a tolerable and efficacious antipsychotic regimen before the initiation of psychosocial treatment. CET: A comprehensive, developmental approach to the remediation of social and non-social cognitive deficits in schizophrenia. CET typically begins with approximately 3 months of weekly 1-hour neurocognitive training in attention, after which participants begin the weekly 1.5-hour social-cognitive groups. Neurocognitive training then proceeds concurrently with social cognitive groups throughout the remaining course of treatment. EST: Is an illness management and psychoeducation approach that draws on components of the basic and intermediate phases of the demonstrably effective personal therapy. In this approach, outpatients are seen on an individual basis to learn and practice stress management techniques designed to forestall late post discharge relapse and enhance adjustment.
Extractable outcomes	Mental state: BPRS-depression-anxiety, BPRS-negative symptoms Psychosocial functioning: GAS Occupation: Number of participants engaging with occupational activities (Major Role Adjustment Inventory, MRAI). Processing speed: Composite score Neurocognition: Composite score Cognitive style: Composite score Social cognition: Composite score Social adjustment: Composite score Symptoms: Composite score Leaving the study early: Leaving due to any reason
Quality	Sequence generation: Low risk Allocation Concealment: Low risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: High risk Missing outcome data: High risk

	Selective outcome reporting: Low risk Other bias: Low risk
Related publications	Eack, S. M., Hogarty, G. E., Greenwald, D. P., *et al.* (2011) Effects of cognitive enhancement therapy on employment outcomes in early schizophrenia: results from a 2-year randomized trial. *Research on Social Work Practice*, *21*, 32-42.

Study ID	**KILLACKEY2008**
Bibliographic reference	Killackey, E., Jackson, H. J. & McGorry P. D. (2008) Vocational intervention in first-episode psychosis: individual placement and support v. treatment as usual. *The British Journal of Psychiatry*, *193*, 114-120.
General info	Funding source: Medical Research Council Program and Bristol Myers Squibb. ORYGEN Research Centre is supported by the Colonial Foundation. Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT Blindness: Participants, providers and outcome assessors unblinded. Duration: Length of follow-up – 26 weeks Duration: No. weeks of treatment– 26 weeks Raters: Independent of treatment. Design: Single site RCT, Melbourne, Australia. Number of people screened, excluded and reasons: 41 individuals assessed for eligibility and all were randomised. Notes about study methods: N/A
Participants	Diagnosis: First episode psychosis (bipolar not specified). Diagnostic tool: DSM-IV Inclusion criteria: • Aged 15–25 • First-episode of psychosis • Living in a defined catchment area • Individuals wanted to find work (including a different job if they currently held one). • Individuals with at least 6 months of care left at EPPIC (EPPIC is limited to providing 18 months of care). Exclusion criteria: • Lack of fluency in English Total sample size: No. randomised – 41 Gender: 80.5% male Age: Mean 21.4 (range not reported).

	Ethnicity: Not reported Setting: Specialist clinic - All were patients of the Early Psychosis Prevention and Intervention Centre (EPPIC).
Interventions	Intervention – group 1: Individual Placement and Support (IPS) + EPPIC TAU, on average the employment consultant had 29.55 (s.d.= 11.45) contacts with each participant, over 26 weeks, N = 20. Intervention – group 2: EPPIC treatment as usual, over 26 weeks, N = 21. Notes about the interventions: IPS: A highly defined form of supported employment that has six key principles: (a) it is focused on competitive employment (b) it is open to any person with mental illness who chooses to look for work and acceptance into the programme is not determined by measures of work-readiness or illness variables (c) job searching commences directly on entry into the programme; (d) the IPS programme is integrated with the mental health treatment team; (e) potential jobs are chosen based on consumer preference; (f) the support provided in the programme is time-unlimited, continuing after employment is obtained, and is adapted to the needs of the individual. A seventh principle, also sometimes considered as part of the model of IPS, is welfare benefits counselling. EPPIC TAU: Consisted of participants continuing to receive EPPIC care. This involves individual case management and medical review, referral to external vocational agencies, as well as involvement with the group programme at EPPIC, which may involve participation in the vocationally oriented groups within the group programme. Treatment as usual was delivered primarily by EPPIC case managers.
Extractable outcomes	Mental state: BPRS, SANS, CES-D. Quality of life: QLS Social Functioning: SOFAS Employment: Number of participants, number of job interviews, weeks/hours worked, pay. Leaving the study early: Leaving due to any reason
Quality	Sequence generation: Low risk Allocation Concealment: Low risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: High risk Missing outcome data: Low risk Selective outcome reporting: High risk Other bias: High risk
Related publications	N/A

Study ID	UELAND2004
Bibliographic reference	Ueland, T. & Rund, B. R. (2004) A controlled randomized treatment study: the effects of a cognitive remediation program on adolescents with early onset psychosis. *Acta Psychiatrica Scandinavica*, *109*, 70-74. Ueland, T. & Rund, B. R. (2005) Cogntiive remediation for adolescents with early onset psychosis: a 1-year follow-up study. *Acta Psychiatrica Scandinavica*, *111*, 193-201
General info	Funding source: Norwegian Research Council and the National Council for Mental Health/Health and Rehabilitation. Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: Available case Blindness: Participant, provider and rater unblinded. Duration: Length of follow-up – 52 weeks Duration: No. weeks of treatment – 26 weeks Raters: Independent of treatment. Design: Single site RCT, Oslo Norway. Number of people screened, excluded and reasons: Not reported Notes about study methods: Patients assessed prior to discharge or after 6 months.
Participants	Diagnosis: schizophrenia (N = 16), schizoaffective disorder (N = 3), schizotypal personality disorder (N = 2), bipolar disorder (N = 3), psychotic disorder NOS (N = 1) and major depressive disorder (N = 1). Diagnostic tool: DSM-IV Inclusion criteria: • Aged between 12 and 18 • A diagnosis within the schizophrenia spectrum or other psychotic disorder and no evidence of organic brain disease. Exclusion criteria: Not reported Total sample size: No. randomised – rot reported Gender: 53.9% male Age: Mean 15.3 (range not reported) Ethnicity: Not reported Setting: All participants were recruited from an inpatient unit for psychotic patients at the Sogn Centre for Child and Adolescent Psychiatry in Oslo.
Interventions	Intervention – group 1: Cognitive Remediation Therapy (CRT) + psychoeducation, 30 hours over 26 weeks, N = 14. Intervention – group 2: Psycho-education over 26 weeks, N = 12. Notes about the interventions:

	Six subjects were not on medication, while 20 subjects were receiving antipsychotic medication at baseline. Ten patients were using atypical and nine were using typical antipsychotic medication. One patient was using both types. CRT: The cognitive remediation group received 30 hours of individual training consisting of four modules: cognitive differentiation, attention, memory and social perception. Psycho-education: Both groups received a psychoeducational treatment program, while only the experimental group received the addition of a cognitive remediation program. Central elements of the psychoeducational treatment program were parent seminars, problem-solving sessions, milieu therapy and network groups.
Extractable outcomes	Mental state: BPRS Psychosocial functioning: GAS Leaving the study early: Leaving due to any reason
Quality	Sequence generation: Low risk Allocation Concealment: Low risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: High risk Missing outcome data: Unclear risk Selective outcome reporting: Low risk Other bias: Low risk
Related publications	Ueland, T and Rund, BR (2005) Cognitive remediation for adolescents with early onset psychosis: a 1-year follow-up study. *Acta Psychiatrica Scandinavica*, 111, 193–201.

Study ID	**WYKES2007**
Bibliographic reference	Wykes, T., Newton, E., Landau, S., *et al.* (2007) Cognitive remediation therapy (CRT) for young early onset patients with schizophrenia: an exploratory randomized controlled trial. *Schizophrenia Research*, *94*, 221-230.
General info	Funding source: Mental Health Foundation Published or unpublished data: Published
Method	Type of study: Individual randomised trial Type of analysis: ITT Blindness: Participants, providers and raters not blind. Duration: Length of follow-up – 26 weeks. Duration: No. weeks of treatment – 14 weeks.

	Raters: Independent of treatment. Design: Single-site RCT, London, UK. Number of people screened, excluded and reasons: 66 people referred, 40 participants met criteria and consented (16 unmet clinical criteria, 6 no consent, 4 unmet cognitive criteria). 40 people randomised. Notes about study methods: Symptom and quality of life assessments were assessed by an independent rater who was blind to group allocation. Self-report assessments (cognition and self-esteem) and informant ratings (social behaviour) were collected by a research assistant who was not blind to group allocation.
Participants	Diagnosis: Schizophrenia Diagnostic tool: DSM-IV Inclusion criteria: • Diagnosis of schizophrenia with an onset prior to the age of 19 and a duration of illness of 3 years or less. • Cognitive difficulties in cognitive flexibility (as demonstrated by a score below the 16th percentile on the Wisconsin Card Sort Test (WCST) and/or memory (as demonstrated by a score falling within the 'poor' performance range or below on the screening test of the Rivermead Behavioural Memory Test. • Difficulties in social functioning (identified as having at least one problem on the Social Behaviour Schedule. • On a stable dose and type of medication, for at least 1 month prior to inclusion. Exclusion criteria: • A history of organic brain disorder (for example, epilepsy) • A diagnosis of current substance abuse as defined by the DSM IV. Total sample size: No. randomised - 40 Gender: 65% male Age: Mean 18.2 (range 14 to 22) years Ethnicity: Not reported Setting: Inpatient
Interventions	Intervention – group 1: Cognitive remediation therapy, 40 hourly sessions over 14 weeks, N = 21. Intervention – group 2: Treatment as usual, over 14 weeks, N = 19. Notes about the interventions: CRT: Forty 1-hour sessions, at an average rate of three per week. In each session, a variety of tasks was presented to practice the component processes in remembering, complex planning and problem solving. The tasks were graded in difficulty with easier ones being presented early in the program. TAU: Details not reported.
Extractable outcomes	Leaving the study early: Leaving due to any reason

Quality	Sequence generation: Unclear risk Allocation Concealment: Low risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: High risk Missing outcome data: High risk Selective outcome reporting: High risk Other bias: Low risk
Related publications	N/A

Study ID	**URBEN2012**
Bibliographic reference	Urben, S., Pihet, S., Jaugey, L., *et al.* (2012) Computer-assisted cognitive remediation in adolescents with psychosis or at risk for psychosis: a 6-month follow-up. *Acta Neuropsychiatric*, published online 4 April. DOI: 10.1111/j.1601-5215.2012.00651.x.
General info	Funding source: Swiss National Science Foundation Published or unpublished data: Published and unpublished
Method	Type of study: Individual randomised trial Type of analysis: LOCF Blindness: Participants, providers and outcome assessors unblinded. Duration: Length of follow-up: 26 weeks Duration: No. weeks of treatment: 8 weeks Raters: Independent of treatment. Design: Single site RCT, Lausanne, Switzerland. Number of people screened, excluded and reasons: NR Notes about study methods: NR
Participants	Diagnosis: Psychotic disorder (65%), at high risk of developing psychosis (35%) Diagnostic tool: DSM-IV Inclusion criteria: • Diagnosis of psychotic disorder according to the Diagnostic and Statistical Manual, 4th edition using the French version of Diagnostic Interview for Genetic Studies; or • Diagnosis of high risk of psychosis using the Structured Interview for Prodromal Symptoms and the Scale of Prodromal Symptoms • A score below the 10th percentile in at least one of five domains of the Repeatable Battery for the Assessment of Neuropsychological Status Exclusion criteria:

	• Mental retardation (IQ < 70) • Known neurological disease or developmental disability • Severe visual or motor disorder that is incompatible with computer use. • Transient exclusion criteria: an acute clinical state that could disrupt the CACR training or a planned absence for more than 2 weeks during period of intervention. Total sample size: No. randomised - 32 Gender: 64% male Age: Mean 15.61 (range 13 to 17) Ethnicity: NR Setting: Outpatient clinic
Interventions	Intervention – group 1: Computer-assisted cognitive remediation (CACR) program, two 45-minute individual sessions per week over 8 weeks (16 individual sessions), N = 18. Intervention – group 2: Computer games (CG), two 45-minute individual sessions per week over 8 weeks (16 individual sessions), N = 14. Notes about the interventions: CACR: The CACR program was based on the Captain's Log software. The program allows training in attention, concentration, memory, visuospatial, visuomotor and conceptualisation with increasing difficulty. CG: A set of action computer games (N = 13), requiring attention and visuomotor skills were used as control.
Extractable outcomes	Mental state: PANSS, SAPS, SANS Global state: CGI-Severity Social functioning: SOFAS Occupation: Number of participants engaging with occupational activities Processing speed: The symbol coding test (WAISIII: >16 years old/WISC-IV: <16 years old) Working memory: Letter-number sequencing (WAIS-III: >16 years old/WISC-IV: <16 years old) Long-term memory: The Hopkins Verbal Learning Test-Revised. The Brief Visuospatial Memory Test-Revised was used to assess visuospatial episodic memory. Executive functions: The Color Stroop task Reasoning and planning abilities: The block design test (WAIS-III/WISC-IV) Neurocognition: Composite score Cognitive style: Assessed cognitive functions were processing speed, memory abilities and executive functions. Social cognition:

	Social adjustment: Leaving the study early: Leaving the study early for any reason
Quality	Sequence generation: Unclear risk Allocation Concealment: Unclear risk Participants blinded: High risk Providers blinded: High risk Outcome Assessors blinded: Low risk Missing outcome data: High risk Selective outcome reporting: Low risk Other bias: High risk
Related publications	Holzer L, Passini MC, Pellanda V et al. A randomised controlled trial of the effectiveness of a computer-assisted cognitive remediation (CACR) program in adolescents with psychosis or at high risk of psychosis. *Behav Res Ther* (submitted).

APPENDIX 13e: EXCLUDED STUDIES

Psychological therapy and psychosocial interventions: excluded studies

Study	Reason for exclusion
ADDINGTON2011A	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
AGHOTOR2010	Adult population
ARCHIE2003	Adult population
BAKER2010	Design: Non-RCT
BARROWCLOUGH2001	Adult population
BARROWCLOUGH2009	Adult population
BEAUCHAMP2011	Adult population
BECHDOLF2004A	Adult population
BECHDOLF2005	Adult population
BECHDOLF2007	Outcomes not of interest.
BECHDOLF2009	Conference abstract
BECHDOLF2010A	Adult population
BECHDOLF2011	Conference abstract
BECHDOLF2012	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
BECKER1997	Adult population
BECKER1998	Design: Non-RCT
BEEBE2001	Adult population
BIRCHWOOD2011	Design: Protocol only
BOLA2006	Intervention not included in the scope
BOWIE2011	Conference abstract
BRADSHAW2000	Adult population
BRESSI2008	Adult population
BUCCISBAKER2010	Intervention not included in the review protocol
CAMPBELL2011	Non clinical population
CARPENTER1987	Adult population
CATHER2005	Adult population
CATTY2008	Adult population
CARPENTER1987	Adult population
CATHER2005	Adult population
CATTY2008	Adult population
CATTY2010	Adult population
CHAMORRO2008	Not in English
CHOI2006	Adult population
CHOI2009	Adult population
CHONG2009	Adult population
CHRISTODOULIDES2008	Design: Non-RCT
COLE1967	Paper unavailable
COMBS2011	Adult population
CORCORAN2005	Design: Discussion on prodromal interventions for schizophrenia
CUNNINGHAMOWENS2001	Adult population
DAPRATI2005	Adult population
DAUMIT2010	Conference abstract

DAVIS1972	Adult population
DIAMOND2001	Design: Non-RCT
DIXON1999	Adult population
DOANNE1985	Adult population
DOERINGSMULLER1998	Adult population
DURHAM2003	Adult population
EACK2007	Adult population
EACK2009	Not relevant to this section. Included in the 'Cognition, Employment & Education' chapter.
EACK2011A	Outcomes not of interest
EACK2011B	Not relevant to this section. Included in the 'Cognition, Employment & Education' chapter.
EDWARDS2003	Conference abstract
ERICKSON1998	Design: Cohort
ERICKSON2010	Adult population
FALLOON1982	Adult population
FALLOON1985	Adult population
FALLOON1987	Adult population
FENTON1979	Adult population
FJELL2007	Design: Discussion
FOWLER2009	Adult population
FRANK1990	Adult population
FRAZIER2007	Design: Cohort
GALLAS2010	Conference abstract
RETT2011	Adult population
GASTAL2010	Not in English
GLEESON2008	Design: Protocol only
GLEESON2010	Outcomes not included in the review protocol
GLICK1985	Adult population
GLICK2011	Adult population
GLICKSOHN2000	Adult population
GOULET1993A	Not in English
GRANHOLM2009	Adult population
GRAWE2006	Adult population
GUANG2005	Not in English
GUMLEY2006	Adult population
GUO2007	Design: Protocol only
GUO2010	Adult population
GUPTA2011	Conference abstract
GUTTGEMANNS2011	Not in English
HAMANN2006	Adult
HAN2004	Not in English
HENGGLER1999	8% of the sample had a diagnosis of thought disorder/schizophrenia
HERVIEUX2009	Not in English
HJORTHO2008	Design: Protocol only
HODGE2010	Adult population
HOGARTY1979	Adult population
HOGARTY1997	Adult population
HOGARTY1997A	Adult population
HOLLOWAY1996	Conference abstract
HOULT1984B	Intervention not included in the review protocol

JACKSON2001	Design: Cohort
JACKSON2005a	Design: Non RCT
JAUGEY2012	Conference abstract
JENNER2001	Design: Non RCT
JENNER2004	Adult population
JOHNSON2008	Adult population
JOLLEY2003	Adult population
JONES2001	Adult population
KARON1969	Adult population
KEMP2007	Intervention not included in the review protocol
KILLACKEY2008	Not relevant to this section. Included in the 'Cognition, Employment & Education' chapter.
KLINGBERGSWITTO2010	Design: Protocol only
KOIKE2011	Design: Protocol only
LANDA2012	Conference abstract
LARSEN2007	Design: Non experimental
LEAVY2004	Outcomes not included in the review protocol
LECARDEUR2009	Adult population
LECOMTE1999	Adult population
LEFF1989	Adult population
LEFF2002	Adult population
LEHTINEN2000	Adult population
LENIOR2002	Design: Non RCT
LENIOR2005	Adult population
LENZENWEGER2002	Non clinical population
LI2005A	Adult population
LIBERMAN2005	Non clinical population
LINSZEN1993	Not in English
LIU2010A	Design: Non RCT
LOBAN2011	Focuses on carers
MALM1982	Adult population
MARTIN2005	Adult population
MCAY2007	Adult population
MCCAYBEANLANDS2006	Adult population
MCFARLANE1996	Adult population
MCGILL1983	Adult population
MCGURK2007	Adult population
MELAU2011	Adult population
MIKLOWITZ2004	Design: Non RCT
MILLER2004	Adult population
MORGAN2011	Adult population
MORRISON2002	Design: Cohort
MORRISON2004	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
MORRISON2007	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
MORRISON2011	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
MORRISON2012	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
NAEEM2005	Adult population
NAEEM2006	Design: Non RCT

NAEEM2008	Adult population
NAOKI2003	Not in English
NORMAN2002	Adult population
NUGTER1997	Outcomes not included in the review protocol
OBRIEN2007	Design: Non RCT
ODONNELL2003	Adult population
OWENS2001	Adult population
PARK2011	Adult population
PATRASKAR2011	Adult population
PAWELCZYK2009	Adult population
PENN2005	Systematic review: No new useable data
PENN2009	Adult population
PETERS2010	Adult population
PILLING2002	Systematic review – adult population
PILLING2002A	Systematic review – adult population
POPOV2011	Adult population
POSNER1992	Adult population
PUIG2009	Conference abstract
RAZALI2000	Adult population
RIETDIJK2010	Design: Protocol only
ROLLINSON2008	Design: Non RCT
ROSENBAUM2005	Design: Non RCT
ROSS2011A	Adult population
ROTONDI2005	Adult population
RUHRMANN2009	Design: Cohort
RUND1994	Design: Non RCT
SENSKY2000	Adult population
SHIMODERASINOUE2000	Adult population
STAIN2010	Conference abstract
STAIN2011	Conference abstract
SUNGUR2003	Not in English
SVENSSON1999	Design: Non RCT
TANG1994	Adult population
TARRIER1999	Adult population
TARRIER1988	Adult population
TAS2012	Adult population
TIFFIN2007	Design: Non RCT
TROWER2004	Adult population
TURKINGTON2000	Adult population
TURKINGTON2002	Adult population
UELAND2004	Not relevant to this section. Included in the 'Education' chapter.
UELAND2005	Not relevant to this section. Included in the 'Education' chapter.
UZENOFF2008	Adult population
VALENCIA2007	Adult population
VALMAGGIA2005	Adult population
VAN DER2011	Conference abstract
VAREZJIMENEZ2009	Design: Non RCT
VELLIGAN2008	Adult population
VELTRO2011	Adult population
VESTERAGER2011	Adult population
WARING1986	Design: review

WKYES2003	Adult population
WYKES2007A	Adult population
WYKES2007B	Not relevant to this section. Included in the 'Cognition, Employment & Education' chapter.
WYKES2009	Adult population
WYKES2011	Adult population
WRIGHT2012	Design: Protocol only
XIONG1994	Adult population
ZASTOWNY1992	Adult population
ZHANG1994	Adult population
ZHANG2005	Not in English

Pharmacological interventions: excluded studies

Study	Reason for exclusion
ABUZZAHAB1973	Adult population
ADDINGTON2002	Adult population
ADDINGTON2011	Adult population
AGID2007A	Adult population
AHLFORS1990	Adult population
AITCHISON2011	Adult population
AKHONDZADEHSSAL2002	Adult population
AKHONDZADEHSSAL2009	Adult population
ALAPIN1967	Adult population
ALBERT1970	Adult population
ALFARO2002	Design: non RCT
ALFREDSSON1984A	Adult population
ALFREDSSON1985	Adult population
ALHAMAD2005	Adult population
ALMANDIL2011	Design: review
ALPTEKIN2008	Design: review
ANAND2010	Intervention not included in the review protocol
ANANTH1972	Not in English
ANDERSEN1990	Adult population
ANDREZINA2006	Adult population
ANGUS1969	Adult population
ANTROPOV1981	Not in English
APIQUIAN2003	Adult population
APIQUIAN2005	Adult population
ARANGO2003	Adult population
ARANGO2004	Design: review
ARATO2002	Adult population
ARDIZZONE2010	Design: non RCT
ARMENTEROS1997	Design: non RCT
ARMENTEROS2006	Design: non RCT
ARRANZ2007	Design: non RCT
ARVANITIS1997	Adult population
ASCHER-SVANUM2011	Intervention not included in the review protocol
ASSION2008	Adult population
AWAD1997	Adult population

AYD1972	Design: non RCT
AZORIN2006A	Adult population
BACHMAN2009	Design: non RCT
BAGADIA1980	Intervention not included in the review protocol
BAGADIA1983	Adult population
BAI2006	Adult population
BALDWIN1995	Design: non RCT
BAN1975A	Intervention not included in the review protocol
BAO1988	Not in English
BATPITAULT2009	Design: case study
BATTAGLIA1997	Adult population
BEASLEY1996	Adult population
BEASLEY2003	Adult population
BEASLEY2006	Adult population
BEHERE2009	Outcomes not included in the review protocol
BELLOMO1988	Not in English
BISHOP2008	Design: non RCT
BITTER2004	Adult population
BOBO2011	Adult population
BONDOLFI1998	Adult population
BONDOLFI2002	Adult population
BONNOT2012	Adult population
BOONSTRA2011	Adult population
BORISON1989	Adult population
BORISON1994	Adult population
BORISON1996	Adult population
BORKOWSKA2002	Adult population
BOTER2009	Adult population
BOULTON2008	Adult population
BREIER2002	Adult population
BRIZER1985	Adult population
BROERSE2002	Adult population
BRYDEN2001	Design: literature review
BUCHANAN2007	Adult population
BUCKLEY2004	Design: combined analysis of three trials
BURKE1995	Design: non RCT
BURNS2001	Design: review
BYERLY2009	Adult population
CAAM2012	Design: non RCT
CAMPBELL1972A	Design: non RCT
CAMPBELL1972B	Design: non RCT
CAMPBELL1973	Design: non RCT
CAMPBELL1976	Design: non RCT
CAMPBELL1995	Design: non RCT
CAMPBELL1999	Design: non RCT
CANUSO2009	Adult population
CARADOCDAVIES1987	Not relevant to review
CARLISLE2011	Design: review
CARMAN1981	Adult population
CARPENTER1983	Adult population
CARRIERE2000	Adult population
CASE1971	Adult population

CASEY2003	Adult population
CASTILLA2002	Conference abstract
CASTROFORNIELES2008	Design: cohort study
CHANPATTANA1999	Adult population
CHARALAMPOUS1974	Not available
CHEN2008	Adult population
CHEN2012	Adult population
CHENGAPPA2003A	Adult population
CHENGSHANNON2004	Design: review
CHIU1976	Adult population
CHIU2006	Adult population
CHOUINARD1989	Adult population
CHOUINARD1990	Adult population
CHOUINARD1994	Adult population
CHOUINARD1998	Adult population
CHOUINARD2007	Adult population
CHOWDURY1999	Adult population
CHRISTODOULIDIS1975	Adult population
CHRZANOWSKI2006	Adult population
CHUE2005	Adult population
CIESLIKI1969	Not in English
CITROME2003	Design: non RCT
CITROME2006	Adult population
CIUDAD2006	Adult population
CIUREZU1976	Not in English
CLAGHORN1972	Not population of interest
CLARK1971	Adult population
CLARK1977	Adult population
CLARK1998	Design: review
CLARK2001	Design: non RCT
COLEMAN1974	Design: non RCT
COLONNA2000	Adult population
CONLEY2005	Adult population
CONLEY2009	Adult population
COOPER2000	Adult population
CORDES2009	Intervention not included in the review protocol
CORRELL2008A	Design: non RCT
CORRELL2008B	Design: review
CORRELL2009	Conference abstract
CORRELL2010A	Conference abstract
CORRELL2010B	Conference abstract
CORRELL2011	Conference abstract
CORRIGAN2004	Adult population
CORSINI1981	Intervention not included in the review protocol
CRESPOFACORRO2006	Adult population
CRESPOFACORRO2007	Adult population
CRESPOFACORRO2011	Adult population
CRESPOFACORRO2011B	Adult population
CRESPOFACORRO2012	Adult population
CUESTA2009A	Outcomes not included in the review protocol
CUTLER2008	Adult population
CZOBOR1995	Adult population

DANIEL1998	Adult population
DANIEL1999	Adult population
DANIEL2007	Adult population
DANION1999	Adult population
DAVIDSON2009	Adult population
DAVIS1977	Intervention not included in the review protocol
DE2009	Adult population
DEGIACOMO2008	Design: non RCT
DEJESUSMARI2004	Adult population
DELBELLO2008	Population: 71% bipolar disorder
DENAYER2003	Adult population
DENBOER1990A	Adult population
DENBOER1990B	Adult population
DENZEL1966	Adult population
DEO1990	Adult population
DERKS2010	Adult population
DESTA2002	Adult population
DICKERSON2009	Adult population
DITTMANN2008	Design: non RCT
DITTMANN2010	Design: non RCT
DOCHERTY2010	Adult population
DODDSCALLALY2010	Design: non RCT
DOLLFUS2005	Adult population
DONLON1980	Adult population
DOSE1987	Adult population
DOSSENBACH2004	Adult population
DOSSENBACH2007	Adult population
ECCLESTON1985	Adult population
EDWARDS2006	Intervention not included in the review protocol
ELIZUR1979	Design: non RCT
EMSLEY1999	Adult population
EMSLEY2000	Adult population
EMSLEY2002	Adult population
EMSLEY2007	Outcomes not included in the review protocol
EMSLEY2008A	Design: non RCT
EMSLEY2008B	Design: non RCT
ENDICOTT2009	Conference abstract
ENGELHARDT1978	Intervention not included in the review protocol
ESCANDE1983	Not in English
ESSOCK2006	Adult population
FABRE1995	Adult population
FAKRA2008	Adult population
FAKRAESALGADOPI2009	Adult population
FALLOON1978	Adult population
FARETRA1970	Intervention not included in the review protocol
FARIES2008	Adult population
FENGJU2006	Not in English
FINDLING1996	Conference abstract
FINDLING1998	Design: review
FINDLING2000	Design: review
FINDLING2002	Design: review
FINDLING2003	Design: non RCT

FINDLING2005	Design: review
FINDLING2007	Design: non RCT
FINDLING2008B	Design: non RCT
FINDLING2010A	Conference abstract
FISH1966	Design: non RCT
FISH1969	Design: non RCT
FLEISCHHACKER2003	Design: non RCT
FLEISCHHACKER2009	Adult population
FLYNN1998	Design: non RCT
FOSTER1997	Adult population
FRAGUS2010	Design: review
FRAGUS2011	Design: review
FRAZIER1994	Design: non RCT
FRAZIER2003	Design: non RCT
FRAZIER2012	Design: review
FREEDMAN1982	Design: non RCT
FREEDMAN1986	Not available
FREUDENREICH2009	Adult population
FRIBERG2009	Adult population
FRUENSGAARD1978	Adult population
GALLEGO2011	Outcomes not of interest
GALLHOFER2007	Adult population
GANGULI2008	Adult population
GAO2007	Not in English
GARCIA2009	Adult population
GARZATREVINO1989	Adult population
GEORGOTAS1981	Adult population
GERLACH1974	Adult population
GERLACH1975	Adult population
GERSTENZANG1977	Adult population
GHARABAWI2006	Adult population
GIBSON2007	Design: non RCT
GILBERG2000	Design: review
GIRGIS2011	Adult population
GITLIN2001	Adult population
GLICK2001	Design: non RCT
GODLESKI2003	Adult population
GOFF2008	Adult population
GOGTAY2008	Design: review
GOLDBERG1972	Adult population
GOLDBERG1987	Adult population
GOLDBERG2009	Outcomes not included in the review protocol
GOLDEN2008	Adult population
GOODE1983	Adult population
GOTHELF2003	Design: non RCT
GOTTFRIES1974	Adult population
GRAM1972	Intervention not included in the review protocol
GRCEVICH1996	Design: non RCT
GREBB1986	Adult population
GREENAWAY2009	Design: review
GREENBAUM1970	Intervention not included in the review protocol
GROOTENS2011	Adult population

GROTHE2000	Design: non RCT
GU1992	Not in English
GUNBY1968	Adult population
GUNDLACH1966	Intervention not included in the review protocol
GUTTGEMANNS2011	Not in English
HAIDER1985	Adult population
HAKOLA1973	Adult population
HAMID1973	Adult population
HAMILL1975	Adult population
HAMILTON1998	Adult population
HARDY2011	Adult population
HARNRYD1984	Adult population
HARRIGAN2004	Adult population
HARRIS1975	Adult population
HARVEY2003A	Adult population
HARVEY2006	Adult population
HAW2010	Design: non RCT
HEBENSTREIT1991	Adult population
HERTLING2003	Adult population
HEYDEBRAND2004	Design: non RCT
HINZESELCH2000	Adult population
HIROSE2000	Design: non RCT
HIRSCH1973	Adult population
HIRSCH2002	Adult population
HOGAN1992	Adult population
HOGARTY1973	Adult population
HOGARTY1974A	Adult population
HOGARTY1974B	Adult population
HOGARTY1995	Adult population
HOLZER2011A	Design: non RCT
HOMMER1984	Adult population
HONER1995	Adult population
HOUGH2011	Adult population
HRDLICKA2007	Design: non RCT
HRDLICKA2010	Conference abstract
HUANG2012	Adult population
HUFFMAN1997	Design: non RCT
HUO2007	Not in English
HUTTUEN1995	Adult population
IONESCU1983	Design: non RCT
ISHIGOOKA2000	Adult population
ITIL1971A	Adult population
JACOBSEN1994	Design: non RCT
JACOBSSON1974	Adult population
JAINER2009	Design: non RCT
JAMES2008A	Design: review
JAMES2008B	Design: review
JAMES2010	Design: review
JANOWSKY1973	Intervention not included in the review protocol
JANSSEN1972	Adult population
JENSEN2007	Design: review
JERRELL2008	Design: non RCT

JIBIKI1994	Adult population
JOHNSON1973	Adult population
JOHNSTONE1978	Adult population
JOHNSTONE1988	Adult population
JONES2006	Adult population
JOSEPH2011	Adult population
KALEDA2000	Conference abstract
KALYANASUNDARAM1981	Adult population
KANE2003	Adult population
KANE2010	Adult population
KAPETANOVICSSIM2006	Design: review
KAPUR2005	Adult population
KARIYA1983	Intervention not included in the review protocol
KECK1998	Adult population
KECK2001B	Adult population
KEEFE2003	Adult population
KEEFE2006	Adult population
KEEFE2007	Outcomes not included in the review protocol
KEKS1994	Adult population
KEMPERMAN2006	Design: non RCT
KENNEDY2007	Design: review
KERWIN2007	Adult population
KIM2008A	Adult population
KINON1993A	Adult population
KINON2008A	Adult population
KINON2008B	Adult population
KLEIN1973	Adult population
KLEMP2011	Adult population
KLUGE2005	Design: non RCT
KLUGE2007	Adult population
KOLIVAKIS1974	Adult population
KONGSAKON2006	Adult population
KOWATCH1995	Design: review
KOZLOVA2001	Not in English
KRAKOWSKI2011	Adult population
KRANZLER2006	Design: review
KRATOCHVIL2010	Design: review
KREISMAN1988	Design: non RCT
KRYZHANOVSKAYA2009A	Design: review
KUDO1972	Adult population
KUMAR2012	Design: Protocol only
KUMRA1999	Design: non RCT
KUMRA2000	Design: review
KUMRA2008B	Design: non RCT
KUMRA2010	Conference abstract
KUMRASOBERSTAR2008	Design: review
KUNIYOSHI1994	Design: non RCT
KUWILSKY2010	Intervention not included in the review protocol
LAMBERT1995	Adult population
LANE2001	Design: non RCT
LANE2008	Adult population
LAPIERRE1975	Adult population

LAPIERRE1990	Adult population
LARMO2005	Adult population
LASSER2004	Adult population
LAURIELLO2005	Adult population
LAURIELLO2008	Adult population
LAUX1990	Adult population
LEE1968	Adult population
LEE2002A	Adult population
LEFF1971	Adult population
LEJEUNE2004	Design: non RCT
LEONG1989	Adult population
LEPOLA1989	Adult population
LERNER1988	Adult population
LEVENSON1976	Intervention not included in the review protocol
LEVINE1997A	Adult population
LIEBERMAN2003B	Adult population
LIM2010	Adult population
LINDENMAYER2007	Adult population
LINDENMAYER2011	Adult population
LINDSTROM1990	Adult population
LOZE2010	Conference abstract
MAAGENSEN1999	Design: non RCT
MADAAN2008	Design: review
MADAAN2009	Design: review
MALHOTRA2000	Design: non RCT
MALIK1980	Intervention not included in the review protocol
MALONE1999	Design: review
MANCHANDA1986	Adult population
MANDOKI1995	Design: non RCT
MANN1987	Adult population
MARCELLI2002	Not in English
MARDER1994	Adult population
MARDER1997	Adult population
MARDER2003	Adult population
MARJERRISON1971	Adult population
MARTIN2002	Adult population
MASI2006	Design: review
MASI2011	Design: review
MATTIA2010	Design: review
MAURI1994	Adult population
MCCLELLAN1976	Adult population
MCCLELLAN2007	Protocol (TEOSS study)
MCCLURE2009	Design: non RCT
MCCONVILLE2000	Design: non RCT
MCCONVILLE2003	Design: non RCT
MCCORMACK2010	Design: review
MCEVOY1991	Adult population
MCGLASHAN2003	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
MCGLASHAN2006	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
MCGORRY2002	Not relevant to this section. Included in the 'At risk states of

	psychosis in children and young people' chapter.
MEHLERWEX2010	Design: review
MELTZER2003	Adult population
MELTZER2004	Adult population
METZ1982	Design: non RCT
MIKKELSEN1982	Design: review
MILLER2007	Adult population
MIN1993	Adult population
MOLDAVSKY1998	Design: non RCT
MOLLER2001	Design: review
MOLLER2004	Adult population
MOLLER2008A	Adult population
MOLLER2008B	Adult population
MORTIMER2004	Adult population
MOYANO1975	Adult population
MOZES2003	Design: non RCT
MULHOLLAND2003	Adult population
MULLEN2001	Adult population
MULLER2002A	Adult population
NABER2005	Adult population
NAHUNEK1970A	Conference abstract
NAHUNEK1970B	Not in English
NAHUNEK1979	Adult population
NAIR1988	Adult population
NAKAZAWA1983	Intervention not included in the review protocol
NEWCOMER2008	Adult population
NISHIZONO1984	Not in English
NOORBALA1999	Adult population
NUECHTERLEIN2008	Design: non RCT
NYILAS2010	Adult population
OKUMA1989	Design: non RCT
PAE2007	Adult population
PALOSCIA2007	Design: review
PANAGIOTOPOULOS2010	Design: review
PAPROCKI1977	Adult population
PARELLADAEKOUNIAKIS2010	Design: non RCT
PARENT1982	Not in English
PARENT1983	Adult population
PENN2009	Adult population
PEREZIGLESIAS2007	Adult population
PEREZIGLESIAS2008A	Adult population
PERICLEOUS2010	Outcomes not included in the review protocol
PERKINS2004A	Design: review
PERKINS2004B	Outcomes not included in the review protocol
PEUSKENS2010	Adult population
PFLUG1990	Adult population
PHILLIPS2007	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
PHILLIPS2009	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
POOL1976	Intervention not included in the review protocol
POTKIN2002A	Adult population

POTKIN2006	Adult population
POTKIN2008	Adult population
POTKIN2009B	Adult population
PROSELKOVA1991	Not in English
PURDON2000	Adult population
QUINTANA2007	Adult population
QUITKIN1975	Adult population
REALMUTO1984	Intervention not included in the review protocol
REMSCHMIDT1994	Design: non RCT
REN2006	Adult population
RIEDEL2007A	Adult population
RIEDEL2007B	Adult population
RIFKIN1976	Adult population
ROSS2003	Design: non RCT
RUAN2010	Design: non RCT
RUBIO2006	Adult population
RUHRMANN2007	Adult population
RUMMELKLUGE2012	Adult population
SAFA2008	Adult population
SALOKANGAS1996	Adult population
SALVENSEN1973	Adult population
SANFORD2007	Design: review
SANFORD2008	Design: non RCT
SCHENNACHWOLFF2011	Adult population
SCHIELE1969	Intervention not included in the review protocol
SCHIMMELMANN2007	Design: non RCT
SCHOEMAKER2010	Intervention not included in the review protocol
SCHOOLER1971	Adult population
SCHOOLER1976	Intervention not included in the review protocol
SCHOOLER1994	Not obtainable
SCHOOLER1997A	Adult population
SECHTER2002	Adult population
SELMAN1976	Intervention not included in the review protocol
SEVYSROBINSON2011	Secondary analysis
SHAW2001	Design: non RCT
SHAW2004	Design: review
SHIN2009	Intervention not included in the review protocol
SHOLEVAR2000	Design: non RCT
SIKICH2001	Conference abstract
SIKICH2008B	Design: review
SIMPSON1976	Adult population
SIMPSON2004	Adult population
SIMPSON2008	Design: pooled analysis
SIRIS1992	Adult population
SIVRIOGLU2007	Design: non RCT
SMITH2005A	Adult population
SPENCER1992	Less than 10 people in each trial arm
SPENCER1994	Design: review
SPIVAK2003	Adult population
SPOHN1977	Adult population
SPORN2007	Design: non RCT
STAUFFER2011A	Secondary analysis

STERLIN1970	Intervention not included in the review protocol
STEVENS1973	Adult population
STEWART2009	Design: non RCT
STROUP2003	Adult population
STROUP2009	Adult population
STROUS2007	Adult population
SUZUKI2011	Adult population
SVESTKA1970	Not in English
SVESTKA1972	Adult population
SVESTKA1973	Adult population
SVESTKA1974	Adult population
SWANSON1967	Intervention not included in the review protocol
SWARTZ2008	Design: review
SZEGEDI1999	Design: non RCT
TAKAHASHI1982	Intervention not included in the review protocol
TANIGUCHI2006	Design: non RCT
TAYLOR2008A	Adult population
THOMAS2006	Design: review
TIMDAHL2007	Adult population
TOLLEFSON1997A	Adult population
TOREN2004	Design: review
TURETZ1997	Design: non RCT
VALENCIA2004	Not in English
VANNIMWEGEN2006	Design: non RCT
VARTIAINEN1995	Adult population
VERSAVEL2005	Intervention not included in the review protocol
VERSIANI1978	Intervention not included in the review protocol
VESER2006	Adult population
VIANNA1975	Intervention not included in the review protocol
VILLARI2008	Adult population
VINAR1968	Adult population
VINAR1971	Intervention not included in the review protocol
WADZISZ1969	Adult population
WAHBA1981	Adult population
WAIZER1972	Design: non RCT
WALTER2001	Design: review
WANG2010	Adult population
WEIDEN2003A	Adult population
WEIDEN2003B	Adult population
WEIDEN2009	Adult population
WEISER1978	Intervention not included in the review protocol
WEISER2000	Adult population
WIESEL1985	Not in English
WILSON1993	Adult population
WOGGON1984	Intervention not included in the review protocol
WOODS2002	Design: non RCT
WOODS2003	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
WRIGHT2001	Adult population
WUDARSKY1999	Design: non RCT
YILMAZ1971	Intervention not included in the review protocol
YOUNG2004	Design: review

YOUNIS2012	Conference abstract
YUNG2011	Not relevant to this section. Included in the 'At risk states of psychosis in children and young people' chapter.
ZALSMAN2003	Design: non RCT
ZHANG2006A	Adult population
ZHANG2007	Adult population
ZHONG2006	Intervention not included in the review protocol
ZIEGENBEIN2006	Adult population
ZIMBROFF1997	Adult population
ZINK2009	Adult population