

Data supplement

Table D1 Studies included in analysis

| Study ^a | Inclusion criteria (diagnosis; definition of early psychosis) | Duration of psychosis in treatment (means reported if otherwise not stated) | Interventions and doses received (means reported if otherwise not stated) | Recruited atypical/typical, n | Length of study | Quality (concealment of sequence of allocation, masking, loss to follow-up or number dropped out reported) |
|--|---|--|--|-------------------------------|--|---|
| Risperidone Working Group (1999) ²⁴ | DSM-III schizophrenia or schizoaffective disorder aged 15–45 years; no previous antipsychotic treatment | No previous antipsychotic treatment (up to 3 days of emergency treatment allowed) | Risperidone 6.1 mg/haloperidol 5.6 mg | 99/84 | 6 weeks | Unclear if allocation was concealed, described as 'double-blind' 25% reported as non-completers |
| Sanger (1999) ¹³ | DSM-III-R schizophrenia, schizoaffective disorder, or schizoaffective disorder, with BPRS > 18 or intolerance of current antipsychotic therapy and aged >18 years; first episode of psychosis with a duration of less than 5 years and before 45 years of age | Duration of treatment for psychosis of 13 months (mean) | Olanzapine 11.6 mg/haloperidol 10.8 mg | 59/4 | 6 weeks | Subsample analysis of randomised controlled trial Unclear if allocation was concealed, described as 'double-blind' Original study reported 1.3% of sample was lost to follow-up ⁴⁹ |
| Mackeprang (2002–2007) ^{25,39,47} | ICD-10 schizophrenia; antipsychotic-naïve patients on their first admission to hospital | All antipsychotic naïve | Risperidone 3.6 mg/zuclopentixol 9.6 mg | 15/10 | 13 weeks | Unclear if allocation was concealed, 'open labelled' LTF 19% |
| Lieberman (2003) ³⁶ | DSM-IV schizophrenia or schizoaffective disorder aged 16–40 years and current psychotic symptoms of moderate severity or allowed greater measured by one of the five psychotic items in BPRS; history of psychosis less than 60 months, no prior treatment with antipsychotic medication or a total lifetime usage of <14 days | All antipsychotic naïve (up to 14 days of antipsychotics allowed) | Clozapine plus placebo 400 mg at 12 weeks, then 300 mg/chlorpromazine plus benzotropine 600 mg at 12 weeks, then 400 mg (median) | 80/80 | 52 weeks | Described as 'double-blind', and authors confirmed that allocation, masking and treatment was concealed 12% of the participants reported to have dropped out |
| De Haan (2003) ³³ | DSM-IV schizophrenia aged 17–28 years admitted to adolescent clinic specialising in recent-onset schizophrenia | Duration of illness of 16.5 months (mean), but unclear duration of treatment | Olanzapine 7.5 mg/haloperidol 2.5 mg (fixed doses) | 12/12 | 6 weeks | Unclear if allocation was concealed, described as 'double-blind' 17% dropped out |
| HGDH Study Group (2003) ^{34,38–52} | DSM-IV schizophrenia, schizoaffective disorder, or schizoaffective disorder aged 16–40 years (onset before 35 years), experienced psychotic symptoms for at least 1 month, scored ≥ 4 on at least two PANSS items or scored ≥ 5 on one psychosis item, had a CGI Severity score ≥ 4 (moderately ill) and required treatment with antipsychotic drugs on a clinical basis; history of psychosis <60 months | 74% receiving antipsychotic for mean time of 5.9 weeks Rest antipsychotic naïve | Olanzapine 9.1 mg in acute phase, 10.2 mg in continuation phase/ haloperidol 4.4 mg in acute phase, 4.8 mg in continuation phase | 131/132 | 24 months | Described as 'double-blind', and authors confirmed that allocation, masking and treatment was concealed LTF of 6% reported at 24 months |
| Early Psychosis Global Network (EPGN) (2006) ²⁶ | DSM-IV schizophrenia, schizoaffective disorder, or schizoaffective disorder aged 16–45 years requiring antipsychotic treatment upon enrolment; history of psychosis for <1 year, less than 12 weeks of cumulative exposure to antipsychotics and no more than two psychiatric hospitalisations for psychosis | 31% antipsychotic naïve | Risperidone 3.3 mg/haloperidol 2.9 mg | 278/277 | Follow-up continued until last participant enrolled had completed 2 years of treatment | Unclear if allocation was concealed, described as 'double-blind' LTF of 7% reported |
| Wu (2006) ^{27,37} | DSM-IV schizophrenia aged 18–45 years; first episode of psychosis, no previous antipsychotic exposure | All antipsychotic naïve | Clozapine 275.6 mg, olanzapine 13.7 mg, risperidone 4.2 mg/sulpiride 733 mg | 83/29 | 8 weeks | Adequate concealment of allocation, unmasked 7% dropped out |

(continued)

Table D1 (continued)

| Study ^a | Inclusion criteria (diagnosis; definition of early psychosis) | Duration of psychosis in treatment or % antipsychotic naïve | Interventions and doses received (means reported if otherwise not stated) | Recruited atypical/typical, n | Length of study | Quality (concealment of sequence of allocation, masking, loss to follow-up or number dropped out reported) |
|--|--|--|---|--|-----------------|---|
| Crespo-Facorro (2006) ^{28,46,53} | DSM-IV schizophrenia, schizoaffective, brief reactive psychosis, schizotypal personality disorder, psychosis not otherwise specified aged 15–60 years, with SAPS psychotic symptoms moderate severity or greater; antipsychotic naïve or total lifetime exposure of less than 6 weeks | All antipsychotic naïve or with a total lifetime exposure of <6 weeks | Risperidone 4 mg, olanzapine 15.3 mg and haloperidol 5.4 mg in acute phase Risperidone 3.6 mg, olanzapine 10.1 mg and haloperidol 2.9 mg at 1 year | 116/56 | 12 months | Unclear if allocation was concealed, unmasked LTF 11% |
| Brewer 2007 ²⁹ | First episode of psychosis defined as onset between 16 and 30 years of at least one of the following: (a) delusions; (b) hallucinations; (c) disorder of thinking/speech, other than simple acceleration or retardation; and (d) disorganized, bizarre, or markedly inappropriate behaviour, without previous antipsychotic treatment. | All antipsychotic naïve | Risperidone 2 mg/haloperidol 2 mg (fixed doses) | 3/4 | 8 weeks | Unclear if allocation was concealed, described as 'double-blind' LTF 12.5% |
| German Research Network on Schizophrenia (GRNS) (2007) ^{30,48} | Diagnosis of schizophrenia DSM-IV was confirmed at 6 months | 57% of the participants had an onset of psychosis less than 6 months before study entry, but unclear duration of treatment | Risperidone 3.8 and 4.2 mg/haloperidol 3.7 mg and 4.1 mg (both in the acute and continuation phase respectively) | 146/143 in acute phase, 83/75 in continuation phase | 2 years | Described as 'double-blind', and authors confirmed that allocation, masking and treatment was concealed 49% reported to have dropped out in the acute phase, 68.2% in continuation trial (including discontinuation of drug) |
| Lee (2007) ^{31,54} | DSM-IV schizophrenia, antipsychotic naïve | Antipsychotic naïve | Risperidone 4.1 mg/haloperidol 7.6 mg | 10/10 | 8 weeks | Unclear if allocation was concealed, described as 'double-blind' |
| Saddichha (2008) ^{32,55-58} | DSM-IV schizophrenia; antipsychotic naïve | Antipsychotic naïve | Risperidone 4.4 mg and olanzapine 16.5 mg/haloperidol 13.4 mg | 68/31 | 6 weeks | Unclear if allocation was concealed, described as 'double-blind' |
| Bustillo (2008) ^{35,59} | DSM-IV schizophrenia, schizoaffective or schizotypal disorder; less than 3 weeks lifetime exposure to antipsychotics | 47% antipsychotic naïve | Quetiapine 100–600 mg/haloperidol 2–12 mg (range allowed) | 17/15 | 2 years | Unclear if allocation was concealed, reported to be 'double-blind' LTF 28% |
| European First-Episode Schizophrenia Trial (EUFEST) (2008) ²² | DSM-IV schizophrenia, schizotypal disorder, or schizoaffective disorder aged 18–40 years; <2 years of onset of positive symptoms and lifetime exposure of antipsychotics of less than 2 weeks in the last year or 6 weeks at any time | 33% antipsychotic naïve | Olanzapine 12.6 mg, ziprasidone 107.2 mg, quetiapine 498.6 mg, aripiprazole 450.8 mg/haloperidol 3 mg | 395/103 | 12 months | Adequate concealment of allocation sequence, unmasked LTF 31% |

LTF lost to follow-up; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression; SAPS, Scale for the Assessment of Positive Symptoms.
a. All references from each selected trial are shown (additional references are cited below).⁴⁹⁻⁵⁹

Additional references

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- 51 Zipursky RB, Christensen BK, Daskalakis Z, Epstein I, Roy P, Furimsky I, et al. Treatment response to olanzapine and haloperidol and its association with dopamine D receptor occupancy in first-episode psychosis. *Can J Psychiatry* 2005; **50**: 462-9.
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- 53 Perez-Iglesias R, Crespo-Facorro B, Amado JA, Garcia-Unzueta MT, Ramirez-Bonilla ML, Gonzalez-Blanch C, et al. A 12-week randomized clinical trial to evaluate metabolic changes in drug-naïve, first-episode psychosis patients treated with haloperidol, olanzapine, or risperidone. *J Clin Psychiatry* 2007; **68**: 1733-40.
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- 55 Saddichha S, Ameen S, Akhtar S. Incidence of new onset metabolic syndrome with atypical antipsychotics in first episode schizophrenia: a six-week prospective study in Indian female patients. *Schizophr Res* 2007; **95**: 247.
- 56 Saddichha S, Manjunatha N, Ameen S, Akhtar S. Effect of olanzapine, risperidone, and haloperidol treatment on weight and body mass index in first-episode schizophrenia patients in India: a randomized, double-blind, controlled, prospective study. *J Clin Psychopharmacol* 2007; **68**: 1793-8.
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- 58 Saddichha S, Manjunatha N, Ameen S, Akhtar S. Metabolic syndrome in first episode schizophrenia – a randomized double-blind controlled, short-term prospective study. *Schizophr Res* 2008; **101**: 266-72.
- 59 Bustillo JR, Lauriello J, Rowland LM, Thomson LM, Petropoulos H, Hammond R, et al. Longitudinal follow-up of neurochemical changes during the first year of antipsychotic treatment in schizophrenia patients with minimal previous medication exposure. *Schizophr Res* 2002; **58**: 313-21.

Details of search

PubMed

((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((sing*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw]))) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT human[mh]))) AND (((amisulprid* OR amitrex OR deniban* OR socian* OR solian* OR sulanid* OR sulamid* OR zyprexa* OR olanzapin* OR quetiapine OR seroquel OR ICI-204636 OR (ICI and 204636) OR ICI204636 OR risperidone OR risperdal OR 9-OH-risperidone OR ziprasidone OR cp-88059 OR abilis OR championyl OR coolspan OR col-sulpir OR digton OR dixibon OR dooren OR dogmatil OR dolmatil OR drominetas OR eglonyl OR equilid OR eusulpid OR guastil OR isnamid OR kapiroide OR lavodina OR lebopride OR lusedan OR miradol OR mirbanil OR misulvan OR neuromyfar OR normum OR omperan OR psicocen OR quiridil OR sato OR sernevin OR sicofrenol OR sulpiride OR sulpisedan OR suprium OR sursumid OR tepavil OR tonofit OR ulpir OR vipral OR zotepine OR lodopin OR nipolect OR zopite

OR setous OR majorpin OR clozapine OR clozaril OR leponex OR ("Antipsychotic Agents"[Mesh] OR "Antipsychotic Agents"[Pharmacological Action] OR "Risperidone"[Mesh] OR "olanzapine "[Substance Name] OR "olanzapine-fluoxetine combination "[Substance Name] OR "9-hydroxy-risperidone "[Substance Name] OR "Dopamine Antagonists"[Mesh] OR "Molindone"[Mesh]) OR "typical antipsychotic*" OR "atypical antipsychotic*") AND ("first episode" OR "first onset" OR "early onset" OR naive OR "never medicated") AND (((psychosis OR psychotic OR schizophreni* OR schizoaffective) OR "Schizophrenia and Disorders with Psychotic Features"[Mesh]))

EMBASE

(exp DEPRESSIVE PSYCHOSIS/ or exp MANIC DEPRESSIVE PSYCHOSIS/ or exp PARANOID PSYCHOSIS/ or exp SCHIZOAFFECTIVE PSYCHOSIS/ or exp MANIC PSYCHOSIS/ or exp AFFECTIVE PSYCHOSIS/ or exp ENDOGENOUS PSYCHOSIS/ or exp ACUTE PSYCHOSIS/ or psychosis.mp. or exp PSYCHOSIS/ or schizophrenia.mp. or exp SIMPLE SCHIZOPHRENIA/ or exp PARANOID SCHIZOPHRENIA/ or exp SCHIZOPHRENIA/ or exp CATATONIC SCHIZOPHRENIA/ or exp RESIDUAL SCHIZOPHRENIA/ or exp LATENT SCHIZOPHRENIA/ or SCHIZOPHRENIFORM DISORDER/ or (schizophrenic or schizophrenics).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]) AND ("first episode" or naive or "never medicated" or (never adj3 (antipsychoti\$ or neurolepti\$))).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] AND (exp Ziprasidone/ or exp Quetiapine/ or exp Olanzapine/ or exp Risperidone/ or exp ATYPICAL ANTIPSYCHOTIC AGENT/ or antipsychotics.mp. or exp Clozapine/ or (risperidon\$ or quetiapin\$ or clozapin\$ or olanzapin\$ or ziprasidon\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]) AND (Randomized Controlled Trial/ or random\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name])

PsycINFO

(exp DEPRESSIVE PSYCHOSIS/ or exp MANIC DEPRESSIVE PSYCHOSIS/ or exp PARANOID PSYCHOSIS/ or exp SCHIZOAFFECTIVE PSYCHOSIS/ or exp MANIC PSYCHOSIS/ or exp AFFECTIVE PSYCHOSIS/ or exp ENDOGENOUS PSYCHOSIS/ or exp ACUTE PSYCHOSIS/ or psychosis.mp. or exp PSYCHOSIS/ or schizophrenia.mp. or exp SIMPLE SCHIZOPHRENIA/ or exp PARANOID SCHIZOPHRENIA/ or exp SCHIZOPHRENIA/ or exp CATATONIC SCHIZOPHRENIA/ or exp RESIDUAL SCHIZOPHRENIA/ or exp LATENT SCHIZOPHRENIA/ or SCHIZOPHRENIFORM DISORDER/ or (schizophrenic or schizophrenics).mp. [mp=title, abstract, heading word, table of contents, key concepts]) AND ("first episode" or naive or "never medicated" or (never adj3 (antipsychoti\$ or neurolepti\$))).mp. [mp=title, abstract, heading word, table of contents, key concepts]) AND (exp Ziprasidone/ or exp Quetiapine/ or exp Olanzapine/ or exp Risperidone/ or exp ATYPICAL ANTIPSYCHOTIC AGENT/ or antipsychotics.mp. or exp Clozapine/ (risperidon\$ or quetiapin\$ or clozapin\$ or olanzapin\$ or ziprasidon\$).mp. [mp=title, abstract, heading word, table of contents, key concepts]) AND (Randomized Controlled Trial/ or random\$.mp. [mp=title, abstract, heading word, table of contents, key concepts])

COCHRANE

(MeSH descriptor Psychotic Disorders explode all trees OR (psychosis OR psychotic OR schizophreni* OR schizoaffective)) AND ("first episode" OR "first onset" OR "early onset" OR naive OR "never medicated") AND (amisulprid* OR amitrex OR deniban* OR socian* OR solian* OR sulanid* OR sulamid* OR zyprexa* OR olanzapin* OR quetiapine OR seroquel OR ICI-204636 OR (ICI and 204636) OR ICI204636 OR risperidone OR risperdal OR 9-OH-risperidone OR ziprasidone OR cp-88059 OR abilify OR championyl OR coolspan OR col-sulpur OR digton OR dixibon OR dobren OR dogmatil OR dolmatil OR drominetas OR eglonyl OR equilid OR eusulpid OR guastil OR isnamid OR kapiride OR lavodina OR lebopride OR lusedan OR miradol OR mirbanil OR misulvan OR neuromyfar OR normum OR omperan OR psicocen OR quiridil OR sato OR sernevin OR siconfrenol OR sulpiride OR sulpisedan OR suprium OR sursumid OR tepavil OR tonofit OR ulpir OR vipropride OR zotepine OR lodopin OR nipolet OR zopite OR setous OR majorpin OR clozapine OR clozaril OR leponex OR "Antipsychotic Agents" OR "Antipsychotic Agents" OR "Risperidone" OR "olanzapine" OR "olanzapine-fluoxetine combination" OR "9-hydroxy-risperidone" OR "Dopamine Antagonists" OR "Molindone" OR "typical antipsychotic*" OR "atypical antipsychotic*")